Therapeutic Class Overview
Short-acting Opioids

Therapeutic Class

- **Overview/Summary:** Pain is one of the most common and debilitating patient complaints, with persistent pain having the potential to lead to functional impairment, disability, psychological distress and sleep deprivation. Pain can be categorized as being either nociceptive or neuropathic, and the treatments for each are specific. Nociceptive pain is caused by damage to tissues and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[1] Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent and anticipated adverse events.[2]

  As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. These agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence and respiratory depression.[3]

  Short acting opioid analgesics are available as single entity and in combination with acetaminophen, aspirin, butalbital, caffeine, carisoprodol and ibuprofen. Acetaminophen, aspirin and ibuprofen are non-opiate analgesics. Butalbital is a barbiturate, which has anxiolytic and muscle relaxant properties. Caffeine is an analgesic adjuvant, as well as a central nervous system stimulant. Carisoprodol is a centrally-acting muscle relaxant.[4,5] In January 2011, the Food and Drug Administration asked manufacturers to limit the amount of acetaminophen in prescription drug products (which are predominantly combinations of acetaminophen and opioids) to 325 mg per dosage form to make these products safer for patient to use.[6]

Table 1. Current Medications Available in Therapeutic Class[7-25]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Butorphanol	Management of moderate to severe pain in patients where an opioid analgesic is appropriate	Injection: 1 mg/mL 2 mg/mL Nasal spray: 10 mg/mL	✔
Codeine	Relief of mild to moderate pain	Solution: 30 mg/5 mL Tablet: 15 mg 30 mg 60 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Hydromorphone (Dilaudid®*)	Management of moderate to severe pain in patients where an opioid analgesic is appropriate	Injection: 1 mg/mL 2 mg/mL 4 mg/mL 10 mg/mL 250 mg Liquid: 1 mg/mL Rectal suppository: 3 mg Tablet: 2 mg 4 mg 8 mg	✔
Meperidine (Demerol®*, Meperitab®*)	Relief of moderate to severe pain	Injection: 10 mg/mL 25 mg/0.5 mL 25 mg/mL 50 mg/mL 75 mg/mL 75 mg/1.5 mL 100 mg/mL 100 mg/2 mL Solution: 50 mg/5 mL Tablet: 50 mg 100 mg	✔
Morphine (MSIR®*, Roxanol®*)	Management of moderate to severe pain in patients where an opioid analgesic is appropriate	Epidural: 10 mg/mL Injection: 0.5 mg/mL 1 mg/mL 2 mg/mL 4 mg/mL 5 mg/mL 8 mg/mL 10 mg/mL 15 mg/mL 15 mg/1.5 mL 25 mg/mL 30 mg/30 mL 50 mg/mL 100 mg/4 mL 100 mg/0.1 L 150 mg/30 mL	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		250 mg/10 mL 250 mg/250 mL Rectal suppository: 5 mg 10 mg 20 mg 30 mg Solution 10 mg/5 mL 20 mg/mL 20 mg/5 mL Tablet: 15 mg 30 mg10 mg 20 mg 30 mg Tablet: 15 mg 30 mg	
Oxycodone (Oxecta®*, Roxicodone®*)	Management of moderate to severe pain in patients where an opioid analgesic is appropriate	Capsule: 5 mg Oral concentrate: 20 mg/mL Solution: 5 mg/5 mL Tablet: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg	✔
Oxymorphone (Opana®*)	Relief of moderate to severe pain	Injection: 1 mg/mL Tablet: 5 mg 10 mg	✔
Tapentadol (Nucynta®)	Management of moderate to severe acute pain in adults	Tablet: 50 mg 75 mg 100 mg	-
Combination Products			
Acetaminophen/ codeine (Capital	Relief of discomfort associated with acute,	Elixir: 12/120 mg/5 mL	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
w/codeine®*, Tylenol-Codeine®*)	painful musculoskeletal conditions in adults	Suspension: 12/120 mg/5 mL Tablet: 15/300 mg 30/300 mg 60/300 mg 30/650 mg 60/650 mg	
Codeine/butalbital/ acetaminophen/ caffeine (Fioricet with Codeine®*)	Relief of tension or muscle contraction headache	Capsule: 30/50/325 mg	✔
Codeine/butalbital/ aspirin/caffeine (Fiorinal with Codeine®*)	Relief of tension or muscle contraction headache	Capsule: 30/50/325 mg	✔
Codeine/ carisoprodol/ aspirin	Relief of discomfort associated with acute, painful musculoskeletal conditions in adults	Tablet: 16/200/325 mg	✔
Dihydrocodeine/ acetaminophen/ caffeine	Relief of moderate to moderately severe pain	Capsule: 16/356/30 mg Tablet: 32/713/60 mg	✔
Dihydrocodeine/ aspirin/ caffeine (Synalgos-DC®*)	Relief of mild to moderate pain	Capsule: 16/356/30 mg	-
Hydrocodone/ acetaminophen (Hycet®*, Lorcet®*, Lorcet-Plus®*, Lortab®*, Maxidone®*, Norco®*, Vicodin®*, Vicodin ES®*, Vicodin HP®*, Xodol®*, Zamicet®*, Zolvit®*, Zydone®*)	Relief of moderate to moderately severe pain	Capsule: 5/500 mg Solution: 2.5/167 mg/5 mL 5/334 mg/10 mL 7.5/325 mg/15 mL 7.5/500 mg/15 mL 10/300 mg/15 mL 10/325 mg/15 mL Tablet: 2.5/500 mg 5/300 mg 5/325 mg 5/400 mg 5/500 mg 7.5/300 mg 7.5/325 mg 7.5/400 mg 7.5/500 mg	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		7.5/650 mg 7.5/750 mg 10/300 mg 10/325 mg 10/400 mg 10/500 mg 10/650 mg 10/660 mg 10/750 mg	
Hydrocodone/ ibuprofen (Ibudone®*, Reprexain®*, Vicoprofen®*)	Short-term (<10 days) management of acute pain	Tablet: 2.5/200 mg 5/200 mg 7.5/200 mg 10/200 mg	✔
Oxycodone/ acetaminophen (Magnacet®*, Percocet®*, Primlev®*, Tylox®*)	Relief of moderate to moderately severe pain	Capsule: 5/500 mg Solution: 5/325 mg/5 mL Tablet: 2.5/325 mg 5/300 mg 5/325 mg 5/400 mg 5/500 mg 7.5/300 mg 7.5/325 mg 7.5/400 mg 7.5/500 mg 10/300 mg 10/325 mg 10/400 mg 10/500 mg 10/650 mg	✔
Oxycodone/aspirin (Percodan®*)	Relief of moderate to moderately severe pain	Tablet: 4.8355/325 mg	✔
Oxycodone/ ibuprofen	Short term (<7 days) management of acute, moderate to severe pain	Tablet: 5/400 mg	✔

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

Evidence-based Medicine

- Overall, clinical trials have demonstrated opioids to be more efficacious than placebo for both pain and function outcomes in patients with nociceptive or neuropathic pain.[26-71] Head-to-head trials involving codeine, levorphanol, butalbital-containing products, dihydrocodeine-containing products or oxycodone/aspirin are not available.
- Systematic reviews and meta-analyses have similar safety and level of analgesia between hydromorphone, morphine, oxycodone and oxymorphone in the management of cancer, non-cancer and acute pain.[59-61,63,64,70,71]

- For postoperative pain, morphine has proven to provide greater pain relief than meperidine, tramadol and codeine.[36,37] In one double-blind, randomized controlled trial involving patients who underwent total hip or knee replacement surgery, patients were significantly more likely to achieve a pain relief of at least 50% following administration of oxymorphone 10 or 20 mg compared to placebo, but not with oxymorphone 30 mg or oxycodone 10 mg. A direct comparison between oxymorphone and oxycodone was not performed.[48]
- When compared to ibuprofen and acetaminophen in children with acute musculoskeletal injury, codeine achieved a level of analgesia that was comparable to acetaminophen but less than that of ibuprofen.[51]
- Several placebo- and active-controlled, randomized studies have demonstrated immediate-release tapentadol to be non-inferior to oxycodone and morphine in the management of pain from various etiologies. Results from these studies also demonstrate that tapentadol may have a more favorable adverse effect profile, specifically in terms of the incidence of gastrointestinal adverse events.[39,40,62]
- The results of randomized controlled trials have generally demonstrated a comparable level of analgesia between codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen and oxycodone/acetaminophen in the management of pain.[42,49,50,52-54]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The World Health Organization suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a “weak opioid” and then to a “strong opioid”, such as morphine.[72,73]
    - Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) experiencing severe pain should receive rapid titration of short-acting opioids.[72,73]
    - 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.[72,73]
    - Opioid-naïve patients experiencing mild pain intensity should receive nonopioid analgesics, such as NSAIDs or acetaminophen or treatment with consideration of slower titration of short-acting opioids.[72,73]
    - Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with “around-the-clock” extended release or long acting formulation opioids with provision of a ‘rescue dose’ to manage break-through or transient exacerbations of pain.[72,73]
    - 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.[72,73]
    - 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.[72,73]
    - Clinicians may consider using a written chronic opioid therapy management plan to document patent and clinician responsibilities and expectations and assist in patient education.[72,73]
- Other Key Facts:
    - Generic products are available for all products with the exception of tapentadol (Nucynta®).[4]

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Therapeutic Class Review
Short-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]

Short acting opioid analgesics are available as single entity and in combination with acetaminophen, aspirin, butalbital, caffeine, carisoprodol and ibuprofen. Acetaminophen, aspirin and ibuprofen are non-opiate analgesics. Butalbital is a barbiturate, which has anxiolytic and muscle relaxant properties. Caffeine is an analgesic adjuvant, as well as a central nervous system stimulant. Carisoprodol is a centrally-acting muscle relaxant.[4,5] In January 2011, the Food and Drug Administration asked manufacturers to limit the amount of acetaminophen in prescription drug products (which are predominantly combinations of acetaminophen and opioids) to 325 mg per dosage form to make these products safer for patient to use.[6]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Butorphanol	Opiate partial agonist	✔
Codeine	Opioid agonist	✔
Hydromorphone (Dilaudid®)	Opioid agonist	✔
Meperidine (Demerol®, Meperitab®)	Opioid agonist	✔
Morphine (MSIR®, Roxanol®)	Opioid agonist	✔
Oxycodone (Oxecta®, Roxicodone®)	Opioid agonist	✔
Oxymorphone (Opana®)	Opioid agonist	✔
Tapentadol (Nucynta®)	Opioid agonist	-
Combination Products		
Acetaminophen/codeine (Capital w/codeine®, Tylenol-Codeine®)	Opioid agonist/analgesic	✔
Codeine/butalbital/acetaminophen/ caffeine (Fioricet with Codeine®)	Opioid agonist/barbiturate/non-opioid analgesic	✔
Codeine/butalbital/aspirin/caffeine (Fiorinal with Codeine®)	Opioid agonist/barbiturate/non-opioid analgesic/CNS stimulant	✔
Codeine/carisoprodol/aspirin	Opioid agonist/muscle relaxant/ non-opioid analgesic	✔
Dihydrocodeine/acetaminophen/caffeine	Opioid agonist/non-opioid analgesic/CNS stimulant	✔
Dihydrocodeine/ aspirin/caffeine (Synalgos-DC®)	Opioid agonist/non-opioid analgesic/CNS stimulant	✔
Hydrocodone/acetaminophen (Hycet®, Lorcet®, Lorcet-Plus®, Lortab®, Maxidone®, Norco®, Vicodin®, Vicodin ES®, Vicodin HP®, Xodol®, Zamicet®, Zolvit®, Zydone®)	Opioid agonist/non-opioid analgesic	✔
Hydrocodone/ibuprofen (Ibudone®, Reprexain®, Vicoprofen®)	Opioid agonist/ NSAID	✔
Oxycodone/acetaminophen (Magnacet®, Percocet®, Primlev®, Tylox®)	Opioid agonist/non-opioid analgesic	✔
Oxycodone/aspirin (Percodan®)	Opioid agonist/non-opioid analgesic	✔
Oxycodone/ibuprofen	Opioid agonist/ NSAID	✔

CNS=central nervous system, NSAID=nonsteroidal anti-inflammatory drug

Indications

Table 2. Food and Drug Administrations Approved Indications for Sing Entity Agents[7-14]

Indication	Butorphanol	Codeine	Hydromorphone	Meperidine	Morphine	Oxycodone	Oxymorphone	Tapentadol
Management of moderate to severe acute pain in adults								✔
Management of moderate to severe pain in patients where an opioid analgesic is appropriate	✔		✔		✔	✔		
Relief of mild to moderate pain		✔						
Relief of moderate to severe pain				✔			✔	

Table 3. Food and Drug Administration Approved Indications for Combination Products[15-25]

Indication	Codeine/ Acetaminophen	Codeine/ Butalbital/ Acetaminophen/ Caffeine	Codeine/ Butalbital/ Aspirin/Caffeine	Codeine/ Carisoprodol/ Aspirin	Dihydrocodeine/ Acetaminophen/ Caffeine	Dihydrocodeine/ Aspirin/Caffeine	Hydrocodone/ Acetaminophen	Hydrocodone/ Ibuprofen	Oxycodone/ Acetaminophen	Oxycodone/ Aspirin	Oxycodone/ Ibuprofen
Relief of discomfort associated with acute, painful musculoskeletal conditions in adults				✔							
Relief of mild to moderate pain	✔					✔					
Relief of moderate to moderately severe pain					✔		✔		✔	✔	
Relief of tension or muscle contraction headache		✔	✔								
Short term (<7 days) management of acute, moderate to severe pain											✔
Short-term (<10 days) management of acute pain								✔			

Pharmacokinetics

Table 4. Pharmacokinetics[5]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Agents				
Butorphanol	70	70 to 80	Hydroxy butorphanol and norbutorphanol	4 to 7
Codeine	Well absorbed	90	Morphine	2.5 to 3.5
Dihydrocodeine	21	35	Dihydromorphine	3.4 to 4.5
Hydromorphone	24	75	Hydromorphone-3-glucuronide	2.5
Meperidine	85	0.5 to 2.0	Normeperidine	3.2 to 3.7
Morphine	<40	90	Morphine-6-glucuronide	1.5 to 2.0
Oxycodone	60 to 87	19	Noroxycodone, noroxymorphone, oxymorphone	3.5 to 4.0
Oxymorphone	10	<1	Oxymorphone-3-glucuronide and 6-OH-oxymorphone	7.25 to 9.43
Tapentadol	32	99	None	4 to 5
Components of Combination Products				
Acetaminophen	85 to 98	<5	N-acetyl-p-benzoquinone imine	1.5 to 4.2
Aspirin	Well absorbed	Not reported	Salicyluric acid, phenolic glucuronide, acyl glucuronide	6
Butalbital	Well absorbed	59 to 88	5-isobutyl-5-(2,3-dihydroxypropyl) barbituric acid and 5-allyl-5(3-hydroxy-2-methyl-1-propyl) barbituric acid	35
Carisoprodol	Not reported	Not reported	Meprobamate	2
Caffeine	Readily absorbed	70	Paraxanthine, theobromine and theophylline	3
Ibuprofen	Not reported	45 to 79	(+)-2-(p-(2hydroxymethyl-propyl)phenyl) propionic acid and (+)-2-(0-2carboxy-propyl) phenyl) propionic acid	1.80 to 2.44

Clinical Trials

Overall, clinical trials have demonstrated opioids to be more efficacious than placebo for both pain and function outcomes in patients with nociceptive or neuropathic pain.[26-71] Head-to-head trials involving codeine, levorphanol, butalbital-containing products, dihydrocodeine-containing products or oxycodone/aspirin are not available.

Systematic reviews and meta-analyses have similar safety and level of analgesia between hydromorphone, morphine, oxycodone and oxymorphone in the management of cancer, non-cancer and acute pain.[59-61,63,64,70,71]

For postoperative pain, morphine has proven to provide greater pain relief than meperidine, tramadol and codeine.[36,37] In one double-blind, randomized controlled trial involving patients who underwent total hip or knee replacement surgery, patients were significantly more likely to achieve a pain relief of at least 50% following administration of oxymorphone 10 or 20 mg compared to placebo, but not with oxymorphone 30 mg or oxycodone 10 mg. A direct comparison between oxymorphone and oxycodone was not performed.[48]

When compared to ibuprofen and acetaminophen in children with acute musculoskeletal injury, codeine achieved a level of analgesia that was comparable to acetaminophen but less than that of ibuprofen.[51]

Several placebo- and active-controlled, randomized studies have demonstrated immediate-release tapentadol to be non-inferior to oxycodone and morphine in the management of pain from various etiologies. Results from these studies also demonstrate that tapentadol may have a more favorable adverse effect profile, specifically in terms of the incidence of gastrointestinal adverse events.[39,40,62]

The results of randomized controlled trials have generally demonstrated a comparable level of analgesia between codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen and oxycodone/acetaminophen in the management of pain.[42,49,50,52-54]

Table 5. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Drendel et al[27] Codeine/ acetaminophen suspension 1 mg/kg/dose (codeine component) vs ibuprofen suspension 10 mg/kg/dose	AC, DB, RCT Children 4 to 18 years of age with a closed fracture of the radius, ulna, or humerus	N=336 72 hours after ED discharge	Primary: Failure of study medication as defined by use of a rescue analgesic Secondary: Pain scores, adverse events, and satisfaction	Primary: The proportion of treatment failures for children receiving ibuprofen (20.3%) was lower than that for codeine/ acetaminophen (31.0%), although not statistically significant. Secondary: The total mean pain scores for day zero to day three were 1.6 for children receiving ibuprofen and 1.6 for children receiving codeine-acetaminophen. At the end of the study, 27.5% of the children said they would not use codeine/acetaminophen again compared to only 10.0% of the children who took ibuprofen (95% CI, 7.3 to 28.3). The primary reason associated with dissatisfaction in children receiving codeine-acetaminophen was taste. There was no significant difference in analgesic failure and pain scores among children with an arm fracture receiving ibuprofen or codeine-acetaminophen.
Davies et al[28] Fentanyl nasal spray vs morphine IR Fentanyl nasal spray was titrated up to 800 µg until the patient reached an effective dose that treated two consecutive BTP episodes. After titration to an effective dose, ten	DB, DD, MC, XO Patients with a diagnosis of cancer, who were receiving fixed-schedule opioid regimens at a total daily dose ≥60 mg/day oral morphine or equivalent and one to four episodes per day of moderate to severe cancer BTP	N=110 10 BTP episodes	Primary: Pain intensity score, SPID, pain relief score, TOTPAR, onset of clinically meaningful pain relief (≥2 point reduction in pain intensity score), patient acceptability score (overall satisfaction, satisfaction with speed of relief and satisfaction with reliability), adverse events	Primary: After ten minutes, fentanyl nasal spray had greater pain intensity difference scores and a higher proportion of episodes showing clinically meaningful pain relief compared to morphine IR (P<0.05 for both). After 15 minutes, 52.3% of patients taking fentanyl had a TOTPAR score ≥33% compared to 43.5% of patients taking morphine (P<0.01). This significant difference was maintained until 60 minutes. Patient-averaged acceptability assessment scores were greater for fentanyl nasal spray than for morphine for all questions at 30 minutes (P<0.01) and 60 minutes (P<0.01). More treatment-emergent adverse effects were reported to be associated with fentanyl than with morphine. Only eight patients (six fentanyl and two morphine) experienced adverse effects that resulted in discontinuation of the drug (P values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
episodes of BTP were randomly treated with fentanyl nasal spray and encapsulated placebo or morphine IR and nasal spray placebo (five episodes of each).			Secondary: Not reported	
Fallon et al[29] Fentanyl nasal spray 100 to 800 µg vs morphine IR Fentanyl nasal spray was titrated up to 800 µg until the patient received adequate pain relief for each BTP episode. IR morphine dose was determined as one-sixth of the total daily oral morphine dose equivalent of the patient's	DB, DD, MC, RCT, XO Adult patients with cancer that were receiving fixed-schedule opioid regimens at a total daily dose equivalent to ≥60 mg/day oral morphine and experiencing one to four BTP episodes per day	N=110 10 BTP episodes	Primary: Pain intensity difference after 15 minutes Secondary: Patient- and episode-averaged pain intensity difference, SPID, pain intensity score, pain relief score, TOTPAR score, onset of analgesia (≥1 point reduction in pain intensity and pain relief), onset of clinically meaningful pain relief (≥2 point reduction in pain intensity and pain relief or 33%	Primary: The mean (±SD) pain intensity difference score after 15 minutes was 3.02 (±0.21) for fentanyl nasal spray compared to 2.69 (±0.18) for morphine IR (*P*<0.05). Fentanyl nasal spray had significantly greater pain intensity difference scores compared to morphine IR from 15 minutes through 60 minutes after initial dose (*P*<0.05). Secondary: After treatment of BTP, fentanyl nasal spray treated episodes had significantly lower pain intensity scores compared to morphine IR treated episodes from 30 minutes through 60 minutes (*P*<0.05). In addition, patient-averaged pain relief scores were significantly higher from 30 through 60 minutes in patients who took fentanyl nasal spray compared to morphine IR (*P*≤0.005). Patient-averaged mean difference in TOTPAR were significant from 15 minutes through 60 minutes (*P*<0.05) favoring fentanyl nasal spray. The proportion of patients experiencing onset of analgesia and clinically meaningful pain relief was significantly greater in the fentanyl nasal spray group compared to the morphine IR group as early as five minutes and ten minutes, respectively (*P*<0.05 for both). There was no significant difference in the proportion of patients requiring rescue medication within 60 minutes between fentanyl nasal spray and morphine IR. More treatment emergent adverse events occurred in patients using fentanyl nasal spray (*P* value not reported). Of the 14 serious adverse events reported, 12 occurred

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
background opioid medication. After titration to an effective dose, ten episodes of BTP were randomly treated with fentanyl nasal spray and encapsulated placebo or IR morphine and nasal spray placebo (five episodes of each).			reductions in pain intensity and SPID), need for rescue medication	following treatment with fentanyl nasal spray.
Shear et al[29] Fentanyl 100 µg transbuccal vs oxycodone/ acetaminophen 5/325 mg	DB, RCT Adult patients who presented to the emergency department with a chief complain of extremity injury	N=60 1 hour	Primary: Time required to achieve a 2-point drop on a 10-point pain scale Secondary: Maximum pain scale reduction and vital signs	Primary: Treatment with fentanyl was associated with faster pain relief onset than oxycodone/acetaminophen (10 vs 35 minutes; *P*<0.0001). Secondary: Overall, rescue medication was required in 22 subjects; rescue analgesia was more frequently administered to those in the oxycodone/acetaminophen group than in the fentanyl group (17 vs 57; *P*=0.003). Treatment with fentanyl was associated with faster time to maximum pain reduction than oxycodone/acetaminophen (40 vs 55 minutes; *P*<0.01). The maximal pain score reduction was greater with fentanyl than oxycodone/acetaminophen (6 vs 3; *P*=0.0004). Patients receiving fentanyl were more likely to be satisfied with the analgesia provided by the study drug. This was true regardless as to whether preference was measured as a median of the 1 to 5 rating scale (*P*=0.00001) or as a proportion of subjects indicating either 1 or 2 (meaning strong or probable preference to receive similar analgesia in the future; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In the fentanyl group, 100% of patients achieved significant pain reduction compared to 83% of patients in the oxycodone/acetaminophen group, which was not significant (*P*=0.52). The monitoring of vital signs identified no adverse effects in any subject in either group. No significant side effects occurred in the emergency department or during the next-day.
Coluzzi et al[30] Fentanyl transmucosal lozenge 200 µg vs morphine IR 15 to 60 mg Fentanyl transmucosal lozenge was titrated up to 1,600 µg until the patient received adequate pain relief for each BTP episode. For any non-target BTP episodes, patients used their usual supply of morphine IR.	DB, DD, RCT, XO Adult patients with cancer-related pain who were regularly having one to four BTP episodes/day while using a stable fixed schedule oral opioid regimen equivalent to 60 to1,000 mg/day of oral morphine or 50 to 300 µg/hour of transdermal fentanyl and who were using a successful dose of 15 to 60 mg of morphine IR to treat target BTP	N=89 Up to 14 days or 10 BTP episodes	Primary: Pain intensity difference at 15, 30, 45 and 60 minutes post dose Secondary: Adverse events	Primary: Mean pain intensity differences across all time points significantly favored transmucosal fentanyl (*P*<0.008 for all). Transmucosal fentanyl produced a >33% change in 15 minute pain intensity difference values for 42.3% of the episodes treated compared to 31.8% for morphine IR (*P*<0.001). Secondary: Most adverse events reported during the study were considered unrelated or unlikely to be related to study medication. The most frequent drug-related adverse events included somnolence, nausea, constipation, and dizziness. Due to the design of the study it is difficult to attribute an adverse event to either of the study medications.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Zeppetella et al[31] Opioid analgesics vs placebo or opioid analgesics All RCTs were concerned with the use of transmucosal fentanyl in the management of BTP. Two trials examined the titration of transmucosal fentanyl, one trial compared transmucosal fentanyl to morphine IR and one trial compared transmucosal fentanyl to placebo. Previous rescue medication included hydrocodone, hydromorphone, morphine,	MA (4 RCTs) Patients of any age with cancer and BTP who were treated with opioids for cancer pain	N=393 Duration not reported	Primary: Reduction in pain intensity, adverse effects, attrition, patient satisfaction, and quality of life Secondary: Not reported	Primary: Results from four trials demonstrated that fentanyl transmucosal lozenge was more efficacious to placebo, morphine IR, and previous rescue medication with a WMD of -0.68 (95% CI, -1.03 to -0.34) for pain improvement at 15 minutes and -0.91 (95% CI, -1.23 to -0.59) for pain improvement at 30 minutes. Transmucosal fentanyl was more efficacious in providing pain relief at 15 minutes (WMD, 0.54; 95% CI, 0.40 to 0.69) and 30 minutes (WMD, 0.61; 95% CI, 0.47 to 0.75). Compared to previous rescue medication and placebo, transmucosal fentanyl was also more efficacious for global performance (WMD, 0.76; 95% CI, 0.58 to 0.95). *Fentanyl transmucosal lozenge dose titration*: Of the 62 patients on around-the-clock transdermal fentanyl, 47 (76%) were able to titrate transmucosal fentanyl to a safe and effective dose to treat their BTP. Three patients administering around-the-clock transdermal fentanyl withdrew during the titration phase because of treatment-emergent adverse effects and four patients titrated to the 1,600 µg dose without obtaining adequate relief. The mean±SD successful transmucosal fentanyl dose was 587±335 µg. Of the 67 patients on around-the-clock oral opioids, 48 (74%) were able to titrate to a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. Eight patients administering around-the-clock oral opioids withdrew during the titration phase because of treatment-emergent adverse effects and five participants titrated to the 1,600 µg dose without adequate obtaining relief. The mean±SD successful transmucosal fentanyl dose was 640±374 µg. It was determined that the optimal dose of transmucosal fentanyl cannot be predicted by the total daily dose of fixed scheduled opioids. The most common adverse events associated with transmucosal fentanyl were somnolence, nausea, dizziness, and vomiting. An OL comparison of transmucosal fentanyl and usual BTP medication demonstrated that transmucosal fentanyl produced significantly better pain relief at all time periods in patients administering around-the-clock transdermal fentanyl or oral opioids (*P*<0.0001 for both). Patient rated global satisfaction of transmucosal fentanyl was significantly higher

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oxycodone, and propoxyphene.				compared to usual BTP medication (around-the-clock transdermal fentanyl, 2.6 vs 2.01; *P*=0.0001 and around-the-clock oral opioids, 2.74 vs 2.09; *P*=0.0002). *Transmucosal fentanyl vs placebo:* Of the 130 participants, 93 (72%) were able to titrate and find a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. The mean±SD successful transmucosal dose was 789±468 µg. Ninety two patients agreed to enter a DB, randomized phase in which results from 86 patients demonstrated that transmucosal fentanyl produced significantly better pain relief than placebo as evidenced by better pain intensity and pain relief scores for all time points (*P*<0.0001). Patient rated global performance of transmucosal fentanyl was significantly better compared to placebo (1.98 vs 1.19; *P*<0.0001) and patients-treated with transmucosal fentanyl required significantly less additional BTP medication (15 vs 34%; *P*<0.0001). Of the original 92 patients, 74 (80%) chose to continue transmucosal fentanyl following the trial. The most frequent adverse effects included dizziness, nausea, somnolence, constipation, asthenia, confusion, vomiting, and pruritus. *Transmucosal fentanyl vs normal release morphine:* Of the 134 patients, 93 (69%) were able to titrate to a safe and effective dose of transmucosal fentanyl using a single unit to treat their BTP. Five patients titrated up to the 1,600 µg dose without obtaining adequate relief. Transmucosal fentanyl was significantly more efficacious to IR morphine in terms of pain intensity difference (*P*<0.008) and pain relief (*P*<0.009) at each time point, and global performance rating (*P*<0.001). Additionally, significantly more (*P*<0.001) more BTP episodes treated with transmucosal fentanyl had a >33% change in pain intensity at 15 minutes. Secondary: Not reported
Mercadante et al[32] Fentanyl transmucosal lozenge, dose proportional to	RCT, XO Adult patients with cancer-related pain, receiving	N=25 Duration not reported	Primary: Pain intensity at zero (T0), 15 (T1), and 30 (T2) minutes post dose; and opioid-	Primary: In BTP episodes treated with IV morphine, pain intensity decreased from 6.9 (95% CI, 6.6 to 7.2) to 3.3 (95% CI, 2.7 to 3.8) and 1.7 (95% CI, 1.2 to 2.3) at T1 and T2, respectively. This reduction was >33% in 39 (74%) and in 46 (87%) episodes at T1 and T2, respectively, and >50% in 29 (55%) and in 40 (75%) episodes at T1 and T2, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
basal daily opioid dose vs IV morphine, dose proportional to basal daily opioid dose Patients were planned to receive fentanyl transmucosal lozenge and IV morphine for each couple of BTP episodes between 0700 to 1900 hours. The order of administration was randomized.	opioids regularly at doses >60 mg/day of oral morphine equivalents, had acceptable pain relief, and presented ≤2 pain flares/day		related symptoms Secondary: Not reported	In BTP episodes treated with transmucosal fentanyl, pain intensity decreased from 6.9 (95% CI, 6.6 to 7.2) to 4.1 (95% CI, 3.6 to 4.7) and 2.4 (95% CI, 1.8 to 2.9) at T1 and T2, respectively. This reduction was >33% in 30 (57%) and 45 (85%) episodes at T1 and T2, respectively, and >50% in 20 (38%) and in 40 (75%) episodes at T1 and T2, respectively. A statistical difference between the two treatments was found at T1 (*P*=0.013), whereas at T2 the difference did not attain a statistical significance (*P*=0.59). At T1, a decrease of 41.1 and 51.7% in pain intensity was observed after transmucosal fentanyl and IV morphine, respectively (*P*=0.026). At T2, a decrease of 65.9 and 73.8% in pain intensity was recorded after transmucosal fentanyl and IV morphine, respectively (*P*=0.136). No differences between the two groups were observed in the number of episodes with a reduction of >33 and >50% at T1 (*P*=0.66 and *P*=0.39) and T2 (*P*=0.23 and *P*=0.20), respectively. Acute adverse effects occurring after IV morphine and transmucosal fentanyl were comparable and correspond to those commonly observed with opioid therapy. Moderate adverse effects in BTP episodes treated with transmucosal fentanyl and IV morphine were nausea, drowsiness and confusion. Secondary: Not reported
Vissers et al[33] Fentanyl nasal spray vs fentanyl transmucosal lozenge vs	MA (six RCT) Adult cancer patients suffering from BTP, treated with opioid analgesics for management of background pain	N=Not available Duration unknown	Primary: Mean pain intensity difference Secondary: Not reported	Primary: Relative to placebo, fentanyl nasal spray provided a 1.7 (95% CI, 1.4 to 1.9) reduction in pain relief after 15 minutes, while the lozenge provided a 0.4 (95% CI, 0.0 to 0.8) reduction and the buccal tablet provided a 0.5 (95% CI, 0.3 to 0.7) reduction. Differences in pain intensity difference scores favoring fentanyl nasal spray were 1.2 (95% CI, 0.8 to 1.5) relative to the buccal tablet, 1.3 (95% CI, 0.9 to 1.6) relative to the transmucosal lozenge and 1.7 (95% CI, 1.1 to 2.3) relative to oral morphine. The significant difference in mean pain intensity difference scores favoring fentanyl nasal spray was maintained up to 45 minutes compared to the buccal tablet and up to 60 minutes compared to the transmucosal lozenge. According the author's analysis fentanyl nasal spray displayed >99% probability of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fentanyl buccal tablet vs oral morphine vs placebo				providing the greatest pain reduction at 15 minutes out of all the interventions in the study. Secondary: Not reported
Jandhyala et al[34] Fentanyl buccal tablet, sublingual tablet or transmucosal lozenge vs morphine IR vs placebo	MA (five studies) Patient population not specified	N=Not available Duration unknown	Primary: Likelihood of more efficacious pain relief (based on pain intensity difference) Secondary: Not reported	Primary: The probability of greater pain relief than placebo during first 60 minutes after dosing was 61% for morphine IR, 97% for fentanyl buccal tablet, 72% for fentanyl sublingual tablet and 66% for fentanyl transmucosal lozenge. The probability of greater pain relief than placebo during first 30 minutes after dosing was 56% for morphine IR, 83% for fentanyl buccal tablet, 66% for fentanyl sublingual tablet and 73% for fentanyl transmucosal lozenge (*P* values not reported). Mean pain intensity difference scores 60 minutes after dosing compared to placebo were 0.44 (95% CI, -2.07 to 2.95) for morphine, 1.16 (95% CI, 0.09 to 2.23) for the buccal tablet, 0.81 (95% CI, -1.40 to 3.04) for the sublingual tablet and 0.88 (95% CI, -0.76 to 2.55) for the transmucosal lozenge. The mean pain intensity difference scores compared to morphine IR were 0.75 (95% CI, -1.92 to 3.41) for the buccal tablet, 0.35 (95% CI, -3.00 to 3.63) for the sublingual tablet and 0.48 (95% CI, -1.34 to 2.34) for the transmucosal lozenge. Secondary: Not reported
Chang et al[35] Hydromorphone 0.015 mg/kg IV as a single dose vs	DB, RCT Patients 21 to 65 years of age who presented to an emergency	N=191 Single dose	Primary: Difference between the two groups in pain reduction at 30 minutes	Primary: The mean change in pain with hydromorphone was not significantly different from morphine (-5.5 numeric rating scale units' vs -4.1; 95% CI, -2.2 to -0.5). Secondary: Adverse effects were similar in both groups, with the exception of pruritus, which did not occur in the hydromorphone group (0 vs 6%; 95% CI, -11 to -1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
morphine 0.1 mg/kg IV as a single dose	department with acute pain (<7 days in duration) warranting use of IV opioids		Secondary: Adverse effects	
Plummer et al[36] Morphine PCA 0.75, 1.0 or 1.5 mg bolus vs meperidine PCA 9, 12 or 18 mg bolus	DB, RCT Adult patients scheduled for major abdominal surgery	N=102 Variable duration	Primary: Pain at rest and on sitting Secondary: Incidence of nausea, unusual dreams, performance on standardized tests measuring mood and ability to concentrate	Primary: There was no significant difference in pain while at rest among the treatment groups (*P*=0.8). There was significantly higher pain relief in morphine group compared to the meperidine group in sitting position (*P*=0.037). Secondary: There were no differences in the incidence of nausea, unusual dreams, or mood measurements between groups. There was a lower ability to concentrate in the meperidine group.
Sudheer et al[37] Morphine PCA (up to 50 mg/4 hours) vs tramadol PCA (up to 200 mg/4 hours) vs codeine 60 mg IM, then 60 mg after 1	RCT Postoperative pain control following elective craniotomy	N=60 Variable duration	Primary: P_aCO_2 four hours after eye opening, analgesia Secondary: Patient satisfaction, adverse effects	Primary: There were no differences between the groups in the change in P_aCO_2 and no change during the study period within each group. Neither the respiratory rate (range of 8 to 28 breaths/minute) nor sedation showed differences between groups. Morphine produced significantly better analgesia than tramadol at all-time points (*P*<0.005) and better analgesia than codeine at four, 12 and 18 hours. Secondary: Patients were more satisfied with morphine than with codeine or tramadol (*P*<0.001). Vomiting and retching occurred in 50% of patients with tramadol, compared to 20% with morphine and 29% with codeine.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hour if needed, then 60 mg every 4 hours as needed				
Karaman et al[38] Morphine 0.2 mg vs sufentanil 5 µg	DB, RCT Female patients undergoing cesarean section who were receiving bupivacaine in spinal anesthesia	N=54 Single dose	Primary: Quality of anesthesia and postoperative analgesia Secondary: Adverse effects on mother and neonate	Primary: There were no differences between the morphine and sufentanil groups in onset time of sensory block, time to sensory block to T10, time to highest sensory block, highest sensory block level, time to regression of sensory block to T10 level and time to resolution of motor blockade. The time to first request for an analgesic was significantly longer (19.5 vs 6.3 hours) in morphine group (P<0.05). Secondary: Perioperative hemodynamic parameters, sedation scores, nausea/vomiting and pruritus incidences were similar in both groups. Neonatal Apgar scores, neurological and adaptive capacity scores and umbilical blood gas values were similar in both groups.
Kleinert et al[39] Tapentadol 25 to 200 mg as a single dose vs morphine 60 mg as a single dose vs ibuprofen 400 mg as a single dose vs	DB, RCT Patients undergoing mandibular third molar extraction and experiencing moderate to severe pain postsurgery	N=400 8 hours	Primary: Mean TOTPAR over eight hours Secondary: Mean TOTPAR over eight hours and onset of analgesia	Primary: Compared to placebo, mean TOTPAR over eight hours was significantly greater for tapentadol 50 mg (P=0.041), 75 mg (P=0.001), 100 mg (P<0.001), and 200 mg (P<0.001); morphine 60 mg (P<0.001); and ibuprofen 400 mg (P<0.001). Secondary: Compared to placebo, mean TOTPAR over four hours was significantly higher for all tapentadol doses ≥50 mg, morphine 60 mg, and ibuprofen 400 mg (P≤0.05). All efficacy variables for tapentadol 100 and 200 mg showed greater analgesia compared to placebo (P≤0.05). The percentages of patients rating study medication treatment as good, very good, or excellent were as follows: tapentadol 25 mg (22%); tapentadol 50 mg (28%); tapentadol 75 mg (35%); tapentadol 100 mg (50%); tapentadol 200 mg (68%); morphine 60 mg (55%); and placebo (12%). Tapentadol 25 mg was not significantly different from placebo in patient global evaluation responses.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				The efficacy measures demonstrate an onset of analgesia for morphine 60 mg between that of tapentadol 100 and 200 mg doses. These data suggest that morphine 60 mg provides an analgesic dose comparable to a dose of tapentadol between 100 and 200 mg.
Etropolski et al[40] Tapentadol IR 50 mg or 75 mg vs oxycodone IR 10 mg vs placebo	AC, PC, PG, RCT Patients had end-stage degenerative joint disease requiring surgical intervention with moderate-to-severe pain that was not controlled on their stable analgesic regimen	N=598 14 days Followed by 28 days with ER formulations or placebo	Primary: Tolerability, measured by the number of SBMs per week, SPID Secondary: The number of SBMs calculated on a weekly basis for each of the two weeks, the total number of all BMs irrespective of spontaneity or completeness, the number of BMs, SBMs, and complete SBMs (CSBM), and a summary of Bristol Stool Form Scale score,17 the number of days without a BM, the average 24-hour scores for bloating, pain in the abdomen, extent of	Primary: The mean number of SBMs per week was not significantly different between the placebo and tapentadol IR groups, but was significantly lower in the oxycodone IR group compared to each of the tapentadol IR groups (*P*<0.001). The mean differences in five-day SPID in the pooled analysis for each tapentadol IR group vs the oxycodone IR group were –37.7 (–73.3, –2.1; tapentadol IR 50 mg) and –34.3 (–69.3, 0.76; tapentadol IR 75 mg), demonstrating noninferiority for tapentadol IR 75 mg (i.e., within the noninferiority margin of –70). Secondary: The mean number of BMs and CSBM also decreased in the oxycodone IR 10 mg group compared to the other treatment groups. The difference was statistically significant for placebo and each tapentadol IR group vs oxycodone IR 10 mg for BMs (*P*<0.001) and was statistically significant for placebo and tapentadol IR 50 mg group vs oxycodone IR 10 mg for CSBM (*P*≤0.003). The mean duration of time without a BM was significantly longer in the oxycodone IR 10 mg group (4.4 days) compared to tapentadol IR 50 mg (2.4 days), 75 mg (2.8 days), and placebo (2.0 days) groups (all *P*<0.001). The mean change from baseline score to endpoint of 14-day IR treatment period in the inability to have a BM, constipation-related bloating, pain in abdomen, lack of appetite, straining, and pain in rectum, was also significantly worse for the oxycodone IR 10 mg group compared to tapentadol IR and placebo groups (all *P*<0.001). The Bristol Stool Form scores (mean change from baseline to endpoint of 14-day IR treatment period) showed a significantly greater level of stool hardness for the oxycodone IR 10 mg group compared to the tapentadol IR and placebo groups (*P*≤0.016). Consistent with the tolerability results for IR formulations, the mean (SD) number of SBMs during the 28-day treatment with ER formulations was again lower for oxycodone ER (6.2 [3.43]) compared to the tapentadol ER (7.9 [3.81]) and placebo (9.2 [4.61])

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			presence of bothersome gas, and the level of lack of appetite, the scores for inability to defecate, incomplete bowel emptying, and BM pain in the rectum, treatment-emergent adverse events of constipation, nausea, and episodes of vomiting	groups. Patients in the oxycodone IR 10 mg group reported more frequent and severe nausea than patients in the placebo and tapentadol IR groups (each *P*<0.001 vs. oxycodone IR 10 mg). Patients in the oxycodone IR 10 mg group also experienced nausea and vomiting for a greater percentage of time (53 and 25% of the time, respectively) than patients in the tapentadol IR (38 and 14% of the time, respectively) and placebo groups (29 and 7% of the time, respectively). Additionally, patients in the oxycodone IR 10 mg group reported a significantly greater number of days with vomiting compared to patients in the tapentadol IR groups (*P*<0.001 for 50 mg and *P*=0.003 for 75 mg, vs oxycodone IR 10 mg).
Özalevli et al[41] Tramadol PCA 0.2 mg/kg bolus vs morphine PCA 0.02 mg/kg bolus	DB, RCT Children 6 to 12 years of age scheduled for tonsillectomy with general anesthesia	N=60 24 hours postoperative	Primary: Pain (as scored on a standardized 10-point scale), sedation (as assessed by a 5-point scale), nausea (as assessed on a 5-point scale) Secondary: Not reported	Primary: Pain scores decreased significantly with time in both groups (*P*<0.05), but were lower in morphine group vs tramadol group at one, two and four hours (*P*<0.05). Sedation scores increased with time in both groups (*P*<0.05), but there were no significant differences in sedation scores between the groups at any time point. Nausea scores were higher in morphine group at four, six and 24 hours (*P*<0.05). Secondary: Not reported
Smith et al[42] Tramadol/ acetaminophen	DB, MC, PC, RCT Patients with	N=305 6 days	Primary: TOTPAR, SPID, and sum of pain relief and pain	Primary: Tramadol/acetaminophen was more effective than placebo for TOTPAR, SPID and sum of pain relief and pain intensity differences (*P*≤0.015); tramadol/acetaminophen and codeine/acetaminophen did not separate (*P*≥0.281).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
75/650 mg vs codeine/ acetaminophen 30/300 mg vs placebo All study meds were administered as 2 tablets stat, then 1 to 2 tablets every 4 to 6 hours as needed.	moderate to severe abdominal or orthopedic postsurgical pain		intensity differences during the four hours after the first dose of study medication on day one Secondary: Average daily pain intensity scores and average daily pain relief scores reported on days one to six; overall rating of study medication by both patients and investigators using a five-point scale; incidence of adverse events	Secondary: For average daily pain relief, average daily pain intensity, and overall medication assessment, tramadol/acetaminophen was more effective than placebo ($P \leq 0.038$). Codeine/acetaminophen did not separate from placebo ($P \geq 0.125$). Discontinuation because of adverse events occurred in 8.2% of tramadol/acetaminophen, 10.1% of codeine/acetaminophen and 3.0% of placebo patients. Except for constipation (4.1% tramadol/acetaminophen vs 10.1% codeine/acetaminophen) and vomiting (9.2 vs 14.7%, respectively), adverse events were similar for active treatments.
Hewitt et al[43] Tramadol/ acetaminophen 75/650 mg vs hydrocodone/ acetaminophen 7.5/650 mg	RCT Patients 18 to 75 years of age with ankle sprain within previous 48 hours; clinical diagnosis of partial ligament tear, pain on ambulation and	N=396 5 days	Primary: Pain relief as measured by patient response to two standardized pain relief/pain intensity scales Secondary: Adverse events	Primary: Tramadol/acetaminophen and hydrocodone/acetaminophen provided greater TOTPAR than placebo ($P<0.001$) during the first four hours, decreased pain intensity during the first four hours and increased average pain relief on days one to five. No efficacy measure was significantly different between the tramadol/acetaminophen and hydrocodone/acetaminophen groups. Secondary: Common adverse events included somnolence, nausea, dizziness, and vomiting.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	ankle swelling			
Zenz et al[44] Buprenorphine, dihydrocodeine sustained release, and morphine sustained release	OL Patients receiving chronic opioids for treatment of non-malignant pain	N=100 Variable duration	Primary: Pain reduction with visual analogue scales; patient function using the Karnofsky Performance Status Scale Secondary: Not reported	Primary: Good pain relief was obtained in 51 patients and partial pain relief was reported by 28 patients. Only 21 patients had no beneficial effect from opioid therapy. There was a close correlation between the sum and the peak visual analogue scale values (P<0.0001). Pain reduction was associated with an increase in performance (P<0.0001). Secondary: Not reported
Yeh et al[45] Nalbuphine 10 µg/mL IV and morphine 1 mg/mL infusion via PCA vs morphine 1 mg/mL IV infusion via PCA	DB, PRO, RCT Female patients undergoing gynecological surgery	N=174 24 hours	Primary: Pain and medication dose Secondary: Nausea, vomiting, use of antiemetics, pruritus, use of antipruritics, opioid related adverse effects	Primary: Numerical pain rating scores and medication requirements were not significantly different between the treatment groups. Secondary: Nausea was lower in the nalbuphine group than the morphine-only group (45 vs 61%; P=0.03). Other secondary outcomes did not differ between the treatment groups.
Levine et al[46] Pentazocine 60 mg IV vs naloxone 0.4 mg IV	DB, RCT Patients undergoing surgery for the removal of impacted third molars	N=105 Single dose	Primary: Pain intensity using a visual-analogue scale Secondary: Not reported	Primary: The mean pain intensity was increased in the group receiving placebo. Mean pain intensity was decreased in the groups that received either morphine (8 and 15 mg; P<0.05 and P<0.01, respectively) or pentazocine (60 mg; P<0.05) as a single agent. The combination of low-dose naloxone and pentazocine produced significantly greater analgesia than either low-dose naloxone (P<0.01), pentazocine (P<0.01), or even high-dose morphine administered alone (P<0.01). The combination of low-dose naloxone and 8 mg morphine produced less analgesia when compared to the same dose of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs morphine 8 or 15 mg IV vs naloxone 0.4 mg + morphine 8 mg IV vs naloxone 0.4 mg + pentazocine 60 mg IV vs placebo				morphine alone (P<0.05) or with high-dose morphine (P<0.01) but not when compared to low-dose naloxone administered alone. The mean pain intensity measured at three hours and 10 minutes after injection of single analgesic agents was not significantly decreased compared to placebo. The analgesia produced by the combination of low-dose naloxone and 8 mg morphine did not differ significantly from the analgesia produced by the same dose of morphine. The combination of low-dose naloxone and pentazocine produced significant analgesia when compared to either agent alone (both P<0.01). By three hours and 10 minutes after injection, only the group of patients receiving low-dose naloxone plus pentazocine still reported significant analgesia.
Petti[47] Pentazocine/ acetaminophen 25/65 mg vs codeine/ acetaminophen 30/300 mg vs propoxyphene napsylate/ acetaminophen	PC, PG, SB Patients with moderate postoperative pain	N=129 6 hours	Primary: Intensity of pain and degree of pain relief Secondary: Not reported	Primary: Pentazocine/acetaminophen was significantly better than placebo and equivalent to codeine/acetaminophen and propoxyphene/acetaminophen in patients with moderate postoperative pain. No adverse events were reported with pentazocine/acetaminophen, propoxyphene napsylate/acetaminophen, or placebo. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100/650 mg vs placebo				
Gimbel et al[48] Oxymorphone IR 10, 20, or 30 mg vs oxycodone IR 10 mg vs placebo	DB, DR, MC, PC, PG, RCT Men and nonpregnant, nonlacting women 18 to 75 years of age receiving total hip or knee replacement surgery and scoring I to III on the ASA physical status classification system	N=300 First phase: 8 hours Second phase: 48 hours	Primary: TOTPAR, SPID and SPRID at four, six, and eight hours, safety Secondary: Not reported	Primary: Mean TOTPAR scores at four, six, and eight hours for all doses of oxymorphone IR were statistically more efficacious compared to placebo (10 mg, $P \leq 0.034$; 20 and 30 mg, $P < 0.001$). Oxymorphone showed a statistically significant dose-response relationship in a regression model (TOTPAR8) by using the arithmetic dose as the regressor (slope estimate, 0.184; $P < 0.001$; 95% CI, 0.089 to 0.279) and reached an analgesic plateau at the 20-mg dose. Oxymorphone IR at 10, 20, and 30 mg was statistically more efficacious compared to placebo for SPID ($P \leq 0.001$ for all doses) and SPRID at four, six, and eight hours ($P \leq 0.007$ for 10 mg and $P < 0.001$ for 20 and 30 mg). Although oxycodone IR was generally numerically greater compared to placebo, the differences were not significant for any efficacy measures. The median time to meaningful pain relief was statistically significantly shorter in all of the oxymorphone IR groups (1 hour) than in the placebo group (1.5 hour; $P < 0.05$). Fifty percent pain relief was achieved by 90.2% of patients in the oxymorphone IR 20 mg group ($P < 0.001$), 82.4% of patients in the oxymorphone IR 10 mg group ($P = 0.022$), 77.2% in the oxymorphone IR 30 mg group (P value not significant), and 69.2% in the oxycodone IR 10 mg group (P value not significant). The most frequent occurring adverse events in the oxymorphone IR groups were mild-to-moderate opioid side effects (i.e., nausea, vomiting, somnolence, and pruritus). During the single-dose phase, the incidence of adverse events was more frequent among the oxymorphone IR groups than in the oxycodone IR 10 mg group (39 to 50 vs 27%). In contrast, the incidence was somewhat more frequent in the oxycodone IR 10

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				mg group (82%) during the multiple-dose phase compared to the oxymorphone IR groups (61 to 71%). Secondary: Not reported
Palangio et al[49] Hydrocodone/ ibuprofen 7.5/200 mg 2 tabs vs oxycodone/ acetaminophen 5/325 mg 2 tablets vs placebo	DB, PC, PG, RCT Subjects >18 years of age with moderate to severe postoperative obstetric or gynecologic pain	N=180 8 hours	Primary: Pan relief, TOTPAR, SPID scores, time to onset, adverse events Secondary: Not reported	Primary: Mean pan relief scores were similar for hydrocodone/ibuprofen and oxycodone/ acetaminophen at 0.5, one, 1.5, two, 2.5, three, four, and seven hours and significantly greater for hydrocodone/ibuprofen than for oxycodone/acetaminophen at five (*P*=0.003), six (*P*=0.043), and eight (*P*=0.044) hours. Mean PR scores were significantly greater for hydrocodone/ibuprofen than for placebo at all measured times (*P*<0.001). Mean PR scores were significantly greater for oxycodone/acetaminophen than for placebo at 0.5 (*P*<0.008), one, 1.5, two, 2.5, three, and four (*P*<0.001), five (*P*=0.016) and six *P*=0.031) hours. The mean TOTPAR was similar for hydrocodone/ibuprofen and oxycodone/ acetaminophen for the 0- to three- and 0- to four-hour intervals and significantly greater for hydrocodone/ibuprofen than for oxycodone/acetaminophen at the 0- to six-hour (*P*=0.043) and 0- to eight-hour (*P*=0.029) intervals. The mean SPID was similar for hydrocodone/ibuprofen and oxycodone/acetaminophen for each interval. The mean SPID was significantly greater for hydrocodone/ibuprofen or oxycodone/acetaminophen than for placebo for each interval (*P*<0.001). The median estimated time to onset of analgesia was similar for hydrocodone/ ibuprofen (12.6 minutes) and oxycodone/acetaminophen (15.4 minutes) and significantly shorter for either of these treatments than for placebo (29.5 minutes; *P*<0.001 and *P*=0.006, respectively). Eleven of 61 patients (18.0%) in the hydrocodone/ibuprofen group experienced adverse events, compared to seven of 59 patients (11.9%) in the oxycodone/acetaminophen group and six of 60 (10.0%) in the placebo groups. These findings were not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Palangio et al[50] Hydrocodone/ ibuprofen 7.5/200 mg (1 tablet) plus 1 tablet of placebo every 6 to 8 hours (HI1) vs hydrocodone/ ibuprofen 15/400 mg (2 tablets) every 6 to 8 hours (HI2) vs codeine/ acetaminophen 60/600 mg (2 tablets) every 6 to 8 hours (CA)	DB, MC, PG, RCT Males and females >18 years of age with a chronic pain condition that required opioid or opioid-nonopioid combination analgesic therapy	N=469 4 weeks	Primary: Pain relief scores, number of daily doses of study medication, number of daily doses of supplemental analgesics, number of patients who discontinued therapy due to an unsatisfactory analgesic response, and global assessment scores Secondary: Not reported	Primary: The overall mean pain relief scores for the entire study period were significantly greater in the HI2 group than either the HI1 group (P=0.003) or the CA group (P<0.001). The weekly pain relief scores were significantly greater in the HI2 group than the HI1 group for weeks one (P<0.001), two (P<0.001), and three (P=0.008). The weekly mean PR scores were also significantly greater in the HI2 group than the CA group for weeks one (P<0.001), two (P<0.001), three (P<0.001) and four (P=0.007), and end point (P=0.003). The overall mean number of daily doses of supplemental analgesics was significantly less in the HI2 drop than either the HI1 group (P=0.21) or the CA group (P=0.01). There were no significant differences in the overall weekly mean number of daily doses of supplemental analgesics between the HI1 group and the CA group. The number of patients who discontinued treatment due to an unsatisfactory analgesic response was significantly less in the HI2 group (2/153; 1.3%) than in the CA group (12/160; 7.5%; P=0.08). There were no significant differences in the number of patients who discontinued treatment due to an unsatisfactory analgesic response between the HI1 group (8/156; 5.1%) and either the HI2 group or the CA group. The weekly mean global assessment scores were significantly greater in the HI2 group than the HI1 group for weeks one (P=0.018), two (P=0.005), and four (P=0.013). The weekly mean global assessment scores were significantly greater in the HI2 group than the CA group for weeks one (P<0.001), two (P<0.001), three (P=0.009), and four (P=0.023), and end point (P=0.016). There were no significant differences in the weekly mean global assessment scores between the HI1 group and the CA group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Clark et al[51] acetaminophen 15 mg/kg vs ibuprofen 10 mg/kg vs codeine 1 mg/kg	RCT Children 6 to 17 years of age presenting to the emergency department with pain from a musculoskeletal injury occurring in the preceding 48 hours	N=336 120 minutes	Primary: Change in pain from baseline to 60 minutes after treatment as measured by a VAS Secondary: Change in VAS from baseline at 30, 90, and 120 minutes, requirement for additional analgesia, and the number of patients achieving a VAS<30 mm at 60 and 120 minutes	Primary: At 60 minutes, patients in the ibuprofen group had significantly greater improvement in pain score than those in the codeine and acetaminophen groups (*P*<0.001). There was no significant difference in the change in pain score between the codeine and acetaminophen groups at any time period. Secondary: At 30 minutes there was no significant difference in change in pain score among the three groups. At 60 minutes, more patients in the ibuprofen group achieved adequate analgesia (as defined by a VAS<30 mm) than the other two groups. There was no statistical difference between the codeine and acetaminophen groups. Over the course of the trial, there was no significant difference in the number of patients requiring additional analgesic (22.2% in the codeine group, 15.6% in the acetaminophen group, and 14.3% in the ibuprofen group; *P*=0.32).
Rodriguez[52] Codeine/ acetaminophen 30/500 mg (CA) every 4 hours vs hydrocodone/ acetaminophen 5/500 mg (HA)	DB, PG, PRO, RCT Subjects aged >18 years of age with chronic moderate to severe cancer-related pain	N=121 23 days	Primary: Proportion of patients who achieved pain relief Secondary: Proportion of patients in whom pain was decreased, adverse events	Primary: Overall, 39/59 (66%) patients who received CA and 44/62 (71%) patients who used HA experienced pain relief (*P*=0.69). Of patients who received CA 34 (58%) experienced pain relief at the initial dosage and five (8%) responded to the double dosage. Twenty (34%) did not experience any pain relief with CA. HA was associated with mild pain intensity in 35 (56%) of patients at the starting dosage. An additional 9 (15%) patients responded to the double dosage and the remaining 18 (29%) patients did not experience any pain relief.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
every 4 hours				The differences in pain relief were not significant between the groups. Secondary: Mean pain intensity decreased to a similar extent in the two treatment groups. The most common adverse events in the CA and HA groups were constipation (21 [36%] and 18 [29%], respectively), dizziness (14 [24%] and 12 [19%]), vomiting (14 [24%] and 10 [16%]), and dry mouth (9 [15%] and 11 [18%]). None of the differences between the two groups were statistically significant.
Marco et al[53] Oxycodone/ acetaminophen as a combination liquid formulation vs hydrocodone/ acetaminophen as a combination liquid formulation	DB, PRO, RCT Emergency department patients over the age of 12 with fractures and severe pain, with pain scores >5 on a 0 to 10 scale	N=73 60 minutes	Primary: Pain score (verbal numeric rating scale) at 30 and 60 minutes Secondary: Presence and severity of side effects	Primary: Patients in both groups had pain relief from baseline to 30 minutes (oxycodone/acetaminophen mean change 3.7; 95% CI, 2.9 to 4.6; hydrocodone/acetaminophen mean change 2.5; 95% CI, 1.7 to 3.3) and from baseline to 60 minutes (oxycodone/acetaminophen mean change 4.4; 95% CI, 3.2 to 5.6; hydrocodone/acetaminophen mean change 3.0; 95% CI, 2.1 to 3.9). There was no difference in pain identified between the patients treated with oxycodone/acetaminophen and hydrocodone/acetaminophen at 30 minutes (mean difference between groups -0.6; 95% CI, -1.8 to 0.5) or at 60 minutes (mean difference -0.5; 95% CI, -2.0 to 1.0). Secondary: There was no difference between the groups in nausea, vomiting, itching, or drowsiness; however, the hydrocodone/acetaminophen patients had a higher incidence of subsequent constipation (oxycodone/acetaminophen 0%, hydrocodone/acetaminophen 21%, difference in proportions 21%; 95% CI, 3 to 39).
Litkowski et al[54] Oxycodone/ ibuprofen 5/400 mg vs oxycodone/ acetaminophen 5/325 mg	AC, MC, PC, PG, RCT Men or women >12 years of age who were scheduled to undergo complete removal of >2	N=249 6 hours	Primary: Total pain relief through six hours after dosing (TOTPAR6), sum of pain intensity differences through six hours (SPID6), and adverse events	Primary: The combination of oxycodone/ibuprofen provided higher pain relief values than any of the other combinations tested or placebo. TOTPAR6 scores were significantly better for each combination treatment compared to placebo (P<0.001). The combination of oxycodone/ibuprofen was associated with a significantly higher TOTPAR6 score compared to oxycodone/acetaminophen, hydrocodone/acetaminophen, and placebo (mean [SD], 14.98 [5.37], 9.53 [6.77], 8.36 [6.68], and 5.05 [6.90], respectively; all, P<0.001). The results for SPID6 were similar, with oxycodone/ibuprofen associated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs hydrocodone/ acetaminophen 7.5/500 mg vs placebo	ipsilateral, partially or completely impacted third molars		Secondary: SPID3,TOTPAR-3, peak pain relief, peak PID, time to onset of pain relief, time to use of rescue medication, proportion of patients reporting pain half gone, and the patient's global evaluation	significantly higher values compared to oxycodone/ acetaminophen, hydrocodone/ acetaminophen, and placebo (7.78 [4.11], 3.58 [4.64], 3.32 [4.73], and 0.69 [4.85]; all *P*<0.001). Both oxycodone/acetaminophen and hydrocodone/acetaminophen were associated with significantly higher SPID6 scores compared to placebo (*P*<0.001 and *P*=0.002, respectively). The combination of oxycodone/ibuprofen was well tolerated, as evidenced by an overall rate of patients experiencing >1 adverse event that was similar to that for placebo (11.3% [7/62] and 11.1% [7/63], respectively). Rates in the groups receiving oxycodone/ acetaminophen and hydrocodone/ acetaminophen (27.9% [17/61] and 25.4% [16/63], respectively) were >2-fold higher. Secondary: For TOTPAR3, SPID3, peak pain relief, pain half gone, and the patient's global assessment, oxycodone/ibuprofen was associated with significantly better scores compared to oxycodone/ acetaminophen, hydrocodone/ acetaminophen, and placebo (all, *P*<0.001). Peak SPID scores were also significantly higher for oxycodone/ibuprofen compared to oxycodone/ acetaminophen (*P*=0.006). Compared to placebo, oxycodone/ acetaminophen and hydrocodone/ acetaminophen also were significantly better in terms of TOTPAR3, SPID3, the patient's global assessment (all, *P*<0.001), and peak pain relief (*P*<0.001 and *P*=0.002, respectively). The median time to the onset of pain relief was significantly shorter for oxycodone/ ibuprofen compared to hydrocodone/ acetaminophen (*P*=0.002) and placebo (*P*<0.001). Both oxycodone/acetaminophen and hydrocodone/acetaminophen were associated with significantly shorter median times to the onset of pain relief compared to placebo (*P*<0.001 and *P*=0.002, respectively).
Macleod et al[55] Codeine/	DB, PG, PRO, RCT	N=82 12 hours	Primary: Comparative pain management,	Primary: The average increase in pain intensity over 12 hours was significantly less in patients receiving codeine/ acetaminophen than in those receiving acetaminophen alone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
acetaminophen 30/1,000 mg as a single tablet vs acetaminophen 1,000 mg	Subjects >17 years of age undergoing surgical removal of impacted third molars		adverse effects Secondary: Not reported	(*P*=0.03). Escape analgesia (ibuprofen 200 mg) was used by 24 (62%) patients receiving codeine/ acetaminophen and 30 (75%) of those receiving acetaminophen alone, a difference that was not statistically significant. A comparison of the adverse event profiles of the two medications showed that only seven (18%) patients receiving codeine/ acetaminophen and 5 (13%) patients receiving acetaminophen alone experienced an adverse event, a difference not statistically significant. Secondary: Not reported
Joshi et al[56] Ibuprofen 600 mg 1 hour before pre-operation vs diclofenac 100 mg 1 hour pre-operation vs codeine/ acetaminophen 60/1,000 mg 1 hour pre-operation vs placebo	DB, PC, RCT Men and women 18 to 44 years of age who were to have third molar teeth removed under general anaesthesia	N=119 24 hours	Primary: Efficacy of pre-emptive dosing of pain medication pre-op as measured by pain (VAS) at 15 and 30 minutes, and (VRS) one hour and three hours post-operation Secondary: Not reported	Primary: Median VAS scores decreased after 30 minutes post-operation. There was no significant difference among the four groups. Verbal rating pain scores showed that at three hours, 17 patients (14%) had moderate pain not controlled by pain medication and three patients (3%) had severe pain. By 24 hours, 68 patients (57%) reported no pain, 24 (20%) had mild pain, 26 (22%) had moderate pain, and one patient had moderate pain not controlled by pain medications. There were no significant differences in total pain and pain intensity scores among the four groups. There was a significant difference between the placebo and diclofenac groups in regard to time to first requirement for postoperative analgesics (*P*<0.009). When the pre-emptive and post-op analgesics were not sufficient to control pain, acetaminophen 500 mg was available as rescue analgesia. Ninety-nine patients (83%) did not require rescue medication and of the 20 patients who requested analgesia, the proportion in each group was not dissimilar. There were no significant differences among the groups with respect to adverse events at six or 24 hours. Adverse events reported six hours post-op included nausea (19%), vomiting (7%), headaches (13%), gastrointestinal discomfort (12%), dizziness (24%) and other discomforts (29%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Rodriguez et al[57] Codeine/ acetaminophen vs hydrocodone/ acetaminophen vs tramadol	DB, RCT Patients with persistent moderate or severe cancer-associated pain	N=177 3 weeks	Primary: Analgesic efficacy Secondary: Adverse effects	Primary: There was no significant difference in the analgesic efficacy of the three opioids (*P*=0.69). Secondary: Tramadol produced higher rates of adverse events than codeine and hydrocodone, including vomiting, dizziness, loss of appetite, and weakness (*P*<0.05).
De Conno et al[58] Morphine 5 mg IR every 4 hours, if taking Step 1 analgesics or morphine 10 mg IR every 4 hours, if taking Step 2 analgesics Patients currently receiving treatment with WHO Step I or Step II analgesics.	OL Cancer patients ≥18 years of age, never treated with strong opioids, and with pain score of >5 points on a 0 to 11 point standard scale for ≥24 hours	N=159 5 days	Primary: Proportion of time with pain control (reduction of ≥50% with respect to the baseline pain score) during the titration phase Secondary: Adverse events	Primary: Pain control was observed for 75% (95% CI, 70 to 80) of the follow-up period in the intent-to-treat population. Overall, 50 and 75% of patients achieved pain control eight to 24 hours after starting 5 and 10 mg morphine therapy respectively. Mean pain score was 7.63 points at baseline, and decreased to 2.43 and 1.67 points (both *P*<0.001) at days three and five respectively. Secondary: The most commonly reported adverse events were somnolence (24% of patients), constipation (22%), vomiting (13%), nausea (10%) and confusion (7%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Reid et al[59] Oxycodone vs morphine vs hydromorphone	MA Patients with moderate to severe cancer pain	N=1,013 Variable duration	Primary: Pain relief, as assessed on two standardized verbal/visual pain scoring methods Secondary: Patient acceptance, quality of life and adverse events	Primary: Mean pain scores did not differ between oxycodone and control drugs (*P*=0.8). Pain scores were higher for oxycodone compared to morphine (0.20; 95% CI, -0.04 to 0.44) and lower compared to hydromorphone (-0.36; 95% CI, -0.71 to 0.00), although these effect sizes were small. The investigators estimated that for oxycodone compared to morphine or hydromorphone, the pooled standardized differences represented only 2 to 3 mm on a 100-mm visual analog scale, and suggested such standardized differences are unlikely to be clinically important or meaningful to patients. Secondary: No differences in patient preference or quality of life were demonstrated, although one study suggested that nighttime acceptability of morphine was better than that of oxycodone. The point estimates for the pooled data comparing oxycodone with control groups were 0.75 (95% CI, 0.51 to1.10) for nausea and 0.2 (95% CI, 0.49 to1.06) for vomiting. Estimates of the association of oxycodone with dry mouth and drowsiness varied widely across trials. When the MA was repeated using only data from the trials with morphine as the control treatment, the pooled OR favored oxycodone for dry mouth and drowsiness. As many as 90% of patients experienced opioid-related adverse effects in each trial.
Quigley et al[60] Hydromorphone, long- or short-acting vs strong opioids, long- or short-acting or	MA (48 RCTs) Patients of any age suffering from any illness with either acute or chronic pain, including cancer pain and postoperative pain	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 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.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo or non-opioids				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. Secondary: Not reported
Bekkering et al[61] Morphine	MA (56 RCTs) Patients with	N= Duration not	Primary: Efficacy and tolerability	Primary: High heterogeneity precluded pair-wise pooling of data on mean change of pain intensity. One study favored other opioids, one favored morphine and the remaining

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs buprenorphine, fentanyl, hydromorphone, methadone, oxycodone, oxymorphone, placebo	cancer and non-cancer pain	specified	Secondary: Not reported	eight studies did not find any difference between the two medicines. In the subgroup of studies with a duration between one week and one month, morphine was more effective than other opioids (eight studies, I^2=56%; WMD, -5.8; 95% CI, -9.5 to -2.1). Other differences were not significant. Network analyses showed that fentanyl (WMD, 6.3; 95% CI, 1.8 to 10.9) and hydromorphone (WMD, 5.1; 95% CI, 0.5 to 9.6) were less effective when compared to morphine. Also placebo was less effective (WMD, 10.7; 95% CI, 7.2 to 14.1). No differences with morphine were found for oxycodone (WMD, 2.9; 95% CI, -0.4 to 6.2), methadone (WMD, 3.3; 95% CI, -4.6 to 11.3), oxymorphone (WMD, 0.4; 95% CI, -5.5 to 6.3) and buprenorphine (WMD, 3.0; 95% CI, -3.0 to 9.0). In sensitivity analyses the 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 studies examining opioids in neuropathic pain. No difference between morphine and 'other step III opioids' were found for risk of treatment discontinuation due to any reason (10 studies, I^2= 56%; RR, 1.06; 95% CI, 0.88 to 1.29), treatment discontinuation due to lack of efficacy (9 studies, I^2=0%; RR, 0.83; 95% CI, 0.55 to 1.25) or treatment discontinuation due to adverse events (9 studies, I^2=69%; RR, 1.05; 95% CI, 0.67 to 1.65). Network analyses showed no differences between morphine and any other step III 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 and OR, 4.12; 95% CI, 2.66 to 6.38, respectively). 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). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hartrick et al[62] Tapentadol 50 to 75 mg every 4 to 6 hours vs oxycodone 10 mg every 4 to 6 hours vs placebo	DB, RCT Patients 18 to 80 years of age who were candidates for primary joint replacement surgery as a result of end-stage degenerative joint disease	N=674 10 days	Primary: SPID over five days Secondary: Two- and 10-day SPID: two-,five-, and 10-day TOTPAR, and the sum of TOTPAR and pain intensity difference (SPRID)	Primary: After five days, both tapentadol treatment groups had a significant reduction in pain intensity compared to placebo (*P*<0.001). A significant difference was also seen between oxycodone and placebo (*P*<0.001). Secondary: Both tapentadol treatment groups had significant reductions in pain intensity compared to placebo, with increasing two- and 10-day SPID values (all, *P*<0.001). Significant reductions in pain intensity were also seen in the oxycodone group compared to placebo (all, *P*<0.001). The proportion of patients with a decrease in pain intensity of ≥30% at day five were 43% in the tapentadol 50 mg group (*P*=0.018 vs placebo), 41% in the tapentadol 75 mg group (*P*=0.033 vs placebo), 40% in the oxycodone group (*P* value not significant), and 30% in the placebo group. The corresponding responder rates of patients with a decrease in pain intensity of at least 50% at day five were 27% (acetaminophen=0.003 vs placebo), 26% (*P*=0.002 vs placebo), 25% (*P*=0.007 vs placebo), and 13%. At the end of the study, overall status was rated as very much improved or much improved by 49 and 42% of patients in the tapentadol 50 and 75 mg groups, respectively (both, *P*<0.001 vs placebo), 41% of those in the oxycodone group (*P*=0.005 vs placebo), and 21% of those in the placebo group. Adverse effects were reported by 52% of patients in the tapentadol 50 mg group, 71% of patients in the tapentadol 75 mg group, 84% of patients in the oxycodone group, and 32% of patients in the placebo group. The most frequently reported adverse effects were dizziness, nausea, vomiting, somnolence, constipation, pruritus, and fatigue. No serious adverse events were reported in the tapentadol groups.
Felden et al[63] 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).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported.
Pigni et al[64] 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
Furlan et al[65] Weak opioids: Tramadol, propoxyphene, codeine Strong opioids: morphine, oxycodone	MA Patients with nociceptive pain (osteoarthritis, rheumatoid arthritis or back pain), neuropathic pain (postherpetic	N=6,019 1 to 16 weeks	Primary: Pain relief; improvement in functional outcome, based upon standardized indices and scoring methods	Primary: Opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive pain, neuropathic pain or fibromyalgia. Strong opioids were significantly more effective than naproxen and nortriptyline for pain relief, but not for functional outcomes. Weak opioids did not significantly outperform NSAIDs or tricyclic antidepressants for either pain relief or functional outcomes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	neuralgia, diabetic neuropathy or phantom limb pain), fibromyalgia, and mixed pain		Secondary: Adverse events	Tramadol reduced pain and improved functional outcomes in patients with fibromyalgia. Secondary: Among the side effects of opioids, only constipation and nausea were clinically and statistically significant.
Steiner et al[66] Buprenorphine transdermal system 5 or 20 µg/hour every 7 days vs oxycodone IR 10 mg every 6 hours	AC, DB, DD, MC, PG, RCT Patients ≥18 years of age with clinical diagnosis of low back pain for ≥3 months, taking between 30 to 80 mg of oral morphine sulfate or opioid equivalent daily, at least 4 days a week, for ≥30 days prior to visit 1	N=1,160 12 weeks	Primary: Average pain score over the last 24 hours on an 11-point numerical pain scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine) at weeks four, eight and 12 Secondary: Treatment differences with respect to less sleep disturbances and the daily number of tablets of supplemental analgesic medication during DB period, and the Oswestry Disability Index at weeks	Primary: The protocol-specified analysis of the primary efficacy variable, in which missing values were not imputed, resulted in a statistically significant treatment difference of -0.67 between buprenorphine 20 and 5 µg/hour in favor of buprenorphine 20 µg/hour (*P*<0.001). The treatment difference of -0.75 between oxycodone IR and buprenorphine 5 µg/hour in favor of oxycodone IR was also statistically significant (*P*<0.001). The four sensitivity analyses of the primary efficacy variable resulted in statistically significant treatment differences in favor of buprenorphine 20 µg/hour and oxycodone IR compared to buprenorphine 5 µg/hour. Secondary: Treatment with buprenorphine 20 µg/hour led to statistically significant treatment differences with respect to less sleep disturbance (*P*<0.001) and decreased use of supplemental analgesic medication (*P*=0.006) compared to buprenorphine 5 µg/hour. The difference between buprenorphine 20 µg/hour and 5 µg/hour with respect to the Oswestry Disability Index was not statistically significant (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			four, eight, and 12	
Conaghan et al[67] Buprenorphine transdermal system 5 to 25 µg/hour every 7 days plus paracetamol 1,000 mg orally four times daily vs codeine 8 mg/ paracetamol 500 mg or codeine 30 mg/paracetamol 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				codeine/paracetamol (*P* value not reported). 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.
Mullican et al[68] Tramadol/ acetaminophen 37.5/325 mg once to twice every 4 to 6 hours vs codeine/ acetaminophen 30/300 mg once to twice every 4 to 6 hours	AC, DB, DD, PG, RCT Men and non-pregnant women >18 years of age with chronic nonmalignant low back pain, osteoarthritis pain, or both	N=462 4 weeks	Primary: Efficacy (measured by patient reported pain relief and pain intensity using Likert scales, and overall efficacy as reported by investigators) Secondary: Safety	Primary: Mean TOTPAR scores were comparable between the two groups at each weekly observation. Mean SPID scores were similar for tramadol/acetaminophen and codeine/ acetaminophen at each visit. The maximum number of doses required in a single day for pain relief was a mean of 5.5 tablets of tramadol/acetaminophen and 5.7 capsules of codeine/acetaminophen. The percentage of patients requiring supplemental ibuprofen at any point was comparable between the two groups and ranged from 21 to 30% for each week of the study. The mean duration of therapy was 25.5 days for tramadol/acetaminophen and 25.0 days for codeine/ acetaminophen. Secondary: The overall rates of treatment-emergent adverse events were comparable for the two groups. 71% of the tramadol/acetaminophen and 76% of the codeine/acetaminophen

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treated patients reported adverse events. Somnolence (24% [37/153] and constipation (21% [32/153]) were significantly more common in the codeine/acetaminophen group than in the tramadol group (17% [54/309] and 11% [35/309]; *P*=0.05 and *P*<0.01, respectively).
Fricke et al[69] Tramadol/ acetaminophen 37.5/325 mg vs tramadol/ acetaminophen 75/650 mg vs hydrocodone/ acetaminophen 10/650 mg vs placebo	AC, DB, PC, PG, SC Men and women 16 to 75 years of age who experiencing moderate or severe pain within 5 hours after surgical removal of > 2 impacted third molars and associated bone	N=200 8 hours	Primary: Efficacy based on TOTPAR, SPID, and SPRID measures Secondary: Efficacy measured by PAR, PID, and PRID scores; onset and duration of pain relief, time to re-medication with a supplemental analgesic agent; and patients' overall assessment of medication	Primary: For TOTPAR, SPID, and SPRID, tramadol/acetaminophen 75/650 mg and hydrocodone/acetaminophen provided statistically superior pain relief during all three intervals (0 to four, four to eight, and 0 to eight hours) compared to placebo (*P*<0.024), but were not significantly different from each other. There was a statistically significant dose response for tramadol/ acetaminophen compared to placebo (two tramadol/acetaminophen tablets >1 tablet >placebo) on all three primary efficacy variables during all three time periods (*P*<0.001, 0 to 4 and 0 to 8 hours; *P*<0.018, four to eight hours) Secondary: The median times to onset of pain relief were 34.0 and 33.3 minutes in the tramadol/ acetaminophen 75/650 mg and tramadol/acetaminophen 37.5/325 mg groups, respectively, and 25.4 minutes in the hydrocodone/acetaminophen group (*P*<0.001, active treatments vs placebo). There was no significant difference between tramadol/acetaminophen 75/650 mg and hydrocodone/acetaminophen in terms of duration of pain relief as measured by the areas under the curve for PAR, PID, and PRID over the second half of the study (four to eight hours). Both treatments had significantly longer duration of activity than placebo (TOTPAR; *P*<0.018; SPID; *P*<0.024; SPRID; *P*<0.019). Fewer patients required supplemental analgesic medication during the eight-hour observation period in the tramadol/acetaminophen 75/650 mg (78.0%) and hydrocodone/acetaminophen (84.0%) groups compared to the tramadol/ acetaminophen 37.5/325 mg (94.0%) and placebo (94.0%) groups. The median time to re-medication with a supplemental analgesic was shortest in the placebo group (78.5 minutes), followed by tramadol/acetaminophen 37.5/325 mg (113.0 minutes), tramadol/acetaminophen 75/650 mg (169.0 minutes), and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				hydrocodone/acetaminophen (204.0) minutes. The time to remedication was significantly longer for all active treatments compared to placebo (tramadol/ acetaminophen 75/650 mg and hydrocodone/acetaminophen; *P*<0.001; tramadol/ acetaminophen 37.5/325 mg; *P*=0.036). Patients' mean overall assessment of study medication was statistically superior in all active-treatment groups compared to placebo (*P*<0.001).
Wiffen et al[70] Morphine, long- or short-acting vs Opioids or non-opioid analgesics	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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
Caraceni et al[71] 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

*Not available in the United State
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double blind, DD= double-dummy, DR=dose-ranging, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective; RCT=randomized controlled trial, SB=single blind, SD=standard deviation, WMD=weight mean difference, XO=crossover
Miscellaneous abbreviations: ASA=American Society of Anesthesiologists, BTP=breakthrough pain, CSBM=complete spontaneous bowel movement, CR=controlled-release, ED=emergency department, ER=extended release, IM=intramuscular, IR=immediate release, ITT=intention to treat, IV=intravenous, NSAID=nonsteroidal anti-inflammatory drug, OA=osteoarthritis, PAR=hourly pain relief, PaCO2=partial pressure of arterial carbon dioxide, PCA=patient-controlled analgesia, SBM=spontaneous bowel movement, SPID=sum of pain intensity differences, SPRID= sum of combined pain relief and pain intensity differences, SR=sustained release, TOTPAR=total pain relief, VAS=visual analog scale, WHO=World Health Organization

Special Populations

Table 6. Special Populations[5,7-25]

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category*	Excreted in Breast Milk
Single Entity Agents					
Butorphanol	Use with caution in the elderly. Safety and efficacy have not been established in patients less than 18 years of age.	Dosage adjustment is not required.	Dosage adjustment is not required.	C	Unknown; use with caution.
Codeine	Use with caution in the elderly. Safety and efficacy have not been established in patients less than 18 years of age.	Use with caution. Start with lower doses or longer intervals.	No formal studies have been conducted in patients with hepatic impairment.	C	Codeine is secreted into human milk. Caution should be exercised when ad-ministered to a nursing woman.
Hydromorphone	Use with caution in the elderly. Safety and efficacy in children have not been established.	Reduce initial dose for moderate impairment. Use even lower dosing or alternative analgesic in severe impairment.	Reduce initial dose for moderate impairment. Use even lower dosing or alternative analgesic in severe impairment.	C	Detected in human milk. Breast feeding is not advised.
Meperidine	Use with caution in the elderly. Safety and efficacy in children have not been established.	Reduce dose by 75% for moderate impairment and 50% for severe impairment.	Use with caution. Reduce initial dose.	C	Detected in human milk. Breast feeding is not advised.
Morphine	Use with caution in the elderly. Safety and efficacy have not been established in patients less than 18 years of age.	Use with caution. Reduce initial dose and titrate slowly.	Use with caution. Reduce initial dose and titrate slowly.	C	Detected in human milk. Breast feeding is not advised.

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category*	Excreted in Breast Milk
Oxycodone	Use with caution in the elderly. Safety and efficacy in children have not been established.	Dose adjustment may be required with slow titration.	Dose adjustment may be required and titrate slowly.	B	Detected in human milk. 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 re-commended 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					
Codeine/ acetaminophen	Use with caution in the elderly. Safety not established in children younger than three years of age.	Information not available.	Use with caution.	C	Detected in breast milk. Caution should be exercised when ad-ministered to a nursing woman.
Codeine/ butalbital/ acetamino-	Use with caution in the elderly.	Use with caution.	Use with caution.	C	Detected in human milk.

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category*	Excreted in Breast Milk
phen/caffeine	Safety and efficacy in children have not been established.				Breast feeding is not advised.
Codeine/ butalbital/ aspirin/caffeine	Use with caution in the elderly. Safety and efficacy in children have not been established.	Use with caution.	Use with caution.	C	Detected in human milk. Breast feeding is not advised.
Codeine/ carisoprodol/ aspirin	Use with caution in the elderly. Safety and efficacy in pediatric patients below the age of 16 years have not been established.	Information not available.	Information not available.	D	Detected in human milk. Breast feeding is not advised.
Dihydrocodeine/ acetamino-phen/caffeine	Use with caution in the elderly. Safety and efficacy in children have not been established	Use with caution. And at a reduced dosage.	Use with caution.	C	Detected in human milk. Breast feeding is not advised.
Dihydrocodeine/ aspirin/caffeine	Use with caution in the elderly.	Information not available.	Information not available.	C	Detected in human milk. Breast feeding is not advised.
Hydrocodone/ acetaminophen	Use with caution in the elderly. Safety and efficacy in children have not been established.	Use with caution.	Use with caution.	C	Detected in human milk. Breast feeding is not advised.
Hydrocodone/ ibuprofen	Use with caution in the elderly. Safety and efficacy in pediatric patients below the age of 16 have not been established.	Information not available.	Information not available.	C	Unknown; caution should be exercised.
Oxycodone/ acetaminophen	Use with caution in the elderly.	Use with caution.	Use with caution.	C	Detected in human milk.

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category*	Excreted in Breast Milk
	Safety and efficacy in children have not been established.				Breast feeding is not advised.
Oxycodone/ aspirin	Use with caution in the elderly. Should not be administered to pediatric patients.	Use with caution. Avoid use with severe renal impairment.	Use with caution. Avoid use with severe renal impairment.	D	Detected in human milk. Breast feeding is not advised
Oxycodone/ ibuprofen	Use with caution in the elderly. Safety and efficacy in pediatric patients below the age of 14 have not been established.	Information not available.	Information not available.	C	Unknown; caution should be exercised.

Adverse Drug Events

Table 7. Adverse Drug Events (%) Single Entity Agents[7-25]

Adverse Events	Butorphanol	Codeine	Hydromorphone	Meperidine	Morphine	Oxycodone	Oxymorphone	Tapentadol
Cardiovascular								
Atrial fibrillation	-	-	-	-	✔	-	-	-
Bradycardia	-	✔	✔	✔	✔	-	✔	<1
Cardiac arrest	-	✔	✔	✔	✔	✔	-	-
Chest pain	-	-	-	-	✔	-	-	-
Circulatory collapse	-	✔	✔	✔	✔	✔	-	-
Congestive heart failure	-	-	-	-	-	<3	-	-
Deep thrombophlebitis	-	-	✔	-	-	-	-	-
Faintness	-	✔	✔	-	✔	-	-	-
Flushing	-	✔	✔	✔	-	-	-	-
Heart failure	-	-	✔	-	-	-	-	-
Hypertension	-	-	✔	-	-	-	-	<1
Hypotension	<1	✔	✔	✔	✔	1 to 5	✔	<1
Myocardial ischemia	-	-	-	-	-	-	-	-
Palpitation	>1	-	✔	✔	✔	<3	-	-
Phlebitis	-	-	-	✔	-	-	-	-
ST suppression	-	-	-	-	-	<1	-	-
Syncope	<1	✔	✔	✔	✔	-	-	<1
Tachycardia	-	✔	✔	✔	✔	<3	✔	<1
Vasodilation	>1	-	-	-	✔	<3	-	-
Central Nervous System								
Abnormal dreams	<1	-	-	-	✔	-	-	1
Abnormal gait	-	-	-	-	✔	-	-	-
Abnormal thinking	-	-	-	-	✔	-	-	-
Agitation	<1	✔	-	✔	✔	<1	-	<1
Amnesia	-	-	-	-	✔	-	-	-
Anxiety	>1	✔	✔	-	✔	-	-	1
Asthenia	>1	-	-	-	✔	6	-	-
Ataxia	-	-	-	-	✔	-	-	<1
Attention disturbances	-	-	-	-	-	-	-	<1
Central nervous system stimulation	-	-	-	-	-	-	✔	-
Coma	-	-	-	-	✔	-	-	-
Confusion	>1	-	-	-	✔	1 to 5	✔	1
Consciousness decreased	-	-	-	-	-	-	-	<1

Adverse Events	Butorphanol	Codeine	Hydromorphone	Meperidine	Morphine	Oxycodone	Oxymorphone	Tapentadol
Convulsion	-	✔	-	✔	✔	<1	-	-
Delirium	-	-	-	-	✔	-		-
Depression	-	-	-	-	✔	<1	✔	-
Disorientation	-	✔	✔	✔	✔	<1	-	<1
Dizziness	19	✔	✔	-	✔	13	-	24
Drowsiness	-	>10	✔	-	✔	-	✔	-
Dysphoria	<1	✔	✔	✔	-	✔	-	-
Emotional lability	-	-	-	-	-	<1	-	-
Euphoria	>1	✔	✔	✔	✔	1 to 5	✔	<1
Fear	-	✔	✔	-	-	-	-	-
Hallucinations	<1	✔	✔	✔	-	<1	✔	<1
Headache	>1	✔	✔	✔	✔	7	✔	<1
Hostility	<1	-	-	-	-	-	-	-
Impairment of performance	-	✔	✔	-	-	-	-	-
Incoordination	-	-	✔	✔	-	-	-	-
Increased intracranial pressure	-	-	✔	-	-	-	-	-
Insomnia	-	✔	✔	-	✔	1 to 5	-	2
Irritability	<1	-	-	-	-	-	-	<1
Lethargy	-	✔	✔	✔	-	-	-	1
Lightheadedness	-	✔	✔	-	✔	-	-	-
Memory impairment	-	-		-	-	-	-	<1
Mental clouding	-	✔	✔	-	-	-	-	-
Migraine	-	-	-	-	-	<3	-	-
Mood changes	-	✔	✔	-	-	-	-	-
Myoclonic movements	-	-	-	✔	-	-	-	-
Nervousness	>1	-	-	-	-	1 to 5		<1
Paranoid reaction	-	-	-	-	-	-	-	-
Paresthesia	>1	-	✔	-	✔	-	-	<1
Personality disorder	-	-	-	-	-	<3	-	-
Restlessness	-	-	-	-	-	-	✔	<1
Sedation	43	✔	✔	✔	✔	23	-	<1
Seizure	-	-	-	-	-	-	-	<1
Somnolence	-	-	-	-	-	-	-	15
Speech disorder	-	-	-	-	-	<1	-	-
Stupor	-	-	-	-	-	<1	-	-
Tremor	>1	-	✔	✔	✔	<3	-	1
Twitching	-	-	-	✔	-	1 to 5	-	-

Adverse Events	Butorphanol	Codeine	Hydromorphone	Meperidine	Morphine	Oxycodone	Oxymorphone	Tapentadol
Vertigo	-	-	-	-	✔	<1	-	-
Weakness	-	✔	✔	✔	✔	-	✔	-
Withdrawal syndrome	<1	-	-	-	✔	<1	-	<1
Dermatological								
Dry Skin	-	-	-	-	✔	-	<1	-
Exfoliative dermatitis	-	-	-	-	-	-	<1	-
Flushing	-	-	-	-	-	-	✔	1
Hyperhidrosis	-	-	-	-	-	-	-	3
Injection site pain/reaction	-	-	✔	-	-	-	-	-
Itching/pruritus	-	✔	✔	-	✔	✔	13	-
Localized skin reaction	-	-	-	-	-	-	-	-
Pruritus	>1	-	-	-	✔	✔	-	3 to 5
Rash	-	-	✔	-	✔	-	1 to 5	1
Skin discoloration	>1	-	-	-	-	-	-	-
Skin ulcer	-	-	-	-	-	-	-	-
Sweating	-	✔	✔	✔	✔	✔	5	-
Urticaria	<1	-	✔	-	✔	-	<3	-
Vesiculobullous rash	-	-	-	-	-	-	-	-
Wheal/flare	-	-	✔	-	✔	-	-	-
Endocrine and Metabolic								
Cyanosis	-	-	-	✔	-	-	-	-
Gout	-	-	-	-	-	-	<3	-
Hyperglycemia	-	-	-	-	-	-	<3	-
Hypokalemia	-	-	-	✔	✔	-	-	-
Hypomagnesemia	-	-	-	✔	-	-	-	-
Gastrointestinal								
Abdominal distention	-	-	-	-	-	-	1 to 5	-
Abdominal pain	-	-	-	-	-	✔	-	<1
Abnormal liver function tests	>1	-	-	-		-	-	-
Anorexia	-	✔	-	-	✔	✔	1 to 5	-
Appetite increased	>1	-	-	-			<1	
Biliary spasm	-	✔	-	✔	✔	✔	✔	-
Colonic motility increased	-	-	-	-	✔	-	-	-
Constipation	-	>10	✔	✔	✔	✔	23	8
Cramps	>1	-	✔	-	✔	-	✔	-
Dry mouth	-	✔	✔	✔	✔	✔	6	4
Diarrhea	-	-	✔	-	✔	-	1 to 5	<1

Adverse Events	Butorphanol	Codeine	Hydromorphone	Meperidine	Morphine	Oxycodone	Oxymorphone	Tapentadol
Dyspepsia	-	-	-	-	✔	-	1 to 5	2
Dysphagia	-	-	-	-	✔	-	<1	-
Eructation	-	-	-	-	-	-	<1	-
Flatulence	-	-	-	-	-	-	<1	-
Gastric emptying decreased	-	-	-	-	-	-	-	<1
Gastritis	-	-	-	-	-	-	1 to 5	-
Gastroenteritis	-	-	-	-	✔	-	-	-
Gastrointestinal disorder	-	-	-	-	-	-	<1	-
Ileus	-	-	✔	-	✔	✔	-	-
Increased biliary tract pressure	-	✔	-	-	-	-	-	-
Intestinal obstruction	-	-	-	-	✔	-	-	-
Nausea	-	✔	✔	✔	✔	✔	23	30
Oral moniliasis	13	-	-	-	-	-	-	-
Rectal disorder	-	-	-	-	✔	-	-	-
Rectal hemorrhage	-	-	-	-	✔	-	-	-
Stomatitis	-	-	-	-	-	-	<1	-
Toxic megacolon	-	-	-	-	-	✔	-	-
Vomiting	-	✔	-	✔	✔	✔	12	18
Weight loss	13	-	-	-	✔	-	-	-
Genitourinary								
Abnormal ejaculation	-	-	-	-	✔	-	-	-
Amenorrhea	-	-	-	-	✔	-	<1	-
Antidiuretic effect	-	✔	✔	✔	-	✔	<1	-
Decreased libido/potency	-	✔	-	-	-	-	-	-
Dysuria	-	-	-	-	✔	-	<1	-
Impotence	-	-	-	-	✔	-	-	-
Libido decreased	-	-	-	-		-	<1	<1
Pollakiuria	-	-	-	-	✔	-	-	-
Polyuria	-	-	-	-	-	-	<1	-
Spasm of vesical sphincters	-	✔	✔	-	✔	-	-	-
Ureteral spasm	-	✔	-	-	✔	✔	-	-
Urinary hesitancy	-	✔	✔	-	✔	✔	-	<1
Urinary incontinence	-	-	✔	-	-	-	-	-
Urinary retention	-	✔	✔	✔	✔	✔	-	-
Urinary tract infection	-	-	-	-	✔	-	-	1
Urinary urgency	<1	-	-	-	-	-	-	-
Hematologic								

Adverse Events	Butorphanol	Codeine	Hydromorphone	Meperidine	Morphine	Oxycodone	Oxymorphone	Tapentadol
Anemia	-	-	-	-	✔	-	-	-
Lymphadenopathy	-	-	-	-	-	-	<1	-
Thrombocytopenia	-	-	-	-	✔		-	-
Laboratory Test Abnormalities								
Alanine transaminase increased	-	✔	-	-	-	-	-	<1
Aspartate aminotransferase increased	-	✔	-	-	-	-	-	<1
Musculoskeletal								
Arthralgia	-	-	-	-	-	-	<3	1
Arthritis	-	-	-	-	-	-	<3	-
Dysarthria	-	-	-	-	-		-	<1
Hypotonia	-	-	-	-	-	<1	-	-
Involuntary muscle contractions	-	-	-	-	-	-	-	<1
Myalgia	-	-	-	-	-	-	<3	<1
Weakness	-	-	-	-	-	-	-	<1
Respiratory								
Bronchitis	-	-	-	-	-	-	<3	-
Cough	>1	-	-	-	-	<3	<3	<1
Dyspnea	-	-	-	-	-	-	1 to 5	<1
Epistaxis	>1	-	-	-	-	-	<3	-
Hemoptysis	>1	-	-	-	-	-	-	-
Hiccoughs	>1	-	-	-	-	-	1 to 5	-
Hypoxia	-	-	-	-	-	-	<3	-
Laryngospasm	-	-	✔	-	✔	-	<3	-
Lung disorder	-	-	-	-	-	-	<3	-
Pharyngitis	-	-	-	-	-	-	-	1
Respiratory arrest	-	✔	✔	✔	✔	-	-	<1
Respiratory depression	-	✔	✔	✔	✔	✔	-	-
Rhinitis	-	-	-	-	-	-	<3	-
Sinusitis	-	-	-	-	-	-	<3	-
Sputum increased	>1	-	-	-		-	-	-
Stertorous breathing	>1	-	-	-	-	-	-	-
Suppressed cough reflex	-	✔	-	-	-	-	-	-
Other								
Abnormal vision	-	-	-	-	-	-	<1	-
Abscess	-	-	-	-	✔	-	-	-
Accidental injury	-	-	-	-	-	-	<3	-
Allergic laryngeal edema	-	-	-	-	-	✔	-	-

Adverse Events	Butorphanol	Codeine	Hydromorphone	Meperidine	Morphine	Oxycodone	Oxymorphone	Tapentadol
Allergic laryngospasm	-	-	-	-	-	✔	-	-
Allergic reaction	-	✔	✔	-	-	✔	<3	<1
Amblyopia	-	-	-	-	-	<3	-	-
Anaphylaxis	-	-	-	✔	✔	-	<1	-
Back pain	-	-	-	-	-	-	<3	-
Blurred vision	-	-	-	-	-	✔		-
Bone pain	-	-	-	-	-	-	<3	-
Chills	-	-	✔	-	✔	-	<3	-
Deep thrombophlebitis	-	-	-	-	-	✔	-	-
Dehydration	-	-	-	-	✔	-	<3	-
Diaphoresis	-	-	-	-	-	-	-	-
Diplopia	-	-	-	-	✔	✔	-	-
Ear pain	>1	-	-	-	-	-	-	<1
Edema	>1	-	-	-	✔	-	-	<1
Eye hemorrhage	-	-	-	-	✔	-	-	-
Fever	-	-	-	-	-	-	-	-
Flank pain	-	-	-	-	-	-	<3	-
Flu syndrome	-	-	-	-	✔	-		-
Fracture	-	-	-	-	-	-	<3	-
Fungal infection	-	-	-	-	-	-	<3	-
Hemorrhage	-	-	-	-	-	<3		-
Herpes simplex	-	-	-	-	-	-	<3	-
Infection	-	-	-	-	✔	-	-	1
Lacrimation disorder	-	-	-	-	-	-	-	-
Malaise	-	-	-	-	✔	-	-	-
Miosis	-	✔	✔	-	✔	✔	-	-
Nystagmus	-	-	✔	-	-	-	-	-
Pain	-	-	-	-	✔	-	<3	-
Pharyngolaryngeal pain	-	-	-	-	-	-	-	<1
Phlebitis	-	-	-	-	✔	-	-	-
Sepsis	-	-	-	-	✔	-	<3	-
Shock	-	✔	✔	✔	-	-	✔	-
Taste perversion	-	-	✔	-	✔	-	<1	-
Tinnitus	--	-	-	✔	-	-	<1	-
Visual disturbances	>1	✔	✔	✔	✔	-	-	<1

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 8. Adverse Drug Events (%) Combination Products for Combination Products[15-25]

Adverse Events	Codeine/ Acetaminophen	Codeine/ Butalbital/ Acetaminophen/ Caffeine	Codeine/ Butalbital/ Aspirin/Caffeine	Codeine/ Carisoprodol/ Aspirin	Dihydrocodeine/ Acetaminophen/ Caffeine	Dihydrocodeine/ Aspirin/Caffeine	Hydrocodone/ Acetaminophen	Hydrocodone/ Ibuprofen	Oxycodone/ Acetaminophen	Oxycodone/ Aspirin	Oxycodone/ Ibuprofen
Cardiovascular											
Arrhythmia	-	-	-	-	-	-	-	✔	-	-	-
Bradycardia	-	-	-	-	-	-	-	-	✔	✔	-
Chest pain	-	✔	✔	-	-	-	-	-	✔	-	✔
Circulatory depression	-	-	-	-	-	-	-	-	✔	✔	-
Dysrhythmias	-	-	-	-	-	-	-	-	✔	✔	-
Flushing	-	✔	✔	✔	-	-	-	-	-	-	-
Hypertension	-	-	-	-	-	-	-	-	✔	-	-
Hypotension	-	✔	✔	✔	✔	-	-	-	✔	✔	✔
Palpitation	-	✔	✔	-	✔	-	-	<3	✔	✔	-
Syncope	-	✔	✔	✔	-	-	-	-	-	-	✔
Tachycardia	-	✔	✔	✔	✔	-	-	-	✔	✔	✔
Vasodilation	-	-	-	-	-	-	-	<3	-	-	✔
Central Nervous System											
Abnormal dreams	-	-	-	-	-	-	-	✔	-	-	-
Abnormal thinking	-	-	-	-	-	-	-	<3	-	-	✔
Agitation	-	✔	✔	✔	-	-	-	✔	✔	✔	-
Anxiety	-	✔	✔	-	✔	-	✔	3 to 9	✔	✔	✔
Asthenia	-	-	-	-	-	-	-	3 to 9	✔	✔	3.3
Ataxia				✔	-						
Central nervous system stimulation	-	-	✔	-	-	✔	-	-	-	-	-
Cerebral edema	-	-	-	-	-	-	-	-	✔	✔	-
Coma	-	-	-	-	-	-	-	-	-	✔	-
Confusion	-	✔	-	-	✔	-	-	<3	✔	✔	-
Consciousness decreased	-	-	-	-	-	-	-	-	✔	-	-
Depression	-	✔	✔	✔	-	-	-	✔	✔	✔	-
Disorientation	-	✔	✔	-	-	-	-	-	-	-	-
Dizziness	✔	✔	2.6	✔	✔	✔	✔	14	✔	✔	5.1
Drowsiness	✔	✔	2.4	✔	✔	✔	✔	-	✔	✔	-

Adverse Events	Codeine/ Acetaminophen	Codeine/ Butalbital/ Acetaminophen/ Caffeine	Codeine/ Butalbital/ Aspirin/Caffeine	Codeine/ Carisoprodol/ Aspirin	Dihydrocodeine/ Acetaminophen/ Caffeine	Dihydrocodeine/ Aspirin/Caffeine	Hydrocodone/ Acetaminophen	Hydrocodone/ Ibuprofen	Oxycodone/ Acetaminophen	Oxycodone/ Aspirin	Oxycodone/ Ibuprofen
Dysphoria	✔	-	-	-	-	-	✔	-	✔	✔	-
Euphoria	✔	✔	-	-	-	-	-	✔	✔	✔	✔
Fainting	-	✔	✔	-	-	-	-	-	-	-	-
Fatigue	-	-	✔	-	✔	-	-	-	✔	-	-
Fear	-	-	-	-	-	-	✔	-	-	-	-
Hallucinations	-	✔	✔	-	✔	-	-	-	✔	✔	-
Headache	-	✔	✔	✔	✔	-	-	27	✔	✔	10.2
High energy	-	✔	✔	-	-	-	-	-	-	-	-
Hot spells	-	✔	✔	-	-	-	-	-	-	-	-
Hyperkinesia	-	-	-	-	-	-	-	-	-	-	✔
Hypertonia	-	-	-	-	-	-	-	<3	-	-	✔
Impairment of performance	-	-	-	-	-	-	✔	-	-	-	-
Insomnia	-	✔	-	✔	✔	-	-	3 to 9	✔	-	✔
Intoxicated feeling	-	✔	1	-		-	-	-	-	-	-
Irritability	-	✔	✔	✔	✔	-	-	-	-	-	-
Lethargy	-	-	-	-	-	-	✔	-	✔	✔	-
Lightheadedness	✔	✔	✔	-	✔	✔	✔	-	✔	✔	-
Mental clouding	-	-	-	-	-	-	✔	-	-	-	-
Mental impairment	-	-	-	-	-	-	✔	-	✔	✔	-
Mood changes	-	-	-	-	-	-	✔	✔	-	-	-
Neuralgia	-	-	-	-	-	-	-	✔	-	-	-
Nervousness	-	✔	✔	-	-	-	-	-	✔	✔	✔
Numbness	-	✔	✔	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	-	-	-	-	<3	✔	✔	-
Psychic dependence	-	-	-	-	-	-	✔	-	-	-	-
Psychosis	-	✔	✔	-	-	-	-	-	-	-	-
Sedation	✔	✔	✔	-	✔	✔	✔	-	✔	✔	-
Seizure	-	✔	-	✔	-	-	-	-	✔	✔	-
Shaky feeling	-	✔	✔	-	-	-	-	-	-	-	-
Somnolence	-	-	-	-	-	-	-	22	-	✔	7.3

Adverse Events	Codeine/ Acetaminophen	Codeine/ Butalbital/ Acetaminophen/ Caffeine	Codeine/ Butalbital/ Aspirin/Caffeine	Codeine/ Carisoprodol/ Aspirin	Dihydrocodeine/ Acetaminophen/ Caffeine	Dihydrocodeine/ Aspirin/Caffeine	Hydrocodone/ Acetaminophen	Hydrocodone/ Ibuprofen	Oxycodone/ Acetaminophen	Oxycodone/ Aspirin	Oxycodone/ Ibuprofen
Speech disorder	-	✔	✔	-		-	-	✔	-	-	-
Stupor	-	-	-	-	-	-	-	-	✔	✔	-
Tingling	-	✔	✔	-	-	-	-	-	-	-	-
Tremor	-	✔	✔	✔	✔	-	-	✔	-	-	-
Twitching	-	✔	✔	-	-	-	-	-	-	-	-
Unconsciousness	-	✔	✔	-	-	-	-	-	-	-	-
Vertigo	-	✔	✔	✔	-	-	-	✔	-	-	-
Vivid dreams	-	-	-	-	✔	-	-	-	-	-	-
Dermatological											
Erythema	-	✔	✔	-	-	-	-	-	-	-	-
Exfoliative dermatitis	-	✔	✔	-	-	-	-	-	✔	-	-
Flushing	-	-	-	-	-	-	-	✔	✔	✔	-
Hives	-	✔	✔	-	-	-	-	-	-	-	-
Hyperhidrosis	-	✔	✔	-	-	-	-	-	-	-	-
Pruritus	✔	✔	✔	-	✔	✔	✔	3 to 9	✔	✔	-
Rash	✔	✔	✔	-	-	-	✔	✔	✔	✔	✔
Skin reactions	-	-	-	-	✔	✔	-	-	-	-	-
Sweating	-	-	-	-	✔	-	-	3 to 9	✔	✔	1.6
Toxic epidermal necrolysis	-	✔	✔	-	-	-	-	-	-	-	-
Urticaria	-	-	-	-	✔	-	-	✔	✔	✔	-
Endocrine and Metabolic											
Hyperglycemia	-	✔	✔	-	-	-	-	-	-	-	-
Hypokalemia	-	-	-	-	-	-	-	-	-	-	✔
Gastrointestinal											
Abdominal distention	-	-	-	-	-	-	-	-	✔	-	-
Abdominal pain	✔	✔	✔	✔	✔	-	-	3 to 9	✔	✔	✔
Anorexia	-	✔	✔	-	✔	-	-	<3	-	✔	-
Appetite increased	-	✔	✔	-	-	-	-	-	-	-	-
Chalky stool	-	-	-	-	-	-	-	✔	-	-	-
Constipation	✔	✔	✔	-	✔	✔	✔	22	✔	✔	4.5

Adverse Events	Codeine/ Acetaminophen	Codeine/ Butalbital/ Acetaminophen/ Caffeine	Codeine/ Butalbital/ Aspirin/Caffeine	Codeine/ Carisoprodol/ Aspirin	Dihydrocodeine/ Acetaminophen/ Caffeine	Dihydrocodeine/ Aspirin/Caffeine	Hydrocodone/ Acetaminophen	Hydrocodone/ Ibuprofen	Oxycodone/ Acetaminophen	Oxycodone/ Aspirin	Oxycodone/ Ibuprofen
Diarrhea	-	✔	✔	-	✔	-	-	3 to 9	✔	✔	2.1
Dry mouth	-	✔	✔	-	✔	-	-	3 to 9	✔	✔	✔
Dyspepsia	-	-	-	-	-	-	-	12	✔	✔	2.1
Dysphagia	-	✔	✔	-	-	-	-	✔	-	-	-
Esophageal spasm	-	-	-	-	-	-	-	✔	-	-	-
Esophagitis	-	✔	✔	-	-	-	-	✔	-	-	-
Eructation	-	-	-	-	-	-	-	-	-	✔	✔
Flatulence	-	✔	-	-	-	-	-	3 to 9	✔	-	1
Gastric/peptic ulcer	-	-	✔	-		-	-	-	-	✔	-
Gastritis	-	-	-	✔	-	-	-	<3	-	-	-
Gastroenteritis	-	✔	✔	-	-	-	-	✔	-	-	-
Gastrointestinal bleeding	-	-	-	✔	-	-	-	-	-	✔	-
Gastrointestinal disorder	-	-	-	-	-	-	-	-	✔	-	-
Gastrointestinal spasm	-	✔	✔	-	-	-	-	-	-	-	-
Glossitis	-	-	-	-	-	-	-	✔	-	-	-
Heartburn	-	✔	✔	-	✔	-	-	-	-	-	-
Hemorrhagic gastric/duodenal ulcer	-	-	-	-	-	-	-	-	-	✔	-
Ileus	-	-	-	-	-	-	-	-	✔	-	✔
Intestinal obstruction	-	-	-	-	-	-	-	-	✔	✔	-
Melena	-	-	-	-	-	-	-	<3	-	-	-
Mouth ulcers	-	-	-	-	-	-	-	<3	-	-	-
Nausea	✔	✔	3.7	✔	✔	✔	✔	21	✔	✔	8.8
Pancreatitis	-	-	-	-	-	-	-	-	✔	✔	-
Pyloric ulcer	-	✔	✔	-	-	-	-	-	-	-	-
Spasm of biliary tract	-	-	-	-	✔	-	-	-	-	-	-
Thirst	-	-	-	-	-	-	-	<3	✔	✔	-
Vomiting	✔	✔	✔	✔	✔	✔	✔	3 to 9	✔	✔	5.3
Weight loss	-	-	-	-	-	-	-	✔	-	-	-
Genitourinary											
Cystitis	-	-	-	-	-	-	-	✔	-	-	-

Adverse Events	Codeine/ Acetaminophen	Codeine/ Butalbital/ Acetaminophen/ Caffeine	Codeine/ Butalbital/ Aspirin/Caffeine	Codeine/ Carisoprodol/ Aspirin	Dihydrocodeine/ Acetaminophen/ Caffeine	Dihydrocodeine/ Aspirin/Caffeine	Hydrocodone/ Acetaminophen	Hydrocodone/ Ibuprofen	Oxycodone/ Acetaminophen	Oxycodone/ Aspirin	Oxycodone/ Ibuprofen
Diuresis	-	✔	✔	-	✔	-	-	-	-	-	-
Glycosuria	-	-	-	-	-	-	-	✔	-	-	-
Impotence	-	-	-	-	-	-	-	✔	-	-	-
Interstitial nephritis	-	-	-	-	✔	-	-	-	✔	✔	-
Kidney impairment	-	✔	✔	-	-	-	-	-	-	-	-
Libido decreased	-	✔	-	-	-	-	-	✔	-	-	-
Papillary necrosis	-	-	-	-	-	-	-	-	✔	✔	-
Proteinuria	-	-	-	-	-	-	-	-	✔	✔	-
Renal insufficiency and failure	-	-	-	-	✔	-	-	-	✔	✔	-
Spasm of vesical sphincters	-	-	-	-	-	-	✔	-	-	-	-
Ureteral spasm	-	-	-	-	-	-	✔	-	-	-	-
Urinary difficulty	-	✔	✔	-	-	-	-	-	-	-	-
Urinary frequency	-	-	-	-	-	-	-	<3	-	-	✔
Urinary incontinence	-	-	-	-	-	-	-	✔	-	-	-
Urinary retention	-	-	-	-	✔	-	✔	✔	✔	✔	✔
Hematologic											
Agranulocytosis	✔	✔	-	-	✔	-	✔	-	✔	-	-
Anemia	-	-	-	-	-	-	-	-	-	-	✔
Disseminated intravascular coagulation	-	-	-	-	-	-	-	-	-	✔	-
Ecchymosis	-	-	-	-	-	-	-	-	-	✔	✔
Hemolytic anemia	-	-	✔	-	-	-	-	-	✔	-	-
Leukopenia	-	-	-	✔	✔	-	-	-	-	✔	-
Neutropenia	-	-	-	-	✔	-	-	-	✔	-	-
Pancytopenia	-	-	-	✔	✔	-	-	-	✔	-	-
Prolongation of prothrombin time	-	-	-	-		-	-	-	-	✔	-
Purpura	-	-	-	-	✔	-	-	-	-	✔	-
Reticulocytosis	-	-	-	-	-	-	-	-	-	✔	-
Thrombocytopenia	✔	✔	-	-	✔	-	✔	-	✔	✔	-
Laboratory Test Abnormalities											
Alanine transaminase increased	-	-	-	-	-	-	-	✔	✔	✔	-

Adverse Events	Codeine/ Acetaminophen	Codeine/ Butalbital/ Acetaminophen/ Caffeine	Codeine/ Butalbital/ Aspirin/Caffeine	Codeine/ Carisoprodol/ Aspirin	Dihydrocodeine/ Acetaminophen/ Caffeine	Dihydrocodeine/ Aspirin/Caffeine	Hydrocodone/ Acetaminophen	Hydrocodone/ Ibuprofen	Oxycodone/ Acetaminophen	Oxycodone/ Aspirin	Oxycodone/ Ibuprofen
Aspartate aminotransferase increased	-	-	-	-	-	-	-	✔	✔	✔	-
Musculoskeletal											
Arthralgia	-	-	-	-	-	-	-	✔	-	-	-
Arthritis	-	-	-	-	-	-	-	-	-	-	✔
Leg pain	-	✔	✔	-	-	-	-	-	-	-	-
Muscle fatigue	-	✔	✔	-	-	-	-	-	-	-	-
Myalgia	-	-	-	-	-	-	-	✔	-	-	-
Rhabdomyolysis	-	-	-	-	-	-	-	-	-	✔	-
Respiratory											
Apnea	-	-	-	-	-	-	-	-	✔	✔	-
Aspiration	-	-	-	-	-	-	-	-	✔	✔	-
Asthma	-	-	-	-	-	-	-	✔	✔	✔	-
Bronchitis	-	-	-	-	-	-	-	✔	-	-	-
Bronchospasm	-	-	-	-	-	-	-	-	✔	✔	-
Cough	-	-	-	-	-	-	-	✔	-	-	-
Cough suppression	-	-	-	-	✔	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-	-	<3	-	✔	-
Epistaxis	-	✔	✔	-	-	-	-	-	-	-	-
Hiccups	-	✔	✔	-	-	-	-	<3	-	-	-
Hoarseness	-	-	-	-	-	-	-	✔	-	-	-
Hyperpnea	-	-	-	-	-	-	-	-	-	✔	-
Hypoventilation	-	-	-	-	-	-	-	-	✔	✔	-
Hypoxia	-	-	-	-	-	-	-	-	-	-	✔
Laryngeal edema	-	-	-	-	✔	-	-	-	✔	✔	-
Lung disorder	-	-	-	-	-	-	-	-	-	-	✔
Pharyngitis	-	-	-	-	-	-	-	<3	-	-	✔
Pneumonia	-	-	-	-	-	-	-	✔	-	-	-
Pulmonary congestion	-	-	-	-	-	-	-	✔	-	-	-
Pulmonary edema	-	-	-	-	-	-	-	-	✔	✔	-
Respiratory arrest	-	-	-	-	-	-	-	-	✔	✔	-

Adverse Events	Codeine/ Acetaminophen	Codeine/ Butalbital/ Acetaminophen/ Caffeine	Codeine/ Butalbital/ Aspirin/Caffeine	Codeine/ Carisoprodol/ Aspirin	Dihydrocodeine/ Acetaminophen/ Caffeine	Dihydrocodeine/ Aspirin/Caffeine	Hydrocodone/ Acetaminophen	Hydrocodone/ Ibuprofen	Oxycodone/ Acetaminophen	Oxycodone/ Aspirin	Oxycodone/ Ibuprofen
Respiratory depression	-	-	-	-	-	-	✔	-	✔	✔	-
Rhinitis	-	-	-	-	-	-	-	<3	-	-	-
Shallow breathing	-	-	-	-	-	-	-	✔	-	-	-
Shortness of breath	✔	✔	-	-	-	-	-	-	-	-	-
Sinusitis	-	-	-	-	-	-	-	✔	-	-	-
Tachypnea	-	-	-	-	-	-	-	-	✔	✔	-
Other											
Abnormal vision	-	-	-	-	-	-	-	✔	-	-	-
Allergic reaction	✔	✔	✔	-	-	-	-	✔	✔	✔	-
Anaphylaxis	-	✔	✔	-	✔	-	-	-	✔	✔	-
Back pain	-	-	-	-	-	-	-	-	-	-	✔
Chills	-	-	-	-	-	-	-	-	-	-	✔
Deep thrombophlebitis	-	-	-	-	-	-	-	-	-	✔	-
Dehydration	-	-	-	-	-	-	-	-	✔	-	-
Dry eyes	-	-	-	-	-	-	-	✔	-	-	-
Ear pain	-	✔	✔	-	-	-	-	-	-	-	-
Edema	-	✔	-	-	-	-	-	3 to 9	-	✔	✔
Fever	-	✔	✔	-	-	-	-	3 to 9	✔	✔	3
Flu syndrome	-	-	-	-	-	-	-	<3	-	-	-
Hearing impairment	-	-	-	-	-	-	✔	-	✔	✔	-
Hemorrhage	-	-	-	-	-	-	-	-	-	✔	-
Hepatitis	-	-	-	-	-	-	-	-	✔	✔	-
Hepatotoxicity	-	-	-	-	✔	-	-	-	-	✔	-
Hyperkalemia	-	-	-	-	-	-	-	-	✔	✔	-
Hypoglycemia	-	-	-	-	-	-	-	-	✔	✔	-
Hypothermia	-	-	-	-	-	-	-	-	✔	✔	-
Infection	-	-	-	-	-	-	-	3 to 9	-	-	✔
Malaise	-	-	-	-	-	-	-	-	✔	✔	-
Miosis	-	✔	✔	-	✔	-	-	-	✔	✔	-
Metabolic acidosis	-	-	-	-	-	-	-	-	✔	✔	-

Adverse Events	Codeine/ Acetaminophen	Codeine/ Butalbital/ Acetaminophen/ Caffeine	Codeine/ Butalbital/ Aspirin/Caffeine	Codeine/ Carisoprodol/ Aspirin	Dihydrocodeine/ Acetaminophen/ Caffeine	Dihydrocodeine/ Aspirin/Caffeine	Hydrocodone/ Acetaminophen	Hydrocodone/ Ibuprofen	Oxycodone/ Acetaminophen	Oxycodone/ Aspirin	Oxycodone/ Ibuprofen
Metabolic alkalosis	-	-	-	-	-	-	-	-	✔	✔	-
Pain	-	-	-	-	-	-	-	<3	-	-	-
Red eye	-	-	-	-	-	-	-	-	✔	✔	-
Respiratory alkalosis	-	-	-	-	-	-	-	-	✔	✔	-
Shock	-	-	-	-	-	-	-	-	✔	✔	-
Taste perversion	-	-	-	-	-	-	-	✔	✔	-	✔
Tinnitus	-	✔	✔	-	✔	-	-	<3	✔	✔	-
Visual disturbances	-	-	-	-	-	-	-	-	✔	✔	-

Contraindications

Table 9. Contraindications Single Entity Agents[7-14]

Contraindications	Butorphanol	Codeine	Hydro-morphone	Meperidine	Morphine	Oxycodone	Oxy-morphone	Tapentadol
Acute or severe bronchial asthma	-	✔	✔	-	✔	✔	✔	✔
Concurrent monoamine oxidase inhibitor therapy or use within the last 14 days	-	-	-	✔	-	-	-	✔
Hepatic impairment, moderate or severe	-	-	-	-	-	-	✔	-
Hypersensitivity to any component or the active ingredient	✔	✔	✔	✔	✔	✔	✔	✔
Postoperative pain management of children undergoing tonsillectomy and/or adenoidectomy	-	✔	-	-	-	-	-	-
Respiratory depression, significant	-	✔	✔	✔	✔	✔	✔	✔
Suspected or documented paralytic ileus	-	✔	-	-	✔	✔	✔	✔
Use in obstetrical analgesia	-	-	✔	-	-	-	-	-

Table 10. Contraindications Combination Products[15-25]

Contraindications	Codeine/ Acetaminophen	Codeine/Butalbital/ Acetaminophen/ Caffeine	Codeine/ Butalbital/Aspirin/ Caffeine	Codeine/ Carisoprodol/ Aspirin	Dihydrocodeine/ Acetaminophen/ Caffeine	Dihydrocodeine/ Aspirin/Caffeine	Hydrocodone/ Acetaminophen	Hydrocodone/ Ibuprofen	Oxycodone/ Acetaminophen	Oxycodone/ Aspirin	Oxycodone/ Ibuprofen
Acute or severe bronchial asthma	✔	✔	✔	-	✔	-	-	-	✔	✔	✔
Allergy to nonsteroidal anti-inflammatory drug products	-	-	✔	✔	-	✔	-	✔	-	✔	✔
Children or teenagers with viral infections, with or without fever	-	-	✔	-	-	✔	-	-	-	✔	-
Hemophilia	-	-	✔	-	-	-	-	-	-	✔	-
Hypersensitivity to any component or the active ingredient(s)	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Peptic ulcer or other serious gastrointestinal lesions	-	-	✔	✔	-	-	-	-	-	-	-
Peri-operative pain in the setting of coronary artery bypass graft surgery	-	-	-	-	-	-	-	✔	-	-	✔
Porphyria	-	✔	✔	✔	-	-	-	-	-	-	-
Postoperative pain management of children undergoing tonsillectomy and/or adenoidectomy	✔	✔	✔	✔	-	✔	-	-	-	-	-
Respiratory depression, significant	-	-	-	-	✔	-	-	-	✔	✔	✔
Suspected or documented paralytic ileus	-	-	-	-	✔	-	-	-	✔	✔	✔

Boxed Warnings

Boxed Warning for Acetaminophen-Containing Products[15,16]

WARNING
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product.

Boxed Warning for Codeine- and Dihydrocodeine-Containing Products[8,15-18]

WARNING
Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

Black Box Warning for Ibuprofen Containing Agents[22,25]

WARNING
Cardiovascular Risk • Nonsteroidal antiinflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. **Gastrointestinal Risk** • NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Warnings and Precautions

- In general, the following warnings and precautions are associated with opioids:[7-25]
    - Abuse potential: may be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing opioids in situation where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.
    - Acute abdominal conditions: administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.
    - Cardiovascular effects have been reported in patients with acute myocardial infarction, ventricular dysfunction or coronary insufficiency. Use should be limited to those situations where the benefits outweigh the risks.
    - Central nervous system (CNS) depression with concurrent use of alcohol, barbiturates, tranquilizers, and antihistamines. Avoid concurrent use.
    - Head injury and increased intracranial pressure: Carbon dioxide retention and secondary elevation of cerebral spinal fluid in patients with head injury have been reported. Use only if benefits outweigh the potential risks.
    - Hypotensive effect: Hypotension associated with syncope has been reported. Avoid activities with potential risks.
    - Impaired mental and physical abilities. Do not drive or operate dangerous machinery for at least 1 hour and until the effects of the drug are no longer present.
    - Pancreatic/biliary tract disease: use with caution in patients with biliary tract disease, including acute pancreatitis.
    - Respiratory depression. Use with caution in patients receiving other CNS active agents or patients suffering from CNS disease or respiratory impairment.

- In addition to the above, meperidine has the following warnings and precautions:[10]
    - Convulsions: use may aggravate preexisting convulsions in patients with convulsive disorders.
    - Prolonged use may increase the risk of toxicity from the accumulation of metabolites.
    - Do not use in pregnancy prior to the labor period.

Drug Interactions

Table 11. Drug Interactions[4]

Drug	Interacting Medication	Potential Result
Codeine, dihydrocodeine, hydrocodone, hydromorphone, meperidine, morphine, oxycodone, oxymorphone, tapentadol	Naltrexone	Naltrexone may decrease or attenuate the pharmacologic effects of opiate agonists. Coadministration of naltrexone and opiate agonists may precipitate withdrawal symptoms in individuals who are physically dependent on opioid drugs.
Codeine, dihydrocodeine, hydrocodone, hydromorphone, meperidine, morphine, oxycodone, oxymorphone	Barbiturate anesthetics	The combination of barbiturate anesthetics and opiate agonists may result in increased respiratory and central nervous system depressive effects. Additive pharmacologic effects may produce increased clinical effects.
Codeine, dihydrocodeine, hydrocodone, hydromorphone, meperidine, morphine, oxycodone, oxymorphone	Rifamycins	Rifamycins may decrease pharmacologic effects and plasma concentrations of opiate agonists. Pain control may be decreased.
Codeine, dihydrocodeine, hydrocodone, hydromorphone, meperidine, morphine, oxycodone, oxymorphone	Sodium oxybate	Concurrent use of sodium oxybate and opiate agonists may result in an increase in sleep duration and central nervous system depression. Pharmacologic effects of sodium oxybate and opiate agonists may be additive.
Codeine, hydrocodone, hydromorphone, meperidine, morphine, oxycodone, oxymorphone	Buprenorphine	Mixed agonist/antagonist opioids may decrease the effects of opiate agonists via competition or antagonism at various opioid receptor sites. Opioid withdrawal symptoms in opioid-dependent patients may occur if buprenorphine therapy is not initiated properly.
Oxycodone, sufentanil	Azole antifungal agents	Pharmacologic effects and adverse reactions of opiates may be increased due to inhibition of CYP3A4 metabolism by azole antifungals.

Drug	Interacting Medication	Potential Result
Acetaminophen	Anticoagulants	The hypoprothrombinemic effects of anticoagulants may be increased by acetaminophen in a dose-dependent manner. Bleeding may occur, especially when acetaminophen use exceeds 2,000 mg daily or is prolonged for several days.
Acetaminophen	Isoniazid	Isoniazid may increase the toxic effects of acetaminophen. The mechanism of this interaction is unknown.
Aspirin	Anticoagulants	The use of anticoagulants with aspirin may increase the risk of bleeding, especially gastrointestinal bleeding. However, when low-dose aspirin is used with anticoagulants, the therapeutic benefit may outweigh the risk of minor bleeding.
Aspirin	Carbonic anhydrase inhibitors	Aspirin may increase the toxic effects of carbonic anhydrase inhibitors; Carbonic anhydrase inhibitors may decrease the pharmacologic effects of aspirin.
Aspirin	Direct thrombin inhibitors	Use of direct thrombin inhibitors with aspirin may increase the risk of bleeding. Inhibition of the clotting cascade by multiple mechanisms may increase the risk of bleeding.
Aspirin	Heparin and factor Xa inhibitors	The risk of bleeding in heparin and factor Xa inhibitors treated patients may be increased by aspirin due to additive anticoagulant effects.
Aspirin	Meglitinides	Hypoglycemic effects of meglitinides may be increased by aspirin. The mechanism of action in unknown.
Aspirin	Nonsteroidal anti-inflammatory drugs	Regular use of nonsteroidal anti-inflammatory drugs may decrease the antiplatelet effects of aspirin. Reduced antiplatelet efficacy in patients with underlying cardiovascular risk may occur. Additionally, the potential for gastrointestinal side effects, including bleeding, may be increased with regular use of full-dose aspirin.
Aspirin	Serotonin reuptake blockers	The risk of upper gastrointestinal bleeding may be increased with concurrent administration of aspirin and serotonin reuptake blockers. The mechanism of action is unknown.
Aspirin	Celecoxib	Aspirin and celecoxib may cause additive adverse effects when co-administered. An increased rate of gastrointestinal ulceration or other complications may occur. Additive toxicity may occur.
Aspirin	Clopidogrel	The risk of life-threatening bleeding such as intracranial or gastrointestinal hemorrhage may be increased in high-risk patients with transient ischemic attack or ischemic stroke when given the combination of clopidogrel with aspirin.
Aspirin	Methotrexate	Therapeutic and toxic effects (bone marrow depression, hepatotoxicity) of methotrexate may be increased by concurrent use of aspirin. Aspirin may inhibit renal excretion of methotrexate and displace it from plasma protein binding sites.
Aspirin	Probenecid	The uricosuric action of probenecid is decreased. Hyperuricemia with possible exacerbation of gout may occur. The effects of this interaction depend on the dose of aspirin.
Aspirin	Sulfinpyrazone	The uricosuric effect of sulfinpyrazone may be decreased. Hyperuricemia with possible exacerbation of gout may occur. The effects of this interaction depend on the dose of aspirin.
Butalbital	Anticoagulants	Butalbital may decrease the hypoprothrombinemic effects of anticoagulants. Induction of hepatic microsomal enzymes by butalbital may increase the metabolism of anticoagulants. Butalbital may decrease the gastrointestinal absorption of

Drug	Interacting Medication	Potential Result
		dicumarol.
Butalbital	Corticosteroids	Pharmacologic effects of corticosteroids may be decreased with possible exacerbation of the disease being treated. Induction of hepatic microsomal enzymes by butalbital may increase the metabolic elimination of corticosteroids.
Butalbital	Estrogens	Butalbital may decrease the pharmacologic effects of estrogens with potential subsequent reductions of contraceptive or non-contraceptive estrogen efficacy. Butalbital may increase hepatic metabolism of estrogens.
Butalbital	Clozapine	Butalbital may decrease pharmacologic effects and plasma concentrations of clozapine. The mechanism of this interaction is unknown.
Butalbital	Doxycycline	The antimicrobial effectiveness of doxycycline may be decreased. Induction of hepatic microsomal enzymes by butalbital may increase the metabolic elimination of doxycycline.
Butalbital	Metronidazole	The antimicrobial effectiveness of metronidazole may be decreased. Induction of hepatic microsomal enzymes by butalbital may increase the metabolic elimination of metronidazole.
Butalbital	Tacrolimus	Plasma concentrations and pharmacologic effects of tacrolimus may be decreased. Increased hepatic metabolism via CYP3A4 of tacrolimus by butalbital may occur.
Butalbital	Teniposide	The therapeutic and toxic effects of teniposide may be decreased by butalbital. The mechanism of this interaction in unknown.
Butalbital	Theophyllines	Pharmacologic effects of theophyllines may be decreased by butalbital. Decreased theophylline plasma concentrations, possibly with a suboptimal therapeutic response, may occur. Hepatic metabolism of theophyllines may be increased by butalbital.
Codeine	Quinidine	Quinidine may decrease pharmacologic effects of codeine. Loss of analgesic effect may occur.
Dihydrocodeine	Human immuno-deficiency virus protease inhibitors	Human immunodeficiency virus protease inhibitors may increase plasma concentrations and pharmacologic effects of opiate agonists. Severe respiratory depression may occur. Inhibition of cytochrome P450 3A4 isoenzymes by Human immunodeficiency virus protease inhibitors may decrease the metabolic elimination of opiate agonists.
Fentanyl	Serotonin reuptake blockers	Toxic effects of serotonin reuptake blockers may be increased by fentanyl resulting in development of serotonin syndrome.
Ibuprofen	Angiotensin-converting-enzyme inhibitor inhibitors	The antihypertensive effects of Angiotensin-converting-enzyme inhibitor inhibitors may be decreased by ibuprofen. Also, the risk Angiotensin-converting-enzyme inhibitor inhibitors or ibuprofen-related nephrotoxicity, including hyperkalemia, may be increased by this drug combination.
Ibuprofen	Anticoagulants	The use of anticoagulants with ibuprofen may increase the risk of bleeding. Ibuprofen may impair platelet function and irritate the gastrointestinal mucosa leading to an increased risk of hemorrhage.
Ibuprofen	Bisphosphonates	Gastrointestinal adverse effects may be increased with

Drug	Interacting Medication	Potential Result
		concurrent administration of bisphosphonates and ibuprofen. The mechanism is unknown.
Ibuprofen	Heparin and factor Xa inhibitors	The risk of bleeding in heparin and factor Xa inhibitors treated patients may be increased by ibuprofen due to additive anticoagulant effects.
Ibuprofen	Loop diuretics	Diuretic effects of loop diuretics may be decreased by ibuprofen. Sodium retention and hypervolemia may occur. Ibuprofen may decrease natriuresis and diuresis of loop diuretics by inhibiting the synthesis of renal prostaglandins.
Ibuprofen	Salicylates	Regular use of ibuprofen may decrease the antiplatelet effects of salicylates. Reduced antiplatelet efficacy in patients with underlying cardiovascular risk may occur. Additionally, the potential for gastrointestinal side effects, including bleeding, may be increased with regular use of full-dose aspirin.
Ibuprofen	Thienopyridines	Use of ibuprofen with thienopyridines may increase the risk of bleeding. Ibuprofen-induced alteration in gastric mucosal function coupled with inhibition of platelet aggregation by thienopyridines may further increase the risk of gastrointestinal bleeding compared to ibuprofen alone.
Ibuprofen	Cyclosporine	Combination therapy with cyclosporine and ibuprofen may increase the probability and severity of renal impairment. Plasma concentrations of cyclosporine and ibuprofen may be increased.
Ibuprofen	Lithium	Pharmacologic effects of lithium may be increased. Elevated lithium serum concentrations and toxicity characterized by gastrointestinal symptoms, polyuria, muscular weakness, lethargy, and tremor may occur.
Ibuprofen	Methotrexate	Plasma concentrations and toxic effects of methotrexate may be increased by ibuprofen. Severe toxicity characterized by bone marrow suppression, nephrotoxicity and mucositis has occurred in patients receiving ibuprofen high-dose methotrexate chemotherapy.
Ibuprofen	Probenecid	Pharmacologic and toxic effects of ibuprofen may be increased by probenecid.
Meperidine	Human immuno-deficiency virus protease inhibitors	Cardiac, hematologic, neurologic (seizures), or other potentially serious toxicities are listed in the manufacturer's package labeling when meperidine and human immunodeficiency virus protease inhibitors are coadministered. The mechanism is unknown.
Meperidine	Monoamine oxidase inhibitors	A severe and potentially fatal reaction may occur shortly after administering meperidine to patients receiving monoamine oxidase inhibitors.
Meperidine	Phenothiazines	Excessive or prolonged central nervous system depression, respiratory depression and hypotension may occur, when phenothiazines and meperidine are used concomitantly.
Meperidine	Serotonin reuptake inhibitors	Risk of serotonin syndrome may be increased due to an unknown mechanism. Monitor closely for adverse reactions.
Meperidine	Sibutramine	Use of sibutramine with opiate agonists has been reported by the manufacturer of sibutramine to increase the potential risk for serotonin syndrome. The mechanism is unknown.
Tapentadol	Monoamine	Toxic effects may be increased with concurrent administration

Drug	Interacting Medication	Potential Result
	oxidase inhibitors	of tapentadol and monoamine oxidase inhibitors. Serious and sometimes fatal reactions have occurred. Pharmacologic effects of tapentadol and monoamine oxidase inhibitors may be additive.

Dosage and Administration

Table 12. Dosing and Administration[5,7-25]

Drug	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Butorphanol	Management of moderate to severe pain in patients where an opioid analgesic is appropriate: Injection: IV, 1 mg IV every three to four hours as needed; IM, 2 mg IM every three to four hours as needed; pre-op, 2 mg IM given 60 to 90 minutes before surgery Nasal spray: one spray (1 mg) in one nostril, an additional dose within 60 to 90 minutes may be given if adequate pain relief is not achieved, the two-dose sequence can be given every three to four hours as needed.	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Injection: 1 mg/mL 2 mg/mL Nasal spray: 10 mg/mL
Codeine	Relief of mild to moderate pain: Solution, tablet: 15 to 60 mg every four to six hours	Safety and efficacy have not been established in patients less than 18 years of age.	Solution: 30 mg/5 mL Tablet: 15 mg 30 mg 60 mg
Hydromorphone	Management of moderate to severe pain in patients where an opioid analgesic is appropriate: Injection: 1 to 2 mg SC or IM every four to six hours, if given IV, inject slowly over at least two to three minutes. Liquid: 2.5 to 10 mg every three to six hours as directed Rectal suppository: one suppository inserted every six to eight hours	Safety and efficacy in the children have not been established.	Injection: 1 mg/mL 2 mg/mL 4 mg/mL 10 mg/mL 250 mg Liquid: 1 mg/mL Rectal suppository: 3 mg Tablet: 2 mg 4 mg

Drug	Adult Dose	Pediatric Dose	Availability
	Tablet: 2 to 4 mg every four to six hours as necessary		8 mg
Meperidine	Management of moderate to severe pain in patients where an opioid analgesic is appropriate: Injection: 50 to 150 mg IM or SC every three to four hours as necessary Solution, tablet: 50 to 150 mg every three to four hours as necessary	Safety and efficacy in the children have not been established.	Injection: 10 mg/mL 25 mg/0.5 mL 25 mg/mL 50 mg/mL 75 mg/mL 75 mg/1.5 mL 100 mg/mL 100 mg/2 mL Solution: 50 mg/5 mL Tablet: 50 mg 100 mg
Morphine	Management of moderate to severe pain in patients where an opioid analgesic is appropriate: Injection: 5 to 20 mg SC or IM every four hours Solution, tablet: 5 to 30 mg every four hours Rectal suppository: 10 to 20 mg every four hours	Safety and efficacy have not been established in patients less than 18 years of age.	Epidural: 10 mg/mL Injection: 0.5 mg/mL 1 mg/mL 2 mg/mL 4 mg/mL 5 mg/mL 8 mg/mL 10 mg/mL 15 mg/mL 15 mg/1.5 mL 25 mg/mL 30 mg/30 mL 50 mg/mL 100 mg/4 mL 100 mg/0.1 L 150 mg/30 mL 250 mg/10 mL 250 mg/250 mL Rectal suppository: 5 mg 10 mg 20 mg 30 mg Solution 10 mg/5 mL 20 mg/mL 20 mg/5 mL Tablet: 15 mg 30 mg

Drug	Adult Dose	Pediatric Dose	Availability
Oxycodone	Management of moderate to severe pain in patients where an opioid analgesic is appropriate: Capsule, oral concentrate, solution, tablet: 5 to 15 mg every four to six hours	Safety and efficacy in the children have not been established.	Capsule: 5 mg Oral concentrate: 20 mg/mL Solution: 5 mg/5 mL Tablet: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg
Oxymorphone	Relief of moderate to severe pain: Tablet: 10 to 20 mg every four to six hours Injection: initial, SC or IM, 1 to 1.5 mg every four to six hours; IV, 0.5 mg; titrate to adequate pain relief	Safety and efficacy have not been established in patients ≤18 years of age.	Injection: 1 mg/mL Tablet: 5 mg 10 mg
Tapentadol	Management of moderate to severe acute pain in adults: Tablet (IR): 50 to 100 mg every four to six hours	Safety and efficacy have not been established in patients ≤18 years of age.	Tablet (IR): 50 mg 75 mg 100 mg
Combination Products			
Codeine/ acetaminophen	Relief of mild to moderate pain: Elixir, suspension: 15 mL every four hours Tablet: 0.5 to two tablets every four hours	Relief of mild to moderate pain: Suspension: three to six years of age, 5 mL three to four times daily; seven to 12 years of age, 10 mL three to four times daily; >12 years of age, 15 mL four times daily as needed to a maximum of 4,000 mg of acetaminophen/ 24 hours Elixer: seven to 12 years of age, 10 mL three to four times daily; >12 years of age, 15 mL four times daily as needed to a	Elixir: 12/120 mg/5 mL Suspension: 12/120 mg/5 mL Tablet: 15/300 mg 30/300 mg 60/300 mg 30/650 mg 60/650 mg

Drug	Adult Dose	Pediatric Dose	Availability
		maximum of 4,000 mg of acetaminophen/24 hours	
Codeine/butalbital/ acetaminophen/ caffeine	Relief of tension or muscle contraction headache: Capsule: one or two capsules every four hours	Safety and efficacy in the children have not been established.	Capsule: 30/50/325 mg
Codeine/ butalbital/aspirin/ caffeine	Relief of tension or muscle contraction headache: Capsule: one or two capsules every four hours	Safety and efficacy in the children have not been established.	Capsule: 30/50/325 mg
Codeine/ carisoprodol/aspirin	Relief of discomfort associated with acute, painful musculoskeletal conditions in adults: Tablet: one or two tablets four times daily	Safety and efficacy in pediatric patients below the age of 16 have not been established.	Tablet: 16/200/325
Dihydrocodeine/ acetaminophen/ caffeine	Relief of moderate to moderately severe pain: Capsule: two capsules every four hours Tablet: one tablet every four hours	Safety and efficacy in the children have not been established.	Capsule: 16/356/30 mg Tablet: 32/713/60 mg
Dihydrocodeine/ aspirin/caffeine	Relief of mild to moderate pain: Capsule: one to two capsules every four to six hours	Safety and efficacy in the children have not been established.	Capsule: 16/356/30 mg
Hydrocodone/ acetaminophen	Relief of moderate to moderately severe pain: Capsule, tablet: one to two every four to six hours; 7.5/300 and 10/300 mg tablets, one every four six hours Solution: 15 mL every four to six hours; 10/300 mg/15 mL solution, 11.25 mL every four to six hours	Safety and efficacy in the children have not been established.	Capsule: 5/500 mg Solution: 2.5/167 mg/5 mL 5/334 mg/10 mL 7.5/325 mg/15 mL 7.5/500 mg/15 mL 10/300 mg/15 mL 10/325 mg/15 mL Tablet: 2.5/500 mg 5/300 mg 5/325 mg 5/400 mg 5/500 mg 7.5/300 mg 7.5/325 mg 7.5/400 mg 7.5/500 mg 7.5/650 mg 7.5/750 mg 10/300 mg

Drug	Adult Dose	Pediatric Dose	Availability
			10/325 mg 10/400 mg 10/500 mg 10/650 mg 10/660 mg 10/750 mg
Hydrocodone/ ibuprofen	Short-term (<10 days) management of acute pain: Tablet: one tablet every four to six hours	Safety and efficacy in pediatric patients below the age of 16 have not been established.	Tablet: 2.5/200 mg 5/200 mg 7.5/200 mg 10/200 mg
Oxycodone/ acetaminophen	Relief of moderate to moderately severe pain: Capsule, tablet: one to two capsules or tablets every six hours Solution: 5 to 10 mL every six hours	Safety and efficacy in the children have not been established.	Capsule: 5/500 mg Solution: 5/325 mg/5 mL Tablet: 2.5/325 mg 5/300 mg 5/325 mg 5/400 mg 5/500 mg 7.5/300 mg 7.5/325 mg 7.5/400 mg 7.5/500 mg 10/300 mg 10/325 mg 10/400 mg 10/500 mg 10/650 mg
Oxycodone/aspirin	Relief of moderate to moderately severe pain: Tablet: one tablet every six hours	Should not be administered to pediatric patients.	Tablet: 4.8355/325 mg
Oxycodone/ ibuprofen	Short term (<7 days) management of acute, moderate to severe pain: Tablet: one tablet every six hours	Safety and efficacy in pediatric patients below the age of 14 have not been established.	Tablet: 5/400 mg

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.

Table 13. Clinical Guidelines

Clinical Guideline	Recommendations
National Comprehensive Cancer Network: **Adult Cancer Pain**	• 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

Clinical Guideline	Recommendations
(2013)[72]	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 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

Clinical Guideline	Recommendations
	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 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

Clinical Guideline	Recommendations
	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. • 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

Clinical Guideline	Recommendations
	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)**[73]	• 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. • 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

Clinical Guideline	Recommendations
	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)**[74]	• 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 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

Clinical Guideline	Recommendations
	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 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

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>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.</td></tr>
<tr><td>Treatment Guidelines from The Medical Letter:
Drugs for Pain (2013)[75]</td><td>• 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 nervous system toxicity and the availability of less toxic, longer-acting alternatives.
• Tolerance to most of the adverse events of opioids, including respiratory and central nervous system 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)[76]</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>Pharmacologic</td><td>Acetaminophen</td><td>Yes</td><td>Yes</td></tr>
</table></td></tr>
</table>

Clinical Guideline	Recommendations

Therapy	Tricyclic antidepressants	No	Yes
	Benzodiazepines	Yes	Yes
	NSAIDs	Yes	Yes
	Skeletal muscle relaxants	Yes	No
	Tramadol, opioids	Yes	Yes
Non-pharmacologic Therapy	Acupuncture	No	Yes
	Cognitive behavior therapy	No	Yes
	Exercise therapy	No	Yes
	Massage	No	Yes
	Progressive relaxation	No	Yes
	Spinal manipulation	Yes	Yes
	Yoga	No	Yes
	Intensive interdisciplinary rehabilitation	No	Yes

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.
- 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**

<u>Nonpharmacologic recommendations for the management of hand osteoarthritis</u>

- It is recommended that health professionals should:
  - Evaluate the ability to perform activities of daily living.
  - Instruct in joint protection techniques.
  - Provide assistive devices, as needed, to help patients perform activities of daily living.
  - Instruct in use of thermal modalities.
  - Provide splints for patients with trapeziometacarpal joint osteoarthritis.

Clinical Guideline	Recommendations
Knee (2012)[77]	Pharmacologic recommendations for the initial management of hand osteoarthritis • 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. Nonpharmacologic recommendations for the management of knee osteoarthritis • 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 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

Clinical Guideline	Recommendations
	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: 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. <u>Pharmacologic recommendations for the initial management of hip osteoarthritis</u> • It is conditionally recommend that patients with hip osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Tramadol.

Clinical Guideline	Recommendations
	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)**[78]	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 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**	Painful polyneuropathy • Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the

Clinical Guideline	Recommendations
Pharmacological Treatment of Neuropathic Pain (2010)[79]	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. • 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)**[80]	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,

Clinical Guideline	Recommendations
	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)**[81]	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 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**	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

Clinical Guideline	Recommendations
(2005)[82]	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)**[83]	• 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)**[84]	• 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

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. 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 short-acting opioids that are available as single entity agents and combination products for the treatment of pain. 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.

Short acting opioid analgesics are available as single entity and in combination with acetaminophen, aspirin, butalbital, caffeine and ibuprofen. Acetaminophen, aspirin and ibuprofen are non-opiate analgesics. Butalbital is a barbiturate, which has anxiolytic and muscle relaxant properties. Caffeine is an analgesic adjuvant, as well as a central nervous system stimulant. Carisoprodol is a centrally-acting muscle relaxant.[4,5]

Overall, clinical trials have demonstrated opioids to be more efficacious than placebo for both pain and function outcomes in patients with nociceptive, neuropathic pain or fibromyalgia.[62,65] Systematic reviews and meta-analyses have similar safety and level of analgesia between hydromorphone, morphine, oxycodone and oxymorphone in the management of cancer, non-cancer and acute pain.[59-61,63,64,70,71] The results of randomized controlled trials have generally demonstrated a comparable level of analgesia between codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen and oxycodone/acetaminophen in the management of pain.[42,49,50,52-54]

As a rule, opioids are contraindicated in patients with a hypersensitivity to the active ingredient or any component, respiratory depression, acute or severe bronchial asthma or suspected or documented paralytic ileus. Opioids have an associated abuse potential and can cause cardiovascular effects, respiratory depression and significant central nervous system depression, especially when used with other central nervous system depressants. The most frequently reported adverse events are light-headedness, dizziness, sedation, nausea and vomiting.[5,7-25] Clinical guidelines have been published addressing pain associated with back pain, cancer pain, neuropathic pain and osteoarthritis pain. These guidelines make recommendations for the specific place in therapies for opioids as a class but do not make any recommendations of the use of one agent over another.[72-84]

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