



Short-Acting Narcotic Analgesics Review

Therapeutic Class Review (TCR)

March 5, 2014

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FDA-APPROVED INDICATIONS

Drug	Federal Schedule	Manufacturer	Indication(s)
butalbital compound/codeine	CIII	generic	Tension or muscle contraction headache
butorphanol NS	CIV	generic	Management of pain when the use of an opioid analgesic is appropriate
codeine	CII	generic	Mild to moderately severe pain In combination with other respiratory agents for the reduction of cough
codeine/acetaminophen (Tylenol #3, Tylenol #4, Capital, Cocet)	CIII	generic	Mild to moderate pain
dihydrocodeine bitartrate/acetaminophen/caffeine (Panlor® SS, Trezix) ¹	CIII	generic, Wraser	Moderate to moderately severe pain
dihydrocodeine bitartrate aspirin/caffeine (Synalgos DC®) ²	CII	Caraco	Moderate to moderately severe pain
fentanyl sublingual (Abstral®) ³	CII	Galena Biopharma	Breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain
fentanyl oral transmucosal (Actiq®) ⁴	CII	generic, Cephalon	
fentanyl buccal (Fentora®) ⁵	CII	Cephalon	
fentanyl nasal spray (Lazanda®) ⁶	CII	Depomed	
fentanyl buccal (Onsolis™) ⁷	CII	Meda	
fentanyl sublingual spray (Subsys®) ⁸	CII	Insys Therapeutics	
hydrocodone/acetaminophen (Hycet®) ⁹	CIII	Eclat Pharmaceuticals	Moderate to moderately severe pain
hydrocodone/acetaminophen (Zydone®) ¹⁰	CIII	Endo	
hydrocodone/acetaminophen (Zamicet™) ¹¹	CIII	Hawthorn	
hydrocodone/acetaminophen (Zolvit™) ¹²	CIII	Atley	
hydrocodone/acetaminophen (Lorcet, Lortab, Margesic H, Maxidone, Norco, Vicodin/ES/HP) ¹³	CIII	generic	

FDA-Approved Indications (continued)

Drug	Federal Schedule	Manufacturer	Indication(s)
hydrocodone/ibuprofen (Ibudone™, Vicoprofen) ¹⁴	CIII	Poly Pharmaceuticals	Short-term management of acute pain
hydrocodone/ibuprofen (Reprexain™) ¹⁵	CIII	Quinnova	
hydromorphone (Dilaudid®) ¹⁶	CII	generic, Purdue	Management of pain in patients where an opioid analgesic is appropriate
levorphanol	CII	generic	Moderate to severe pain
meperidine (Demerol) ¹⁷	CII	generic	Moderate to severe pain
morphine immediate-release ¹⁸	CII	generic	Moderate to severe acute and chronic pain
oxycodone immediate-release (Oxecta™) ¹⁹	CII	King Pharmaceuticals	Moderate to severe acute and chronic pain
oxycodone (Dazidox, OxyIR, Roxicodone)	CII	generic	Moderate to severe pain
oxycodone/acetaminophen (Endocet, Magnacet, Percocet, Primlev, Roxicet, Tylox, Xolox)	CII	generic	
oxycodone/aspirin (Endodan, Percodan)	CII	generic	
oxycodone/ibuprofen (Combunox®) ²⁰	CII	generic	Short term (seven days or less) treatment of acute, moderate to severe pain
oxymorphone IR (Opana®) ²¹	CII	generic	Moderate to severe acute pain
pentazocine/acetaminophen ²²	CIV	generic	Mild to moderate pain
pentazocine/naloxone ²³	CIV	generic	Moderate to severe pain
tapentadol (Nucynta™) ²⁴	CII	Janssen	Relief of moderate to severe acute pain
tramadol (Rybix™ ODT) ²⁵	Not scheduled	Shionogi	Management of moderate to moderately severe pain in adults
tramadol (Ultram®) ²⁶	Not scheduled	generic, Janssen	Management of moderate to moderately severe pain in adults
tramadol/acetaminophen (Ultracet®) ²⁷	Not scheduled	generic, Janssen	Short term (five days or less) treatment of acute pain

Hydrocodone combination products are under review for possible Federal Schedule promotion from III to II. In early December 2013, the FDA submitted a formal recommendation to the Department of Health & Human Services to make the change. However, the Drug Enforcement Agency (DEA) will make the final decision regarding appropriate scheduling of hydrocodone-containing presentations. Meperidine should only be used for the acute treatment of moderate to severe pain. It should not be used for the treatment of chronic pain. Prolonged use can increase the risk of toxicity (e.g., seizures) from the accumulation of the metabolite, normeperidine.

OVERVIEW

Pain is often under-treated, and pain management is greatly misunderstood. Different management techniques are utilized for acute and chronic pain. It has been cited in studies that up to 73 percent of hospitalized medical patients receiving opiates were found in severe or moderate distress despite their analgesic regimen.²⁸ Caregivers' misconceptions regarding opiate doses, duration of analgesic effect, and fear of addiction were partly responsible for this under-treatment in both hospital and ambulatory care settings.²⁹

The World Health Organization's (WHO) guidelines for cancer pain management recommend a three-stepped approach with consideration for the type of pain and response to therapy.^{30,31} Therapy for mild pain should include non-opioid analgesics, such as acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs). For mild to moderate pain, oral combinations of acetaminophen and NSAIDs with opioids are recommended. For moderate to severe pain, opioid analgesics are the mainstay.

The American Pain Society does not distinguish amongst the available products in their 2009 clinical guidelines for the use of chronic opioid therapy for the treatment of chronic non-cancer pain.³² Titration of dose and frequency should be individualized to the patient's response and experience of adverse effects.

A FDA Advisory Committee in 2009 recommended that all propoxyphene-containing products be removed from the market based on their low benefit-to-risk ratio. In 2010, the FDA enforced this recommendation and requested that manufacturers of propoxyphene-containing products remove them from the market.

PHARMACOLOGY^{33,34,35,36,37,38,39,40,41,42,43,44,45,46,47}

Opioid agonists reduce pain by acting primarily through interaction with opioid mu-receptors located in the brain, spinal cord, and smooth muscle. The primary site of therapeutic action is the central nervous system (CNS). Stimulation at this receptor produces supraspinal analgesia, respiratory depression, euphoria, and physical dependence. Opioid agonists produce respiratory depression by direct action on the brain stem respiratory center.

The opioid agents in this review can be divided into full agonists and mixed agonist/antagonists. The weaker full agonists, such as hydrocodone, codeine, and tramadol, are often prescribed in combination with nonopioid analgesics. Strong full agonists such as fentanyl, meperidine, morphine, hydromorphone, oxymorphone, levorphanol, and oxycodone are generally used for treatment of moderate to severe pain.

Butorphanol and pentazocine are mixed agonist-antagonist agents. They are both weak antagonists at μ -receptors and agonists at kappa-receptors. Due to their action at the kappa-receptors, these agents may produce dysphoric effects and increased blood pressure and heart rate in some individuals. Due to their opioid antagonist properties, there is a ceiling on the analgesic effects of pentazocine and butorphanol.

Tramadol (Rybix ODT, Ultram, and Ultracet) are centrally acting analgesics with dual opioid and nonopioid mechanisms. In addition to activity at opioid receptors, tapentadol (Nucynta) inhibits norepinephrine re-uptake and tramadol weakly inhibits norepinephrine and serotonin re-uptake.

Aspirin and NSAIDs work by blocking cyclooxygenase (COX)-1 and COX-2, which prevent the synthesis of various prostaglandins. These prostaglandins are partially responsible for the development of pain and inflammation.

The exact mechanism of action for acetaminophen is unknown, but it mediates its actions centrally. Acetaminophen is thought to act primarily in the CNS and increase the pain threshold by inhibiting COX-1 and COX-2. Unlike NSAIDs, acetaminophen does not inhibit cyclooxygenase in peripheral tissues. Acetaminophen may also decrease sensitization of pain receptors to mechanical or chemical stimulation.⁴⁸

Caffeine causes cerebral vasoconstriction, which decreases blood flow and oxygen tension. In combination with acetaminophen, caffeine may provide a quicker onset of action and enhance pain relief allowing for lower doses of analgesics.⁴⁹

Naloxone, an opioid antagonist, has no pharmacologic activity when administered orally at 0.5 mg. Studies in animals indicate that the presence of naloxone does not affect pentazocine analgesia when the combination is given orally. If the combination is given by injection, the action of pentazocine is neutralized.⁵⁰

PHARMACOKINETICS

Drug	Half-Life (hr)	Tmax (hr)	Excretion
Opioid Component			
butorphanol NS ⁵¹	4.7-6.6 (parent) 18 (metabolite)	0.6-1	Extensively metabolized; excreted in urine and feces
codeine ⁵²	3-4 (parent) 2 (metabolite-morphine)	No data available	Primarily urine
dihydrocodeine ^{53,54}	3.3-4.5	No data available	metabolized to active dihydromorphine; renally eliminated
fentanyl sublingual (Abstral) ⁵⁵	5-13.5	0.5-1	>90% metabolized and renally eliminated
fentanyl oral transmucosal (Actiq) ⁵⁶	3.2-6.4	0.33-0.67	>90% metabolized and renally eliminated
fentanyl buccal (Fentora) ⁵⁷	2.63 – 11.7	0.5 – 0.75	>90% metabolized and renally eliminated
fentanyl nasal spray (Lazanda) ⁵⁸	15.0-24.9	0.25-0.35	Primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites.
fentanyl sublingual spray (Subsys) ⁵⁹	5.25-11.99	1.25-0.69*	Primarily (>90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites
fentanyl buccal (Onsolis) ⁶⁰	14	1	>90% metabolized and renally eliminated
hydrocodone ^{61,62,63,64}	3.8	1.3 - 3	hydrocodone and metabolites renally eliminated
hydromorphone ⁶⁵	2.3	0.73	highly metabolized
levorphanol ⁶⁶	11-16	1	extensively metabolized and renally eliminated

Pharmacokinetics (continued)

Drug	Half-Life (hr)	Tmax (hr)	Excretion
Opioid Component (continued)			
meperidine ⁶⁷	3-4 (parent) 15-30 (metabolite)	2	highly metabolized; renally eliminated
morphine immediate-release ⁶⁸	2-15	0.5	extensively metabolized and renally eliminated
oxycodone ^{69,70}	3.1-3.7	1.3-2.1	primarily metabolized and renally eliminated
oxymorphone IR ⁷¹	7.3-9.4	No data available	highly metabolized; eliminated in urine and feces
pentazocine ⁷²	0.5-4	3.6	extensively metabolized and renally eliminated
tapentadol ⁷³	4	1.25	highly metabolized eliminated in urine
tramadol ^{74,75,76}	6.3 (tramadol) 7.4 (metabolites)	2-3	60 percent metabolized to active metabolites

*Data for Tmax presented as a range

Drug	Half-Life (hr)	Tmax (hr)	Excretion
Non-opioid Component			
butalbital ⁷⁷	35	No data available	metabolized eliminated in urine
acetaminophen ^{78,79,80,81}	1-3	1.2-3	highly metabolized and renally eliminated
aspirin ⁸²	0.25-0.3	2-3 (low dose) 15-30 (high dose)	highly metabolized and renally eliminated
caffeine ^{83,84}	No data available	3	highly metabolized and renally eliminated
ibuprofen ⁸⁵	1.8-2.6	1.6-3.1	highly metabolized renally excreted
naloxone ⁸⁶	2-3	1-3	highly metabolized and renally eliminated

CONTRAINDICATIONS/WARNINGS^{87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104}

These agents are contraindicated in patients with known hypersensitivity to opioids or other component of the product. Patients known to be hypersensitive to opioids may exhibit cross sensitivity in the class. Hydromorphone liquid formulation contains sodium metabisulfite which may cause allergic-type reactions in susceptible patients.

In general, opioids are contraindicated in patients who have acute or severe bronchial asthma or hypercarbia; situations of significant respiratory depression (in the absence of resuscitative equipment or monitors); and patients with known or suspected paralytic ileus. Agents containing butorphanol, hydrocodone, levorphanol, meperidine, and pentazocine do not list these conditions as contraindications, but warnings to use with caution if any of the conditions are present.

Hydromorphone (Dilaudid) liquid and 8 mg tablets are contraindicated in patients for obstetrical analgesia.

Opioids should be used with caution in patients with renal or hepatic impairment and dosage adjustments may be warranted depending on the specific agent and degree of impairment. Oxymorphone is contraindicated in patients with moderate or severe hepatic impairment.

Monoamine oxidase inhibitors (MAOI) can markedly potentiate the action of opioid agents, therefore opioid use is not recommended in patients currently taking MAOIs or within the previous 14 days. Caution should be observed in administering pentazocine to patients who are currently receiving MAOIs or who have received them within the preceding 14 days, due to potential CNS excitation and hypertension due to catecholamines effects.

Opioids may induce or aggravate seizures in some clinical settings, particularly in those patients with a history of seizure disorders. Concomitant use of tapentadol or tramadol-containing products with MAO inhibitors, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants (TCAs), triptans, linezolid, or lithium increases the risk of adverse events, including seizure and serotonin syndrome.

Tramadol-containing products are contraindicated in any situation where opioids are contraindicated including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids, or psychotropic drugs. Tramadol may worsen central nervous system and respiratory depression in these patients.

Oxycodone/ibuprofen (Combunox) and hydrocodone/ibuprofen (Ibudone, Repraxin, and Vicoprofen/ES/HP) are contraindicated in the treatment of peri-operative pain in the coronary artery bypass graft (CABG) setting. The black box warnings for NSAID-containing products cite the increased risk for adverse events seen with NSAID use such as serious cardiovascular thrombotic events, myocardial infarction, stroke, and gastrointestinal adverse events, all of which can be fatal.

Tramadol (Rybix ODT, Ultram) and tramadol/acetaminophen (Ultracet) are contraindicated in any situation where opioids are contraindicated including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids, or psychotropic drugs. Tramadol may worsen central nervous system and respiratory depression in these patients. Concomitant use of tramadol with MAO inhibitors or selective serotonin reuptake inhibitors (SSRIs) increases the risk of adverse events, including seizure and serotonin syndrome. Withdrawal symptoms may occur if

tramadol is discontinued abruptly. Clinical experience suggests that withdrawal symptoms may be avoided by tapering tramadol at the time of discontinuation.

Acetaminophen/caffeine/dihydrocodeine (Panlor SS) is contraindicated in patients with hypersensitivity to any of the components or in situations where opioids are contraindicated. These include significant respiratory depression, particularly in unmonitored settings or in the absence of resuscitation equipment, acute or severe bronchial asthma, hypercapnia, or paralytic ileus.

Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine. Codeine containing products including aspirin/caffeine/dihydrocodeine (Synalgos DC) are contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy.

All products in this class should be used with caution in patients who may be susceptible to intracranial effects of carbon dioxide retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be employed only if clinically warranted.

Opioids produce peripheral vasodilation which may result in orthostatic hypotension for some patients. Additionally, gastrointestinal opioid-induced effects may include a reduction in gastric, biliary, and pancreatic secretions.

Butorphanol and pentazocine can elevate blood pressure and heart rate. Particular caution should be exercised in conditions where alterations in vascular resistance and blood pressure might be particularly undesirable, such as in the acute phase of myocardial infarction.

Meperidine should be used with caution in patients with atrial flutter or other supraventricular tachycardias due to a possible vagolytic action that may produce a significant increase in ventricular response rate.

Opioids depress the cough reflex by direct effect on the cough center in the medulla. Caution should be exercised in postoperative use and in patients with pulmonary disease.

Other warnings instruct prescribers to be aware of the abuse potential of these products, the possibility of hypoventilation, the dangers to pediatric patients if used, and the increased risk of respiratory depression when used with CYP450 3A4 inhibitors. Impairment of physical and/or mental abilities, increased seizure risk, use of caution when performing hazardous tasks, respiratory depression, abuse potential, and increased sedation when used with other central nervous system depressants are also associated with opioid use. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Monitor for decreased bowel motility.

Opiate agonists can cause urinary retention and oliguria due to increased tension of the detrusor muscle. Patients more prone to these effects include those with prostatic hypertrophy, urethral stricture, bladder obstruction, or pelvic tumors. Drug accumulation or prolonged duration of action can occur in patients with renal impairment. Fentanyl buccal (Fentora) contains a black box warning regarding abuse potential; while both fentanyl buccal and fentanyl sublingual (Subsys) include a black box warning citing risks of respiratory depression and, when dispensing, there should be no substitution of any other fentanyl products.

Opioids inhibit the secretion of adrenocorticotrophic hormone (ACTH) and cortisol. Also, thyroid stimulating hormone may be stimulated or inhibited by opioids. Patients with adrenal insufficiency, thyroid disease (i.e., hypothyroidism), or myxedema may not be appropriate candidates for codeine administration.

Patients receiving therapeutic doses of pentazocine/apap have experienced hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. Visual blurring, dysphoria, and hallucinations have been reported rarely with butorphanol. Hallucinations, suicidal ideation, and panic attack have been reported in after-market surveillance of tapentalol (Nucynta).

Particular caution should be exercised in administering pentazocine to patients with porphyria since it may provoke an acute attack in susceptible individuals.

Opioid analgesics may cause tolerance and/or physical dependence with chronic use. Withdrawal symptoms may occur if these agents are discontinued abruptly and may be avoided by tapering opioid dosage at the time of discontinuation.

Due to their opioid antagonist properties, pentazocine and butorphanol can precipitate withdrawal symptoms in patients physically dependent on full agonists. Such patients should have an adequate period of withdrawal from opioid drugs prior to beginning butorphanol therapy.

Serotonin syndrome may occur with concomitant use of tapentalol and other drugs that impair the metabolism of serotonin, such as various antidepressants.

Fentanyl nasal spray (Lazanda) and fentanyl sublingual spray (Subsys) should not be used for acute or post-operative pain. On a microgram per microgram basis, fentanyl nasal spray and sublingual spray are not equivalent to any other fentanyl products due to differences in pharmacokinetics.

In 2009, an FDA Advisory Committee recommended that the FDA put more restrictions on acetaminophen use in an effort to curb overdoses that can cause liver failure and/or death. These recommendations include limiting single doses for adults to 650 mg, as well as a decrease to the current maximum total daily dose of 4,000 mg. The same committee moved that prescription products that combine acetaminophen with other medications should be eliminated.

As a follow-up to the FDA Advisory Committee recommendations, on January 13, 2011, the FDA asked manufacturers of prescription acetaminophen combination products to limit the maximum amount of acetaminophen in these products to 325 mg per tablet, capsule, or other dosage unit by January 1, 2014. The FDA believes that limiting the amount of acetaminophen per tablet, capsule, or other dosage unit in prescription products will reduce the risk of severe liver injury from acetaminophen overdosing, an adverse event that can lead to liver failure, liver transplant, and death. Many manufacturers voluntarily complied with the FDA's request; however, some prescription combination products containing more than 325 mg acetaminophen per dosage unit remain available. In the near future, the FDA will begin withdrawing approval of applicable combination products that remain on the market.

Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndromes of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma). Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye syndrome. Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks

involved with chronic, heavy alcohol use while taking aspirin. Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

Risk Evaluation and Mitigation Strategy (REMS)^{105,106,107,108,109,110,111,112}

Fentanyl sublingual (Abstral), fentanyl oral transmucosal (Actiq), and fentanyl buccal (Onsolis, Fentora) are dispensed with medication guides. Elements for safe use include certification for prescribers and dispensing pharmacies and assurance that these products will only be dispensed if conditions for use are safe (all enrollment criteria are met). The implementation system ensures that distributors are enrolled in the REMS program, as well. The manufacturer for fentanyl buccal must also execute a communication plan to prescribers that supports this program.

Due to the risk of misuse, abuse, addiction, and overdose related to transmucosal fentanyl formulations, these agents are only available through a restricted access program called Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program. Outpatient health providers including prescribers, pharmacies, and distributors must enroll in this program. In addition, outpatients must sign a Patient-Prescriber Agreement to ensure they understand the risks and benefits of therapy. Wholesalers and distributors must enroll in order and distribute only to authorized pharmacies.

Because of the risk for misuse, abuse, addiction, and overdose, fentanyl nasal spray (Lazanda) and fentanyl sublingual spray (Subsys) are available only through a restricted program, required by the FDA, called the TIRF REMS program. Under the TIRF REMS program, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program to prescribe, receive, dispense, and distribute the medications, respectively.

Oxycodone and morphine oral solution and tapentadol (Nucynta) are dispensed with a medication guide.

DRUG INTERACTIONS^{113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128}

All opioid agents should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, muscle relaxants, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Monoamine oxidase inhibitors (MAOI) may intensify the actions of opioid agents. Risk of seizure and serotonin syndrome is increased with concurrent use of fentanyl buccal (Fentora, Onsolis), fentanyl sublingual (Abstral), fentanyl transmucosal (Actiq), fentanyl nasal spray (Lazanda), fentanyl sublingual spray (Subsys), hydrocodone/acetaminophen (Hycet, Zamicet, Zolvit), hydrocodone/ibuprofen (Ibudone, Reprexain), and tapentadol (Nucynta) are not recommended for use within 14 days of a MAOI due to severe and unpredictable potentiation. Tramadol-containing products (Rybix ODT, Ultracet, and Ultram) should not be used with selective serotonin reuptake inhibitors (SSRIs, SNRIs, MAOIs, triptans, linezolid, or lithium) due to the risk of adverse effects including seizure and serotonin syndrome.

Fentanyl and tramadol are mainly metabolized by the CYP450 enzyme pathway; coadministration of these agents with CYP450 enzyme inducers or inhibitors may adversely affect their metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol;

concurrent administration of carbamazepine and tramadol is not recommended due to the increased tramadol metabolism by carbamazepine and because of the seizure risk associated with tramadol.

Patients taking cytochrome CYP450 enzyme inducers or inhibitors may demonstrate an altered response to codeine, therefore analgesic activity should be monitored. Acyclovir may increase the plasma concentration of meperidine and normeperidine. Ritonavir may increase the plasma concentration of normeperidine. Phenytoin may increase the metabolism and clearance of meperidine. Caution should be used with concomitant use of meperidine with any of these agents.

Concurrent use of medications with anticholinergic activity and opioid analgesics may result in increased risk of urinary retention and/or severe constipation and paralytic ileus.

CNS side effects have been reported (e.g., confusion, disorientation, respiratory depression, apnea, seizures) following coadministration of cimetidine with opioid analgesics; a causal relationship has not been established.

Agonist/antagonist analgesics (pentazocine, butorphanol) should be administered with caution to patients receiving a pure opioid agonist analgesic. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of the full opioid agonist and/or may precipitate withdrawal symptoms in these patients.

A slower onset can be anticipated if butorphanol tartrate nasal spray is administered concomitantly with, or immediately following, a nasal vasoconstrictor due to a decreased rate of absorption.

Co-administration of a vasoconstrictive nasal decongestant, such as oxymetazoline, to treat allergic rhinitis leads to lower peak plasma concentrations and a delayed T_{max} of fentanyl that may cause fentanyl nasal spray (Lazanda) to be less effective in patients with allergic rhinitis who use such decongestants, thus potentially impairing pain management.

Due to the ibuprofen component, hydrocodone/ibuprofen and oxycodone/ibuprofen (Combunox) are associated with interactions with ACE inhibitors, methotrexate, and warfarin that are more frequently seen with NSAID coadministration. Ibuprofen has been shown to reduce the natriuretic effect of furosemide and thiazides in some patients. Ibuprofen has been shown to elevate plasma lithium concentration and reduce renal lithium clearance.

Chronic and excessive consumption of alcohol may increase the hepatotoxic risk of acetaminophen. The potential for hepatotoxicity with acetaminophen also may be increased in patients receiving anticonvulsants that induce hepatic microsomal enzymes (including phenytoin, barbiturates, and carbamazepine) or isoniazid.

Aspirin may enhance the effects of anticoagulants and inhibit the uricosuric effects of uricosuric agents.

Caffeine may enhance the cardiac inotropic effects of beta-adrenergic stimulating agents. Coadministration of caffeine and disulfiram may lead to a substantial decrease in caffeine clearance. Caffeine may increase the metabolism of other drugs such as phenobarbital and aspirin. Caffeine accumulation may occur when products or foods containing caffeine are consumed concomitantly with quinolones, such as ciprofloxacin.

ADVERSE EFFECTS

Drug	Asthenia	Constipation	Dizziness	Dyspnea	Headache	Nausea	Rash	Somnolence	Vomiting
morphine immediate-release ¹²⁹	nr	reported	reported	nr	reported	reported	reported	reported	reported
acetaminophen/ caffeine/ dihydrocodeine bitartrate (Panlor SS, Trezix) ^{130,131}	nr	reported	reported	nr	nr	reported	nr	reported	reported
aspirin/caffeine/ dihydrocodeine bitartrate (Synalgos DC®) ¹³²	nr	reported	reported	nr	nr	reported	nr	reported	reported
fentanyl (Actiq) ¹³³	9-38	4-20	16-17	4-22	6-20	23-45	2-8	15-17	12-31
fentanyl (Abstral) ¹³⁴	reported	4.8	reported	0.6	3	6	reported	reported	reported
fentanyl (Fentora) ¹³⁵	11	12	13-19	9	9-10	17-29	<1	7-9	5-20
fentanyl (Lazanda) ¹³⁶	≥1	1-10	≥1	≥1	≥1	4-9	nr	≥1	7-13
fentanyl (Onsolis) ¹³⁷	13	11	7-11	12	9	14-26	reported	6-7	8-21
fentanyl (Subsys) ¹³⁸	9.7	5-10.4	7.2	10.4	≥1	10.4-13.1	nr	9.5	10.3-16
butalbital compound /codeine ¹³⁹	nr	nr	reported	nr	nr	reported	reported	reported	reported
butorphanol NS ¹⁴⁰	>1	>1	19	>1	>1	≤13	>1	43	≤13
codeine ¹⁴¹	nr	reported	reported	nr	reported	reported	reported	reported	reported
codeine/acetaminophen (Tylenol #3, Tylenol #4) ¹⁴²	nr	reported	reported	reported	nr	reported	reported	nr	reported
hydrocodone/ acetaminophen (Hycet, Lortab, Lorcet, Margesic H, Maxidone, Norco, Vicodin/ES/HP, Zamicet, Zolvit, Zydone) ^{143,144,145,146}	nr	reported	reported	reported	nr	reported	reported	reported	reported

Adverse Effects (continued)

Drug	Asthenia	Constipation	Dizziness	Dyspnea	Headache	Nausea	Rash	Somnolence	Vomiting
hydrocodone/ ibuprofen (Ibudone, Reprexain, Vicoprofen) ^{147,148}	3-9	22	14	<3	27	21	<1	22	3-9
hydromorphone (Dilaudid) ¹⁴⁹	reported	reported	reported	reported	reported	reported	reported	reported	reported
levorphanol ¹⁵⁰	nr	nr	reported	nr	nr	reported	reported	nr	reported
meperidine (Demerol) ¹⁵¹	reported	reported	reported	nr	reported	reported	reported	nr	reported
oxycodone (Dazidox, Oxecta, OxyIR, Roxicodone) ^{152,153}	≥3	≥3	≥3	<3	≥3	≥3	<3	≥3	≥3
oxycodone/acetaminophen (Endocet, Magnacet, Percocet, Primlev, Roxicet, Tylox, Xolox) ¹⁵⁴	reported	reported	reported	reported	reported	reported	reported	reported	reported
oxycodone/aspirin (Endodan, Percodan) ¹⁵⁵	reported	reported	reported	reported	reported	reported	reported	reported	reported
oxycodone/ibuprofen (Combunox) ¹⁵⁶	3.3	4.5	5.1-19.2	<1	10.2	8.8-25.4	<2	7.3-17.4	4.5-5.3
oxymorphone IR (Opana) ¹⁵⁷	<1	4	7	<1	7	19	<1	9	9
pentazocine/APAP ¹⁵⁸	reported	reported	reported	nr	reported	reported	reported	reported	reported
pentazocine/naloxone ¹⁵⁹	reported	reported	reported	nr	reported	reported	reported	reported	reported
tapentadol (Nucynta) ¹⁶⁰	nr	8	24	<1	reported	30	1	15	18
tramadol (Rybix ODT, Ultram) ^{161,162}	6-12	24-46	26-33	<1	18-32	24-40	1<5	16-25	9-17
tramadol/acetaminophen (Ultracet) ¹⁶³	>1	6	3	<1	>1	3	>1	6	>1

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

SPECIAL POPULATIONS^{164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184}

Pediatrics

Fentanyl buccal (Fentora, Onsolis), sublingual (Abstral), fentanyl nasal spray (Lazanda), fentanyl sublingual spray (Subsys), and tapentadol (Nucynta) are indicated for patients 18 years of age or older. Fentanyl transmucosal (Actiq) is approved for patients 16 years old or older. The safety and efficacy of tramadol-containing (Rybix ODT, Ultracet, Ultram) products in children under 16 years of age have not been studied, and their use is not recommended. Hydrocodone/ibuprofen (Ibudone, Reprexain, Vicoprofen) has no established safety and efficacy in patients less than 16 years of age. Oxycodone/ibuprofen (Combunox) is safe and effective in patients 14 years and older. The safety and efficacy of pentazocine-containing products in children under 12 years of age have not been established. Hydrocodone/acetaminophen (Hycet, Zamicet, Lortab Elixir only, Zolvit) has not been studied in patients younger than two years old. Hydrocodone/acetaminophen (Lorcet, Lortab tablets, Magesic H, Maxidone, Norco, Vicodin/ES/HP) has not been adequately studied in pediatric patients. The safety and efficacy of the remaining products in this review have not been established in the pediatric population.

Pregnancy

The products listed in this review are Pregnancy Category C, except oxycodone single-ingredient products (Dazidox, OxyIR, Roxicodone, Oxecta) which are Category B, and oxycodone/ibuprofen (Combunox) which is Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation.

Geriatrics

Opioid products should be used with caution in elderly patients due to greater sensitivity of primary effects and adverse effects. Doses should be titrated to provide adequate efficacy while minimizing risk.

Plasma levels of oxymorphone may be seen up to 40 percent higher in elderly patients over age 65 years than seen in younger patients. For elderly patients over 75 years old, total tramadol dose should not exceed 300 mg/day.

In the 2009 Management of Persistent Pain in Older Persons guideline, the American Geriatric Society (AGS) advises that in the elderly even pain that is causing severe impairment may not be spontaneously revealed for a variety of personal, cultural, or psychological reasons. Older persons may under report pain, but there are also inherent difficulties in recognizing pain experienced by patients with cognitive impairment.¹⁸⁵ However, all patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy and should be reassessed for ongoing attainment of therapeutic goals, adverse effects, and safe and responsible medication use. Tramadol has opioid activity with apparently low abuse potential and is reportedly about as effective and safe as codeine or hydrocodone. However, tramadol has the additional low risk of inducing seizures.

Hepatic and Renal Impairment

All agents in this review should be used with caution in patients with hepatic or renal impairment. Dosage reductions may be warranted.

Oxymorphone is contraindicated in patients with moderate to severe hepatic impairment.

Tapentadol should be used with caution in patients with moderate hepatic impairment. Patients with severe renal or hepatic impairment should not use tapentadol.

Tramadol should be given every 12 hours for patients with CrCl < 30mL/minute with a maximum dose of 200 mg per day. Patients with cirrhosis should receive tramadol 50 mg every 12 hours.

Other

Some individuals may be ultra-rapid metabolizers of codeine due to a specific CYP2D6 phenotype and may convert codeine into its active metabolite, morphine, more rapidly and completely resulting in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1 percent in Chinese and Japanese, 0.5 to 1 percent in Hispanics, 1 to 10 percent in Caucasians, 3 percent in African Americans, and 16 to 28 percent in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

Cardiac Disease

Fentanyl buccal, sublingual tablet/spray, transmucosal, and nasal spray should be used with caution in patients with bradyarrhythmias.

DOSAGES 186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204

Drug	Starting Dose	Dosing Instructions	Available Strengths
acetaminophen / caffeine / dihydrocodeine (Panlor SS, Trezix)	Panlor SS: One tablet every four hours Trezix: two capsules every four hours as needed	Panlor SS: Dosage should be adjusted to the severity of the pain and patient response. Dosage should not exceed one tablet in a four hour period or five doses in a 24 hour period. Trezix: Do not exceed ten capsules per 24 hours	Panlor SS tablets: acetaminophen 712.8mg / caffeine 60 mg / dihydrocodeine 32 mg Trezix capsules: acetaminophen 356.4mg / caffeine 30 mg / dihydrocodeine 16 mg
aspirin/caffeine/dihydrocodeine (Synalgos DC)	Two capsules every four hours as needed	Do not exceed ten capsules per 24 hours	Capsule aspirin 356.4mg/caffeine 30 mg/dihydrocodeine 16mg Tablet aspirin 712.8mg/caffeine 60mg/dihydrocodeine 32mg
fentanyl sublingual tablets (Abstral)	100 mcg as needed	Doses may be supplemented one time after 30 minutes. Do not use more than two doses per episode of breakthrough pain; wait two hours before treating another episode. Titrate to a successful dose and limit use to four episodes per day.	100 mcg 200 mcg 300 mcg 400 mcg 600 mcg 800 mcg
fentanyl oral transmucosal units (Actiq)	200 mcg as needed	Until the appropriate dose is reached, patients may find it necessary to use an additional unit during a single episode. If treatment of several consecutive breakthrough cancer pain episodes requires more than one unit per episode, an increase in dose to the next higher available strength should be considered. Patients must wait at least four hours before treating another episode of breakthrough pain.	200 mcg 400 mcg 600 mcg 800 mcg 1,200 mcg 1,600 mcg
fentanyl buccal tablets (Fentora)	100 mcg as needed*	Until the appropriate dose is reached, patients may find it necessary to use an additional unit during a single episode of breakthrough pain not relieved in 30 minutes. One tablet of the same dose may be taken. If pain is not relieved, patients must wait four hours before treating another episode of breakthrough pain. If treatment of several consecutive breakthrough cancer pain episodes requires more than one unit per episode, an increase in dose to the next higher available strength should be considered. *If patient is currently on Actiq see mfg dosing recommendations	100 mcg 200 mcg 300 mcg 400 mcg 600 mcg 800 mcg

Dosages (continued)

Drug	Starting Dose	Dosing Instructions	Available Strengths
fentanyl nasal spray (Lazanda)	100 mcg as needed	Individually titrate to an effective dose, from 100 mcg to 200 mcg to 400 mcg, and up to a maximum of 800 mcg, that provides adequate analgesia with tolerable side effects. Maximum dose is a single spray into one nostril or single spray into each nostril per episode; no more than four doses per 24 hours. Wait at least 2 hours before treating another episode of breakthrough pain with fentanyl nasal spray.	100 mcg 400 mcg
sublingual spray (Subsys)	100mcg as needed	Titrate as tolerated to an effective dose. One dose of Subsys should be used per breakthrough pain episode. If those cases where the pain may not be relieved within 30 minutes of the dose, one additional dose of the same strength may be used for that breakthrough episode. At least four hours must elapse prior to initiating treatment for another episode of pain. Maintenance dosing should not exceed four doses per 24 hours. Dose increase should be considered when several consecutive attempts to control breakthrough pain have failed.	100 mcg 200 mcg 400 mcg 600 mcg 800 mcg 1,200 mcg 1,600 mcg
fentanyl buccal soluble films (Onsolis)	200 mcg as needed	Titrate using 200 mcg increments (maximum of four 200 mcg films or a single 1,200 mcg film) to adequate analgesia without undue side effects. Not to exceed four doses per day, separated by at least two hours.	200 mcg 400 mcg 600 mcg 800 mcg 1,200 mcg
butalbital compound /codeine	One to two capsules every four hours	Do not exceed six capsules per day	Capsules: butalbital 50 mg / aspirin 325 mg/ caffeine 40 mg / codeine 30 mg
butorphanol NS	One spray into one or both nostrils. May repeat after three to four hours.	If one spray is administered and adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given. The initial 2-dose sequence may be repeated in 3 to 4 hours as required after the second dose of the sequence.	Solution: 10 mg/mL
codeine	15 to 60 mg every four to six hours as needed	Do not exceed 360 mg in 24 hours	Tablets: 15, 30, 60 mg
codeine/APAP (Tylenol #3, Tylenol #4, Capital, Cocet)	Tablet: one to two every four hours as needed Elixir: 15 mL every four hours	Do not exceed: codeine 60 mg per dose and 360 mg per day and acetaminophen 4 g per day	Tablet: codeine/ APAP - 15 mg/300 mg, 30 mg/ 300 mg, and 60 mg/ 300 mg, Cocet (60 mg/650mg) Elixir: codeine/ APAP – 12 mg/ 120 mg per 5 mL Syrup (Capital): codeine/APAP 12mg/120mg per 5 mL

Dosages (continued)

Drug	Starting Dose	Dosing Instructions	Available Strengths
hydrocodone / acetaminophen liquid (Hycet, Lortab, Zamicet) <small>205, 206, 207</small>	15 mL every four to six hours	Not to exceed 90 mL in 24 hours. See dosing chart in prescribing information for initial doses for children.	Hycet: hydrocodone 7.5 mg/ acetaminophen 325 mg per 15 mL Lortab: hydrocodone 7.5 mg/ acetaminophen 500 mg per 15 mL Zamicet: hydrocodone 10 mg/ acetaminophen 325 mg per 15 mL
hydrocodone / acetaminophen (Lorcet, Lortab, Margesic H, Maxidone, Norco, Vicodin ES/HP, Zydone)	One to two tablets every four to six hours	Not to exceed six tablets/capsules in 24 hours. For tablets/capsules that contain 8 mg hydrocodone, may take up to eight tablets per 24 hours. For tablets that contain 7.5 or 10 mg hydrocodone, take one tablet/capsule every four to six hours Maxidone: Do not exceed five tablets per day	Norco: hydrocodone 5, 10 mg/acetaminophen 325 mg tablet Zydone: hydrocodone 5, 7.5, 10 mg/acetaminophen 400 mg tablets Lortab: hydrocodone 5, 7.5, 10 mg/acetaminophen 500 mg tablets Margesic H: hydrocodone 5 mg/acetaminophen 500 mg capsule Lorcet: hydrocodone, 10 mg/acetaminophen 650 mg tablets Maxidone: hydrocodone 10 mg/acetaminophen 750 mg tablet Vicodin: hydrocodone 5 mg/acetaminophen 500 mg tablet Vicodin ES: hydrocodone 7.5 mg/acetaminophen 750 mg tablet Vicodin HP: hydrocodone 10 mg/acetaminophen 660 mg tablet
hydrocodone / ibuprofen tablets (Ibudone, Reprexain)	One tablet every four to six hours	Not to exceed a maximum of five tablets in 24 hours	Ibudone: hydrocodone 5, 10 mg/ ibuprofen 200 mg tablets Reprexain: hydrocodone 2.5, 5, 10 mg/ibuprofen 200 mg tablets

Dosages (continued)

Drug	Starting Dose	Dosing Instructions	Available Strengths
hydromorphone (Dilaudid)	Tablets: 2 to 8 mg every four to six hours Liquid: 2.5 – 10 mg every three to six hours	Dose should be adjusted so that at least three to four hours of pain relief may be achieved. Dose should be increased as needed according to patient's response.	Tablets: 2, 4, 8 mg Liquid: 5 mg/5 mL
levorphanol	2 mg every six to eight hours	Total oral daily doses of more than 6 to 12 mg in 24 hours are generally not recommended as starting doses.	2 mg tablet
mepiridine (Demerol)	Adult: 50 to 150 mg every three to four hours Pediatric: 1.1 to 1.8 mg/ kg every three to four hours	Not for chronic use	Tablets: 50, 100 mg Solution: 50 mg/ 5 mL
morphine immediate-release	Tablets: 15 to 30 mg every four hours as needed Solution: 10 to 20 mg every four hours as needed	The dose should be titrated based upon the individual patient's response	Tablet: 15, 30 mg Solution: 10 mg/ 5 mL, 20 mg/ 5 mL, 100 mg/ 5 mL
oxycodone (Oxecta)	Opioid-naïve: 5 to 15 mg every four to six hours as needed with water	The dose must be swallowed whole and is not amenable to crushing and dissolution. Do not use for administration via nasogastric, gastric or other feeding tubes as it may cause obstruction of the feeding tube.	Tablet: 5 and 7.5 mg (Resistant to crushing, chewing, snorting, and injection related abuse; dissolution with water or alcohol causes tablet to form viscous gel that traps the active ingredient)
oxycodone (Dazidox, OxyIR,Roxicodone)	5 to 15 mg every four to six hours as needed	The dose should be titrated based upon the individual patient's response	Capsule: 5 mg Tablet: 5, 10, 15, 20, 30 mg Solution: 5 mg/ 5 mL, 20 mg/ mL

Dosages (continued)

Drug	Starting Dose	Dosing Instructions	Available Strengths
oxycodone/ APAP (Endocet, Magnacet, Percocet, Primlev, Roxicet, Tylox, Xolox)	One to two tablets/capsules every six hours	Do not exceed oxycodone 60 mg or acetaminophen 4 g per day in adults Children: Maximum dose per day – < 45 kg body weight – do not exceed 90 mg/kg per day based on the acetaminophen component >45 kg body weight – Do not exceed 4 g per day based on the acetaminophen component	Percocet and Endocet: oxycodone 2.5, 5, 7.5, 10 / APAP 325 mg; oxycodone 7.5/ APAP 500 mg; oxycodone 10 / APAP 650 mg tablets
			Magnacet: oxycodone 5, 10 / APAP 400 mg tablets
			Primlev: oxycodone 5, 7.5, 10 / APAP 300 mg tablets
			Roxicet: oxycodone 5 mg / APAP 325, 500 mg tablets oxycodone 5 mg/ APAP 325 mg per 5 mL solution
			Tylox: oxycodone 5 mg/ APAP 500 mg capsule
			Xolox: oxycodone 10 mg/ 500 mg tablet
oxycodone/aspirin (Endodan, Percodan)	One tablet every six hours	The maximum daily dose of aspirin should not exceed 4 grams or 12 tablets.	Percodan: 4.5 mg oxycodone HCl/ 0.38 mg oxycodone terephthalate/ 325 mg aspirin tablet Endodan: 4.8 mg oxycodone HCl/ 325 mg aspirin tablet
oxycodone/ ibuprofen (Combunox)	One tablet per dose	Not to exceed a maximum of four tablets in 24 hours. Do not exceed seven days of therapy.	oxycodone 5 mg/ ibuprofen 400 mg tablet
pentazocine/ APAP	One tablet every four hours	Do not exceed six tablets per day	pentazocine 25 mg/ APAP 650 mg tablet
pentazocine/ naloxone	One to two tablets every three or four hours	Do not exceed 600 mg pentazocine per day	pentazocine 50 mg/ naloxone 0.5 mg tablet
tapentadol (Nucynta)	One tablet every four hours	Doses greater than 700 mg on the first day and doses of greater than 600 mg on subsequent days are not recommended.	50, 75,100 mg tablets
tramadol (Rybix ODT) ²⁰⁸	50 mg to 100 mg every four to six hours	Titrate in 50 mg increments as tolerated every 3 days to reach 200 mg/day (50 mg four times daily). After titration, tramadol 50-100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg per day. Do not break, split, or chew tablets. Place Rybix ODT tablet on the tongue until it completely disintegrates and then swallow it. It may take approximately one minute for the tablet to disintegrate on the tongue.	50 mg orally disintegrating tablet

Dosages (continued)

Drug	Starting Dose	Dosing Instructions	Available Strengths
tramadol (Ultram)	50 mg to 100 mg every four to six hours	Initiate at 25 mg every morning. Titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times daily). Then the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times daily). After titration, tramadol 50-100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg per day.	50 mg tablet
tramadol / acetaminophen (Ultracet)	Two tablets every four to six hours	Not to exceed a maximum of eight tablets in 24 hours; the elimination half-life of tramadol is increased in patients with severe renal impairment (CrCl <30 mL/min), cirrhosis of the liver, or over 75 years, so the dosing interval should be extended. For the short-term (five days or less) management of acute pain.	37.5 mg tramadol / 325 mg acetaminophen tablet

Oxymorphone IR (Opana) should be given on an empty stomach; maximum concentration and area under the curve were increased 38 percent when given with a high-fat meal.²⁰⁹ Bioavailability of oxymorphone may also be increased in patients with hepatic or renal insufficiency. Formal studies have not yet been done.

CLINICAL TRIALS**Search Strategies**

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

butorphanol nasal spray and butalbital compound/codeine

In a double-blind, parallel-group study, patients with migraine (n=321) were randomly assigned to receive either butorphanol nasal spray 1 mg followed in one hour by an optional second 1-mg dose or butalbital compound with codeine administered orally (one capsule containing butalbital 50 mg, caffeine 40 mg, aspirin 325 mg, and codeine phosphate 30 mg).²¹⁰ Patients were instructed to self-

administer medication when migraine pain reached intensity of moderate or severe and to record study-related events in a diary for 24 hours posttreatment. Efficacy analyses were performed on data from 275 patients who received study medication and returned a patient diary. During the first two hours after treatment, butorphanol was more effective than butalbital compound/codeine in treating migraine pain as measured by pain intensity difference scores, percentage of responders (pain decreased to mild or none), percentage of pain-free patients, and degree of pain relief, with a more rapid time to onset of 15 minutes. A similar percentage of patients in the two groups used rescue medication during the first four hours, after which more butorphanol-treated than butalbital compound/codeine-treated patients used rescue medication. Butorphanol patients had more side effects, less improvement in digestive symptoms, and less improvement in functional ability than butalbital compound/codeine patients.

fentanyl oral transmucosal (Actiq) and morphine IR

In a randomized, double-blind, cross-over trial with 134 adult ambulatory cancer patients, fentanyl oral transmucosal and morphine sulfate immediate release (MSIR) were compared for the management of breakthrough pain.²¹¹ Enrolled patients were stabilized on a fixed schedule opioid regimen of either morphine sulfate or transdermal fentanyl and an effective MSIR dose of 15 to 60 mg up to four times daily for breakthrough pain. In an open-label fashion, fentanyl oral transmucosal was administered to establish the effective dose for breakthrough pain for 69 percent of patients. Double-blind randomization occurred and then a set of capsules and oral transmucosal delivery systems (one placebo unit per set being either capsule or transmucosal unit) were administered for each breakthrough pain dosing. During the blinded study, fentanyl oral transmucosal was significantly better than MSIR for pain intensity reduction, pain relief, and pain intensity differences. Patients favored the fentanyl oral transmucosal for breakthrough pain based on global performance.

fentanyl buccal film (Onsolis)

The pivotal data for this product were provided by a clinical trial in opioid-tolerant adults experiencing moderate to severe breakthrough cancer pain.²¹² Patients were maintained on stable opioid doses consisting of at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for one week or longer. A double-blind, placebo-controlled, crossover study was performed in patients with cancer to evaluate the effectiveness of fentanyl buccal film for the treatment of breakthrough cancer pain. Open-label titration identified a successful dose of fentanyl within the range of 200 to 1,200 mcg. Patients were then randomized to a sequence of nine treatments (six with the successful fentanyl dose and three with placebo). Of the patients who entered the study, 54 percent achieved a successful dose during the titration phase and four percent withdrew for lack of effective pain relief. The primary outcome measure, the mean sum of pain intensity differences at 30 minutes (SPID30), for fentanyl-treated episodes was statistically significantly higher than for placebo-treated episodes.

fentanyl buccal tablet (Fentora)

A double-blind, randomized, placebo-controlled study evaluated the efficacy, safety, and tolerability of fentanyl buccal tablets in opioid-treated patients (n=123) with cancer-related breakthrough pain.²¹³ After an open-label titration to identify an effective fentanyl dose to treat breakthrough pain episodes, fentanyl patients were randomly assigned to a pre-specified dose sequence of 10 tablets (seven fentanyl, three placebo). Sixty-five percent of patients were titrated to an effective dose. Measures of

pain relief and patient ratings of global performance of medication significantly favored fentanyl over placebo at 30 minutes.

fentanyl sublingual tablet (Abstral)

This randomized, placebo-controlled, multicenter trial evaluated the efficacy and long-term tolerability of fentanyl sublingual for the treatment of breakthrough pain in opioid-tolerant patients with cancer.²¹⁴ Following a two-week open-label titration phase, patients (n=61) received fentanyl sublingual or placebo, in a double-blind manner. The primary efficacy endpoint was the sum of pain intensity difference (SPID) over 30 minutes post-administration. Following efficacy evaluation, patients entered a long-term safety phase of up to 12 months. Fentanyl provided significant improvements in SPID relative to placebo at 30 minutes (49.5 versus 36.6, p=0.0004) and 60 minutes post-administration (143 versus 104.5, p=0.0002). The most common adverse events included nausea (12.2 percent), vomiting (5.3 percent) and somnolence (4.6 percent).

fentanyl nasal spray (Lazanda)

A randomized, double-blind, crossover study assessed the efficacy and tolerability of nasal fentanyl formulation for breakthrough cancer pain.^{215,216} Patients (n=114) were experiencing one to four breakthrough pain episodes per day while taking ≥ 60 mg/day of oral morphine or equivalent. Patients (n=83) successfully identified an effective dose of fentanyl nasal spray during an open-label titration phase and entered a double-blind phase in which 10 pain episodes were treated with the effective dose (seven episodes) or placebo (three episodes). Six percent of patients withdrew for lack of effective pain relief, and five percent withdrew due to adverse events during the titration phase. Seventy-eight percent of patients required 400 or 800 mcg per pain episode. Pain intensity (11-point scale) and pain relief (five-point scale) were assessed between five and 60 minutes. Use of rescue medications was recorded, and acceptability assessments were conducted 30 and 60 minutes post dose. Fentanyl nasal spray significantly improved mean summed pain intensity difference (SPID) from 10 minutes (p<0.05) until 60 minutes (p<0.0001), including the primary endpoint at 30 minutes (p<0.0001). Fentanyl nasal spray significantly improved pain intensity (PI) scores as early as five minutes (p<0.05); pain intensity difference (PID) from 10 minutes (p<0.01); and pain relief (PR) scores from 10 minutes (p<0.001). More patients showed a clinically meaningful (≥ 2 -point reduction in PI) pain reduction from 10 min onward (p \leq 0.01) and 90.6 percent of the fentanyl nasal spray-treated episodes versus 80 percent of placebo-treated pain episodes did not require rescue medication (p<0.001). Approximately 70 percent of patients were satisfied or very satisfied with the convenience and ease of use of fentanyl nasal spray.

fentanyl sublingual spray (Subsys)

In a randomized, double-blind, placebo-controlled phase III trial conducted in opioid-tolerant patients with break through cancer pain (BTCP).²¹⁷ An open-label titration period was followed with a double-blind treatment period where patients received fentanyl sublingual spray (100-1,600mcg) or placebo.

There were 130 patients that entered the titration phase with 98 of them who successfully achieved a successful dose for fentanyl sublingual spray that provided tolerable side effects and reduced pain to begin the double-blind period (75.4 percent). Relative to placebo, fentanyl sublingual spray significantly improved mean summed pain intensity difference (SPID) scores from five minutes (p=0.0219) through 60 minutes (p<0.0001), including the primary endpoint at 30 minutes (p<0.0001). Fentanyl sublingual spray produced significantly greater pain relief (expressed in terms of total pain

relief (TOTPAR) from five to 60 minutes ($p < 0.0001$), and significantly greater global evaluation of treatment effectiveness ($p < 0.0001$), compared with placebo.

oxycodone immediate-release (Oxecta)

In a double-blind, active-comparator, crossover study in 40 non-dependent recreational opioid users, the "drug liking" responses and single-dose safety of crushed Oxecta tablets were compared with crushed immediate-release oxycodone tablets which the trial subjects self-administered intranasally.²¹⁸ The presence of sequence effects resulted in questionable reliability of the second period data. First period data demonstrated small numeric differences in the median and mean drug liking scores, lower in response to Oxecta than immediate-release oxycodone. Thirty percent of subjects exposed to Oxecta responded that they would not take the drug again compared to 5 percent of subjects exposed to immediate-release oxycodone. Subjects self-administering Oxecta reported a higher incidence of nasopharyngeal and facial adverse events and a decreased ability to completely inhale two crushed tablets within a fixed time period (21 of 40 subjects). There is no evidence that Oxecta has a reduced abuse liability compared to immediate-release oxycodone.

oxymorphone IR (Opana) and oxycodone IR

In a double-blind, parallel-group study, oxymorphone IR was compared with placebo for efficacy and with oxycodone IR and placebo for safety in patients with acute moderate to severe post surgical pain.²¹⁹ Three hundred patients received oxymorphone IR 10, 20, or 30 mg; oxycodone IR 10 mg; or placebo. All oxymorphone IR doses were superior to placebo for providing pain relief for eight hours ($p < 0.05$), each with a significant analgesic dose response compared to placebo ($p < 0.001$). All oxymorphone IR groups maintained analgesia for 48 hours. The median dosing interval was over 9.5 hours for oxymorphone IR 30 mg. Opioid-related adverse events, similar among groups, were generally mild or moderate; the overall safety profile was comparable to that of oxycodone IR.

oxycodone/ibuprofen (Combunox) versus oxycodone/acetaminophen (Percocet) versus hydrocodone/acetaminophen (Vicodin ES)

In a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, single-dose study, patients experiencing moderate to severe pain after surgical removal of two or more ipsilateral impacted third molars were randomly assigned to receive oxycodone 5 mg/ibuprofen 400 mg, oxycodone 5 mg/acetaminophen 325 mg, hydrocodone 7.5 mg/acetaminophen 500 mg, or placebo.²²⁰ The primary outcome measures were total pain relief through six hours after dosing, sum of pain intensity differences through six hours (SPID6), and adverse events. Oxycodone 5 mg/ibuprofen 400 mg provided significantly greater analgesia compared with oxycodone 5 mg/acetaminophen 325 mg, hydrocodone 7.5 mg/acetaminophen 500 mg, and placebo ($p < 0.001$, oxycodone 5 mg/ibuprofen 400 mg versus all other treatments) six hours after dosing. Values for SPID6 also differed significantly for oxycodone 5 mg/ibuprofen 400 mg compared with all other treatments ($p < 0.001$). Oxycodone 5 mg/ibuprofen 400 mg was significantly more effective compared with the other treatments on all secondary endpoints ($p < 0.001$), with the exception of the time to onset of analgesia. The lowest frequency of nausea and vomiting occurred in the groups that received oxycodone 5 mg/ibuprofen 400 mg (6.5 and 3.2 percent, respectively) and placebo (3.2 and 1.6 percent).

oxycodone/ibuprofen (Combunox) versus oxycodone (Roxicodone) versus ibuprofen (Motrin)

In a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group trial, women experiencing moderate to severe pain between 14 and 48 hours after surgery were randomized to receive a single dose of oxycodone/ibuprofen, ibuprofen, oxycodone, and placebo.²²¹ Four hundred fifty-six women participated in the study. Combination treatment was associated with significantly better scores for total pain relief six hours after dosing and sum of pain intensity differences six hours after dosing compared with ibuprofen alone ($p<0.02$ and $p<0.015$, respectively), oxycodone alone ($p<0.009$ and $p<0.001$), or placebo (both $p<0.001$). Fewer patients receiving combination treatment required rescue medication, and the time to use of rescue medication was significantly longer in the combination treatment group compared with the other groups ($p<0.05$). The onset of pain relief occurred within 15 minutes of dosing with all regimens. Nausea was the most frequently reported adverse event in all groups, highest with placebo and followed by oxycodone, ibuprofen, and combination treatment.

In the multicenter, double-blind, double-dummy, parallel-group investigation, 498 patients with moderate to severe pain within five hours after extraction of two or more impacted third molars were randomized to single doses of oxycodone 5 mg/ibuprofen 400 mg, ibuprofen 400 mg, oxycodone 5 mg, or placebo.²²² Combination therapy was associated with greater analgesia than ibuprofen alone, oxycodone alone, or placebo, as measured by the sum of pain intensity difference over six hours ($p<0.001$ versus oxycodone or placebo, $p=0.002$ versus ibuprofen) and total pain relief through six hours ($p<0.001$ versus oxycodone or placebo, $p=0.012$ versus ibuprofen). Combination therapy was well tolerated, and pharmacokinetic evaluation implied no interaction between oxycodone and ibuprofen.

oxymorphone (Opana) versus oxycodone IR versus placebo

A multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group study was conducted in men and women aged 18 years and older undergoing abdominal surgery.²²³ Patients were randomized to receive oxymorphone 10 or 20 mg, oxycodone 15 mg, or placebo every four to six hours. The study included single-dose and 48-hour efficacy assessments. The primary efficacy endpoint was the median time to study discontinuation for all causes. Three hundred thirty-one patients were included in the study. The median time to study discontinuation was significantly longer for all active treatments compared with placebo (oxymorphone 10 mg, 17.9 hours; oxymorphone 20 mg, 20.3 hours; oxycodone 15 mg, 24.1 hours; placebo, 4.8 hours; $p<0.006$). Oxymorphone 20 mg was significantly more effective than placebo over the six-hour single-dose evaluation ($p<0.05$). With multiple dosing, all active-treatment groups had significantly lower least squares mean current and average pain intensities compared with placebo ($p<0.004$ and $p<0.005$, respectively). Discontinuations due to treatment-emergent adverse events did not differ significantly among the groups.

tapentadol (Nucynta) versus morphine IR

Patients ($n=400$) undergoing molar extraction were randomized to receive single doses of tapentadol 25, 50, 75, 100, or 200 mg, morphine sulfate 60 mg, ibuprofen 400 mg, or placebo.²²⁴ Mean total pain relief over eight hours (TOTPAR-8) was the primary endpoint. Secondary endpoints included mean total pain relief over four hours (TOTPAR-4) and onset of analgesia. Of all measured endpoints, only mean TOTPAR-4 was higher (and onset of action appeared more rapid) for tapentadol 200 mg than

morphine sulfate 60 mg. Pain relief scores with morphine sulfate 60 mg were between those of tapentadol 100 and 200 mg. The incidence of nausea and vomiting appeared to be lower with all doses of tapentadol compared with morphine sulfate 60 mg but was not statistically significant.

tapentadol (Nucynta) versus oxycodone (Roxicodone)

A 10-day, phase III, randomized, double-blind, active- and placebo-controlled study compared the efficacy and tolerability of tapentadol, oxycodone, and placebo in 666 patients with uncontrolled osteoarthritis pain who were candidates for primary replacement of the hip or knee as a result of end-stage degenerative joint disease.²²⁵ Patients received tapentadol 50 mg or 75 mg, oxycodone 10 mg, or placebo every four to six hours while awake. The primary endpoint was the sum of pain intensity difference (SPID) over five days. Prespecified noninferiority comparisons with oxycodone were performed with respect to efficacy and tolerability. Five-day SPID was significantly lower in those treated with tapentadol or oxycodone (all $p < 0.001$). Tapentadol 50 and 75 mg and oxycodone 10 mg were associated with significant reductions in pain intensity compared with placebo based on two- and 10-day SPID, as well (all $p < 0.001$). The efficacy of tapentadol 50 and 75 mg was noninferior to that of oxycodone 10 mg; however, the incidence of nausea, vomiting, and constipation was significantly lower for both doses of tapentadol compared with oxycodone ($p < 0.001$).

tramadol/acetaminophen (Ultracet) versus tramadol (Ultram)

A total of 456 patients with moderate to severe pain within five hours of extraction of two or more third molars were randomized to receive two identical encapsulated tablets containing tramadol/acetaminophen 37.5 mg/325 mg, tramadol 50 mg, or placebo.²²⁶ Tramadol/acetaminophen was superior to tramadol ($p < 0.001$) or placebo ($p < 0.001$) on all efficacy measures, including total pain relief over six hours, sum of pain intensity differences, and sum of both. The most common adverse events with active treatment were nausea, dizziness, and vomiting, which occurred more frequently in the tramadol group than in the tramadol/acetaminophen group.

tramadol (Rybix ODT)

No clinical trials were identified.²²⁷ The clinical trials in the prescribing information discuss the immediate-release oral tablets of tramadol. The pharmacokinetics section of the prescribing information for tramadol ODT states that there is no difference in systemic exposure, peak exposure, time to peak exposure, and apparent elimination half-life of tramadol and metabolites M1 and M5 between administration of tramadol ODT with and without water and oral tramadol immediate release tablets. Additionally, there are no studies of tramadol ODT that indicated that its onset of action is faster than tramadol immediate release tablets.

tramadol/acetaminophen (Ultracet) versus codeine/acetaminophen

A randomized, double-blind, parallel-group, active-control, double-dummy trial compared the efficacy and tolerability of tramadol/acetaminophen (37.5 mg/325 mg) tablets with codeine/acetaminophen capsules (30 mg/300 mg) in 462 patients with chronic nonmalignant low back pain, osteoarthritis, or both.²²⁸ Pain intensity was assessed hourly for six hours each week over a four-week period. Pain relief and changes in pain intensity were comparable in both groups throughout the study. Equivalent mean doses and maximum daily doses used in each group were similar. The overall incidence of adverse events was comparable, with more patients in the codeine/acetaminophen group reporting

somnolence (24 versus 17 percent, $p=0.05$) and constipation (21 versus 11 percent, $p<0.01$) than the tramadol/acetaminophen group.

A multicenter, randomized, double-blind, active- and placebo-controlled trial evaluated tramadol plus acetaminophen for orthopedic and abdominal post surgical pain.²²⁹ Patients with moderate pain or greater were randomized to an initial two tablets of 37.5 mg tramadol plus 325 mg acetaminophen ($n=98$), codeine 30 mg plus acetaminophen 300 mg ($n=109$), or placebo ($n=98$). Thereafter, they received one to two tablets every four to six hours, as needed for pain, for six days. Tramadol plus acetaminophen was superior to placebo for total pain relief, sum of pain intensity differences, and sum of pain relief and pain intensity differences ($p\leq 0.015$). For average daily pain relief, average daily pain intensity, and overall medication assessment, tramadol plus acetaminophen was superior to placebo ($p\leq 0.038$); codeine plus acetaminophen did not separate from tramadol plus acetaminophen in any criteria. Discontinuation because of adverse events occurred in 8.2 percent of tramadol plus acetaminophen, 10.1 percent of codeine plus acetaminophen, and three percent of placebo patients. Except for constipation and vomiting being more prevalent in codeine plus acetaminophen patients, adverse events were similar for active treatments.

A four-week, randomized, double-blind, parallel-group, multicenter trial compared tramadol/acetaminophen 37.5 mg/325 mg with codeine/acetaminophen 30 mg/300 mg for the management of chronic nonmalignant low back pain, osteoarthritis pain, or both in 462 adults.²³⁰ Pain relief (scale, 0 = none to 4 = complete) and pain intensity (scale, 0 = none to 3 = severe) were measured after 30 minutes and then hourly for six hours after the first daily dose each week. Pain relief and changes in pain intensity were comparable from Day 1 and lasted for at least six hours. Total pain relief scores and sum of pain intensity differences were also comparable throughout. Overall assessments of safety and efficacy by patients and investigators were similar for the two treatment groups.

tramadol/acetaminophen (Ultracet) versus hydrocodone/acetaminophen (Vicodin)

In a single-center, double-blind, parallel-group, placebo- and active-controlled study in adults with at least moderate pain after extraction of two or more impacted third molars, patients were randomized to receive one to two tramadol/acetaminophen 37.5 mg/325 mg tablets, one hydrocodone/acetaminophen 10 mg/650 mg tablet, or placebo.²³¹ Two hundred adults took part in the study. The median time to onset of pain relief was approximately 34 minutes with tramadol/acetaminophen tablets and 25.4 minutes with hydrocodone/acetaminophen. Although the median time to onset of pain relief was shorter with hydrocodone/acetaminophen, two tramadol/acetaminophen tablets had comparable efficacy to hydrocodone/acetaminophen. The median time to re-medication with a supplemental analgesic agent was 169 minutes in the tramadol/acetaminophen group and 204 minutes in the hydrocodone/acetaminophen group; however, the duration of pain relief was not significantly different between the groups. The overall incidence of adverse events was lower with tramadol/acetaminophen (zero percent) than with hydrocodone/acetaminophen (four percent) or placebo (ten percent).

SUMMARY

Pain management must be individualized for each patient. There are many equally effective opioid analgesic products available, differing in specific opioid (and co-analgesics), dosage form, and duration of action. Many are available in clinically effective generic forms, including combinations of non-narcotic acetaminophen, aspirin, or ibuprofen with the opioids hydrocodone or oxycodone. Although some manufacturers market unique strengths of these combination agents, the minor changes in the doses of acetaminophen, ibuprofen, and/or opioid in these products have not been shown to offer any advantage over similar generic combinations. Similarly, there are no data to suggest that a particular formulation of fentanyl (Abstral, Actiq, Fentora, Onsolis, Lazanda, Subsys) is safer or more effective for breakthrough cancer pain.

Dihydrocodeine/caffeine/acetaminophen (Panlor SS), tapentadol (Nucynta), tramadol/acetaminophen (Ultracet), and oxymorphone (Opana) have not shown increased efficacy when compared to other opioids.

Oxecta is an immediate-release opioid analgesic intended to discourage abuse of the medication. The main difference between Oxecta and other oxycodone formulations is the technology used to discourage common methods of tampering with such analgesics. The manufacturer identifies the system as employing common pharmaceutical manufacturing ingredients in a proprietary manner to prevent misuse. These preventative measures offer no analgesic advantage over existing products. While it is acknowledged that diversion and misuse of opioids may be commonplace, patients should be evaluated to determine whether such preventative measures are indicated or required. Consequently, Oxecta may best be reserved for potential abuse/misuse situations while employing traditional or current analgesics in non-questionable settings.

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