Drug Class Review

Short-Acting and Rapid-Acting Opioid Agents

28:08.08 Opiate Agonists

Final Report
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Executive Summary

Introduction: The opioid analgesic agents have been used for centuries and are the most commonly used pharmacologic agents for the treatment of moderate to severe pain. Opioid analgesics stimulate opiate receptors and produce pain relief without producing loss of consciousness. This report reviewed the efficacy of the short-acting and rapid-onset opioid agents in the treatment of pain disorders. Seventeen opioid agents were included in the review.

Current American Pain Society guidelines recommend a short-acting opioid for the treatment of breakthrough pain and a long-acting opioid for the treatment of around-the-clock pain. The World Health Organization analgesic ladder addresses pain relief strategies at three levels. Non-opioid pain relievers are used at the lowest level, weak opioid agents (codeine) are used for moderate pain and strong opioid agents (morphine, hydromorphone, oxymorphone, methadone and fentanyl) are recommended for the highest level of pain. Patients may be switched from one opioid to another using equipotent dosing. Appropriate management of breakthrough pain is important as patients with breakthrough pain have a higher frequency of hospital admissions and higher estimated annual medical costs.

Clinical Efficacy: Clinical experience with the short-acting agents in treating patients with pain is extensive. The majority of comparative evidence evaluated in this report comes from 6 systematic review trials involving 170 clinical trials and over 27,000 patients. Overall, the evidence evaluating oral morphine demonstrates efficacy in the treatment of pain. Hydromorphone demonstrates efficacy as a potent analgesic with equal efficacy and similar rates of adverse events compared to morphine. In addition, evidence from eight randomized, controlled trials suggests similar rates of efficacy when the opioid agents (oxycodone, hydrocodone, codeine, tramadol) are dosed with equipotent doses. Very limited comparative clinical evidence is available for the rapid-onset opioid agents. Evidence comparing the short-acting opioid agents to the rapid-onset agents does not provide sufficient conclusive evidence to support the use of new fentanyl products over the non-fentanyl comparators.

Five patient populations may require special consideration when being treated with opioid analgesic agents: geriatric patients, pediatric patients, liver disease, opioid naïve patients, and patients with a history of drug and alcohol abuse. In general, these patients may require changes in dosing schemes, reductions in duration of therapy, judicious medication selections and frequent follow-ups.

Adverse Drug Reactions: The most common adverse effects associated with the opioid analgesics include nausea, vomiting, sedation, pruritus and constipation. Serious adverse effects frequently reported with opioid use include: respiratory depression, urinary retention, hypotension and delirium. Clinical trials demonstrate no differences in rates of serious adverse events when morphine and morphine-like agents are dosed with equianalgesic dosing schemes. Unintentional drug overdose death rates in the United States have increased five-fold since 1990 and this has been driven by increased use of opioid analgesics. Hydromorphone, morphine, oxymorphone, oxycodone, fentanyl and methadone are potent schedule II controlled opioid agonists that have the highest potential for abuse and risk of producing respiratory depression.

Summary: Overall, the opioid analgesic agents are effective treatment options for pain disorders. When compared at equianalgesic doses, the opioid agents demonstrate similar rates of safety and efficacy. The opioid analgesic products are available in many dosage forms, varying potencies and differing durations of action. Pain management must be individualized for each patient and include careful evaluation of patient history, age, comorbidities, type of pain, underlying diseases and concurrent medications.

Introduction

The opioid analgesics are a class of agents which stimulate opiate receptors and produce pain relief without producing loss of consciousness.[1, 2] These agents may be naturally occurring, semisynthetic, or synthetic but have equianalgesic dosing, which allows for conversion between agents and routes of administration. The opioid analgesics are divided into categories based on receptor subtype and potency. These agents can also be divided into groups based on onset and duration of action: long-acting, short-acting, and rapid-onset. See Table 1 for a summary of agents within each category. This review will focus on the short-acting and rapid-onset opioid agents. Currently, seventeen agents are approved for use in the United States: buprenorphine, butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, opium, oxycodone, oxymorphone, paregoric, pentazocine, tapentadol, and tramadol.[3, 4] Each of these agents is available in multiple formations and many are available in combination with other agents, including aspirin, acetaminophen, ibuprofen, caffeine, naloxone and butalbital. See Table 2 for a summary of all currently available short-acting and rapid onset opioid agents.

Table 1. Opioid Categories[1-4]

Long-Acting Opioids	Short-Acting Opioids	Rapid-Onset Opioids
Transdermal systems with fentanyl (Duragesic patches)	Codeine	Oral transmucosal fentanyl citrate (OTFC)
Buprenorphine patch (Butrans)	Buprenorphine	Fentanyl buccal tablet (FBT)
Extended release morphine (Kadian, MS Contin, or Avinza).	Morphine (MSIR)	Fentanyl buccal soluble film (FBSF)
Extended release oxymorphone (Opana ER)	Oxymorphone (Opana)	Sublingual fentanyl
Extended release oxycodone (Oxycontin)	Oxycodone (OxyIR, Percocet)	Intranasal fentanyl
Levorphanol (Levo-dromoran)	Tapentadol (Nucynta)	
Methadone	Hydrocodone (Vicodin)	
Extended release hydromorphone (Exalgo)	Hydromorphone (Dilaudid)	

Disease Overview

Pain is defined as an unpleasant sensation often expressed as both a physical process and an emotional reaction.[2, 5-7] Pain of higher intensities may also be accompanied by anxiety. Pain is indicative of physical harm or a disease process and is used to promote the physiological healing process. Pain is divided into two main categories: acute and chronic. Acute, or nociceptive, pain is a rapid warning relay within the central nervous system (CNS) to the motor neurons as a result of detected physical harm. Nociceptors are found below the skin, tendons, joints and body organs and detect cutaneous, somatic and visceral pain.[5-7] In general, opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are very effective in the treatment of acute pain. Chronic pain typically is not a symptom of a disease process but is a disease process itself. Chronic pain can be defined as inflammatory nociceptive or neuropathic. Inflammatory nociceptive pain is associated with tissue damage while neuropathic pain is produced by damage to the neurons in

the peripheral and central nervous systems resulting in sensitization of these systems. The treatment of chronic pain is more challenging, as the cause is not always clear, and often requires several types and combinations of treatments. These treatments may include opioids, NSAIDs, antidepressants, topical agents, cognitive behavioral therapies and/or surgery.[2]

The American Pain Society (APS) guidelines recommend a short-acting opioid for the treatment of breakthrough pain (BTP) and a long-acting opioid for the treatment of around-the-clock pain.[8] Agents used for the treatment of breakthrough pain include: immediate-acting opioids and rapid-onset opioids. The onset and predictability of a BTP episode influences the selection of a BTP agent.[9] If an exacerbating activity causes the BTP, an immediate-acting opioid should be administered 30 to 40 minutes before the activity. If the BTP is unpredictable and spontaneous, a lipophilic agent which is distributed rapidly into tissues, such as the rapid-onset fentanyl products, may be a more suitable treatment option.[10, 11] Currently, the rapid-onset fentanyl products are only approved for treatment of BTP in opioid-tolerant patients with cancer.[3, 4]

The World Health Organization (WHO) analgesic ladder addresses pain relief strategies at three levels. Non-opioid pain relievers are used at the lowest level, weak opioid agents (codeine) are used for moderate pain and strong opioid agents (morphine, hydromorphone, oxymorphone, methadone and fentanyl) are recommended for the highest level of pain. Patients can be switched from one opioid to another or the dose can be adjusted until a satisfactory response is achieved, which is known as opioid rotation. For example, a patient on a relatively high potency opioid could be switched to a lower potency opioid to regain analgesia or reduce adverse effects.[12, 13] Appropriate management of breakthrough pain is important. Patients with BTP have a higher frequency of hospital admissions (36.9% vs 22.5%) and higher estimated annual medical costs ($12,000 vs $2,400) related to hospitalizations, emergency room visits, and physician visits compared to those without BTP.[9, 14]

Table 2. Comparison of Short-Acting Opioid Agents[3, 4]

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Buprenorphine (Buprenex; Butrans)	C-III	Injection (IM, IV), Oral, Transdermal	Transdermal patch: 5 mcg/hr; 10 mcg/hr; 15 mcg/hr; 20 mcg/hr Injection solution (IM, IV): 0.3 mg/mL Oral tablet; Sublingual: 2 mg, 8 mg	Injection and Transdermal patch: Management of moderate-to-severe pain Sublingual tablet: Treatment of opioid dependence	Injection: Management of opioid withdrawal in heroin-dependent hospitalized patients	Acute pain; injection: 0.3 mg every 6-8 hours as needed; may be repeated once in 30-60 minutes Chronic pain; patch: 5-20 mcg/hour applied once every 7 days Opioid dependence; tablet: Day 1: 8 mg; Day 2 and subsequent induction days: 16 mg; *The combination product, buprenorphine and naloxone, is preferred therapy over buprenorphine monotherapy	Product Dependent
Buprenorphine and Naloxone (Suboxone; Zubsolv)	C-III	Oral	Film, sublingual: buprenorphine 2 mg and naloxone 0.5 mg; buprenorphine 4 mg and naloxone 1 mg; buprenorphine 8 mg and naloxone 2 mg; buprenorphine 12 mg and naloxone 3 mg Tablet, sublingual: buprenorphine 1.4 mg and naloxone 0.36 mg; buprenorphine 2 mg and naloxone 0.5 mg; buprenorphine 5.7 mg and naloxone 1.4 mg, buprenorphine 8 mg and naloxone 2 mg	Opioid dependence: For the maintenance treatment of opioid dependence. *Buprenorphine/naloxone should be used as part of a complete treatment plan to include counseling and psychosocial support	N/A	Target dose: 16 mg daily as a single daily dose; dosage should be adjusted in increments of 2 mg or 4 mg to a level which maintains treatment and suppresses opioid withdrawal symptoms; usual range: 4-24 mg daily	Yes: Sublingual tablet

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Butorphanol	C-IV	Injection (IV, IM), Nasal	Injection solution (IV, IM):1 mg/mL; 2 mg/mL (available in preservative-free formulation) Nasal solution: 10 mg/mL	Injection (IV, IM): Management of pain when the use of an opioid analgesic is appropriate; preoperative or preanesthetic medication; supplement to balanced anesthesia; management of pain during labor. Nasal spray: Management of pain when the use of an opioid analgesic is appropriate.	N/A	Pain (IV, IM): 1-2 mg, may repeat every 3-4 hours as needed; usual range: 0.5-4 mg every 3-4 hours as needed Pain (Intranasal): 1 spray in 1 nostril; if adequate pain relief is not achieved within 60-90 minutes, an additional 1 spray in 1 nostril may be given; may repeat initial dose sequence in 3-4 hours after the last dose as needed Preoperative medication: I.M.: 2 mg 60-90 minutes before surgery Supplement to balanced anesthesia: I.V.: 2 mg shortly before induction and/or an incremental dose of 0.5-1 mg (up to 0.06 mg/kg) Pain during labor (IV, IM): 1-2 mg; may repeat in 4 hours	Yes
Codeine	C-II	Oral	Oral solution, as sulfate: 30 mg/5 mL (500 mL) Oral tablet, as sulfate: 15 mg, 30 mg, 60 mg	Management of mild-to-moderately-severe pain	Short-term relief of cough in select patients	Initial: 15-60 mg every 4 hours as needed Maximum total daily dose: 360 mg/day	Yes

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Codeine/Acetaminophen (Capital® and Codeine; Tylenol® with Codeine No. 3; Tylenol® with Codeine No. 4)	C-V: Oral Solution, Suspension C-III: Oral Tablet	Oral	Oral solution: 12mg/120mg per 5 mL Oral suspension: 12mg/120mg per 5 mL Oral tablet: 15mg/300mg, 30mg/300mg, 60mg/300mg	Relief of mild-to-moderate pain	N/A	Antitussive: 15-30mg/dose every 4-6 hours (max: 360 mg/24 hours based on codeine component) Analgesic: 30-60 mg/dose every 4-6 hours (max: 4000 mg/24 hours based on acetaminophen component) Adult doses ≥60 mg codeine not recommended.	Yes; excludes suspension
Codeine/Butalbital/Acetaminophen/ Caffeine (Fioricet with Codeine)	C-III	Oral	Oral Capsule: Butalbital 50 mg, acetaminophen 300 mg, caffeine 40 mg, and codeine 30 mg	Relief of symptoms of complex tension (muscle contraction) headache	N/A	1-2 capsules every 4 hours. Total daily dosage should not exceed 6 capsules.	Yes
Codeine, Butalbital, Aspirin, Caffeine (Ascomp® with Codeine; Fiorinal® with Codeine)	C-III	Oral	Oral capsule: Butalbital 50 mg, aspirin 325 mg, caffeine 40 mg, and codeine 30 mg	Relief of symptoms of complex tension (muscle contraction) headache	N/A	1-2 capsules every 4 hours as needed (maximum: 6 capsules per day)	Yes
Codeine, Carisoprodol, Aspirin	C-III	Oral	Oral tablet: Carisoprodol 200 mg, aspirin 325 mg, and codeine16 mg	Skeletal muscle relaxant	N/A	1 or 2 tablets 4 times daily (maximum: 8 tablets per day) Treatment should not exceed 2-3 weeks	Yes
Codeine, Chlorpheniramine, Pseudoephedrine (Tricode® AR)	C-V	Oral	Oral liquid: Chlorpheniramine maleate 2 mg, pseudoephedrine 30 mg, and codeine 8 mg per 5 mL	Temporary relief of cough associated with minor throat or bronchial irritation or nasal congestion due to common cold, allergic rhinitis, or sinusitis	N/A	10 mL every 4 hours (maximum: 40 mL/24 hours)	No

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Codeine and Guaifenesin (Allfen CD; Allfen CDX; Codar® GF; Dex-Tuss; Guaiatussin AC; Iophen C-NR; M-Clear; M-Clear WC; Mar-Cof® CG; Robafen AC; Virtussin A/C)	C-V: Capsule C-V: Liquid products C-III: Tablets	Oral	Oral capsule: Guaifenesin 200 mg and codeine 9 mg Oral liquid: Guaifenesin 200 mg and codeine 8 mg per 5 mL; Guaifenesin 300 mg and codeine 10 mg per 5 mL; Guaifenesin 100 mg and codeine 10 mg per 5 mL; Guaifenesin 100 mg and codeine 6.33 mg per 5 mL Oral solution: Guaifenesin 100 mg and codeine 10 mg per 5 mL; Guaifenesin 225 mg and codeine 7.5 mg per 5 mL Oral tablet: Guaifenesin 400 mg and codeine 10 mg; Guaifenesin 400 mg and codeine 20 mg	Temporary control of cough due to minor throat and bronchial irritation	N/A	5-15 mL or 1 tablet every 4-6 hours (maximum: 120 mg/24 hours)	Yes: Oral solution, syrup
Codeine, Guaifenesin, Pseudoephedrine	C-V	Oral	Oral syrup: Guaifenesin 100 mg, pseudoephedrine 30 mg, codeine 10 mg per 5 mL; Guaifenesin 200 mg, pseudoephedrine 30 mg, codeine 8 mg per 5 mL	Temporarily relieves nasal congestion and controls cough associated with upper respiratory infections and related conditions (common cold, sinusitis, bronchitis, influenza)	N/A	10 mL every 4 hours (maximum: 40 mL/24 hours)	Yes
Codeine and Promethazine	C-V	Oral	Oral syrup: Promethazine 6.25 mg and codeine 10 mg per 5 mL	Temporary relief of coughs and upper respiratory symptoms associated with allergy or the common cold	N/A	5 mL every 4-6 hours (maximum: 30 mL per 24 hours)	Yes
Codeine, Promethazine, Phenylephrine (Promethazine VC/Codeine)	C-V	Oral	Oral syrup: Promethazine 6.25 mg, phenylephrine 5 mg, codeine 10 mg per 5 mL	Temporary relief of coughs and upper respiratory symptoms including nasal congestion associated with allergy or the common cold	N/A	5 mL every 4-6 hours (maximum: 30 mL per 24 hours) Children <6 years: Use of this combination is contraindicated	Yes

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Codeine and Pseudoephedrine (Codar® D; Notuss®-DC)	C-V	Oral	Oral liquid: Pseudoephedrine 30 mg and codeine 8 mg per 5 mL; Pseudoephedrine 30 mg and codeine 10 mg per 5 mL	Temporary symptomatic relief of congestion and cough due to upper respiratory infections including common cold, bronchitis, sinusitis, and influenza	N/A	5-10 mL every 4-6 hours as needed (maximum: 40 mL/24 hours)	No
Dihydrocodeine, Aspirin, and Caffeine (Synalgos®-DC)	C-III	Oral	Oral capsule: dihydrocodeine bitartrate 16 mg, aspirin 356.4 mg, and caffeine 30 mg	Management of mild-to-moderate pain	N/A	1-2 capsules every 4-6 hours as needed	Yes
Dihydrocodeine, Chlorpheniramine, and Phenylephrine (Coldcough PD; Novahistine DH; Tusscough DHC™)	C-III: Liquid, Syrup C-V: Syrup	Oral	Oral liquid: Dihydrocodeine bitartrate 7.5 mg, chlorpheniramine maleate 2 mg and phenylephrine hydrochloride 5 mg per 5 mL [C-III] Oral syrup: Dihydrocodeine bitartrate 3 mg, chlorpheniramine maleate 2 mg, and phenylephrine hydrochloride 7.5 mg per 5 mL [C-V]; Dihydrocodeine bitartrate 3 mg, chlorpheniramine maleate 5 mg, and phenylephrine hydrochloride 20 mg per 5 mL [C-III]	Symptomatic relief of cough and congestion associated with the upper respiratory tract	N/A	7.5-15 mg every 4-6 hours as needed (maximum: 60 mg/24 hours)	Yes

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Fentanyl (Abstral; Actiq; Duragesic; Fentora; Lazanda; Onsolis; Subsys)	C-II	Injection (IV, IM), Nasal, Oral	Film, buccal: 200 mcg; 400 mcg; 600 mcg; 800 mcg; 1200 mcg Injection solution (preservative free): 0.05 mg/mL Intranasal solution: 100 mcg/spray; 400 mcg/spray Liquid, sublingual: 100 mcg; 200 mcg; 400 mcg; 600 mcg; 800 mcg Oral lozenge: 200 mcg; 400 mcg; 600 mcg; 800 mcg; 1200 mcg; 1600 mcg Oral tablet, buccal: 100 mcg; 200 mcg; 400 mcg; 600 mcg; 800 mcg Oral tablet, sublingual: 100 mcg; 200 mcg; 300 mcg; 400 mcg; 600 mcg; 800 mcg Patch, transdermal: 12.5 mcg/hr; 25 mcg/hr; 50 mcg/hr; 75 mcg/hr; 100 mcg/hr Powder, for prescription compounding: USP: 100%	Injection: Relief of pain, preoperative medication, adjunct to general or regional anesthesia Transdermal patch: Management of persistent moderate-to-severe chronic pain in opioid-tolerant patients Transmucosal lozenge, buccal tablet, buccal film, nasal spray, sublingual tablet, sublingual spray: Management of breakthrough cancer pain in opioid-tolerant patients	N/A	Varies depending on indication and dosing form. See Table 3.	Yes: Injection, lozenge, patch
Hydrocodone (Zohydro ER) *FDA approved October 2013; anticipated availability is first quarter of 2014		Oral		Management of pain severe enough to require around-the-clock opioid, long-term treatment and for which alternative treatment options (eg, nonopioid analgesics or immediate release opioids) are inadequate	N/A		No

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Hydrocodone and Acetaminophen (hycet®; Lorcet® 10/650; Lorcet® Plus; Lortab®; Margesic® H; Maxidone®; Norco®; Stagesic™; Vicodin ES®; Vicodin HP®; Vicodin®; Xodol® 10/300; Xodol® 5/300; Xodol® 7.5/300; Zamicet™; Zolvit®; Zydone®)	C-III	Oral	Oral capsule: Hydrocodone 5 mg and acetaminophen 500 mg Oral elixir: Hydrocodone 10 mg and acetaminophen 300 mg per 15 mL Oral solution: Hydrocodone 7.5 mg and acetaminophen 325 mg per 15 mL; hydrocodone 7.5 mg and acetaminophen 500 mg per 15 mL; hydrocodone 10 mg and acetaminophen 325 mg per 15 mL; Hydrocodone 10 mg and acetaminophen 300 mg per 15 mL Oral tablet: Hydrocodone 2.5 mg and acetaminophen 325 mg; 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; 10/325 mg; 10/400 mg; 10/500 mg; 10/650 mg; 10/660 mg; 10/750 mg	Relief of moderate-to-severe pain	N/A	Oral (doses should be titrated to appropriate analgesic effect): Average starting dose in opioid naive patients: Hydrocodone 2.5-10 mg 4 times/day; the dosage of acetaminophen should be limited to ≤4 g/day (and possibly less in patients with hepatic impairment or ethanol use).	Yes: Oral solution, tablet

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Hydrocodone and Chlorpheniramine (TussiCaps; Tussionex Pennkinetic; Vituz)	C-III	Oral	Oral capsule, extended release: Hydrocodone bitartrate 5 mg and chlorpheniramine 4 mg; Hydrocodone 10 mg and chlorpheniramine 8 mg Oral solution: Hydrocodone bitartrate 5 mg and chlorpheniramine 4 mg per 5 mL Oral suspension, extended release: Hydrocodone bitartrate 10 mg and chlorpheniramine 8 mg per 5 mL	Symptomatic relief of cough and upper respiratory symptoms associated with cold and allergy	N/A	Capsules: 1 capsule every 12 hours (max: 2 capsules daily) Solution: 5 mL every 4-6 hours as needed (max 20 mL daily) Suspension: 5 mL every 12 hours (max 10 mL daily)	Yes: Extended release suspension
Hydrocodone and Homatropine (Hydromet®; Tussigon®)	C-III	Oral	Oral syrup: Hydrocodone bitartrate 5 mg and homatropine 1.5 mg per 5 mL Oral tablet: Hydrocodone bitartrate 5 mg and homatropine 1.5 mg	Symptomatic relief of cough	N/A	1 tablet or 5 mL every 4-6 hours as needed (maximum: 6 tablets/24 hours or 30 mL/24 hours) Children 6-11 years: 1/2 tablet or 2.5 mL every 4-6 hours as needed (maximum: 3 tablets or 15 mL/24 hours)	Yes
Hydrocodone and Ibuprofen (Ibudone; Reprexain; Vicoprofen)	C-III	Oral	Oral tablet: Hydrocodone bitartrate 2.5 mg and ibuprofen 200 mg; Hydrocodone bitartrate 5 mg and ibuprofen 200 mg; Hydrocodone bitartrate 7.5 mg and ibuprofen 200 mg; Hydrocodone bitartrate 10 mg and ibuprofen 200 mg	Short-term (generally <10 days) management of moderate-to-severe acute pain; is not indicated for treatment of such conditions as osteoarthritis or rheumatoid arthritis	N/A	1 tablet every 4-6 hours as needed for pain; maximum: 5 tablets/day. *Short-term use is recommended (<10 days)	Yes
Hydrocodone and Pseudoephedrine (Rezira™)	C-III	Oral	Oral solution: Hydrocodone bitartrate 5 mg and pseudoephedrine 60 mg per 5 mL	Symptomatic relief of cough and nasal congestion associated with common cold	N/A	5 mL every 4-6 hours as needed (maximum: 20 mL/24 hours)	No
Hydrocodone, Chlorpheniramine, and Pseudoephedrine (Zutripro™)	C-III	Oral	Oral Solution: Hydrocodone bitartrate 5 mg, chlorpheniramine 4 mg, and pseudoephedrine 60 mg per 5 mL	Temporary relief of cough and nasal congestion due to colds or upper respiratory allergies	N/A	5 mL every 4-6 hours as needed; do not exceed 4 doses/24 hours	No

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Hydromorphone (Dilaudid; Dilaudid-HP; Exalgo)	C-II	Injection (IV, IM SubQ), Oral, Rectal	Injection solution: 1 mg/mL; 2 mg/mL; 4 mg/mL; 10 mg/mL; 50 mg/5 mL; 500 mg/50 mL Injection solution, reconstituted: 250 mg Oral liquid: 1 mg/mL Oral tablet: 2 mg, 4 mg; 8 mg Rectal suppository: 3 mg *Also available in an extended release, abuse-deterrent oral tablet formulation: 8 mg, 12 mg, 16 mg, 32 mg	Management of moderate-to-severe pain Exalgo: Management of moderate-to-severe pain in opioid-tolerant patients	N/A	Acute pain: Oral: 2-4 mg every 4-6 hours as needed IV: 0.2-1 mg every 2-3 hours as needed; Continuous infusion: 0.5-3 mg/hour IM, SubQ: 0.8-1 mg every 3-4 hours as needed; *IM route not recommended Rectal: 3 mg every 6-8 hours as needed *Parenteral doses are up to 5 times more potent. Therefore, when administered parenterally, one-fifth of the oral dose will provide similar analgesia. Chronic pain (Exalgo): 8-64 mg every 24 hours	Product Dependent
Levorphanol	C-II	Oral	Oral Tablet: 2 mg	Relief of moderate-to-severe pain; preoperative sedation/analgesia; management of chronic pain (eg, cancer) requiring opioid therapy	N/A	2-4 mg every 6-8 hours as needed	Yes
Meperidine (Demerol; Meperitab)	C-II	Injection (IM, SubQ), Oral	Injection solution: 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 Oral solution: 50 mg/5 mL Oral tablet: 50 mg; 100 mg	Management of moderate-to-severe pain; adjunct to anesthesia and preoperative sedation	Reduce postoperative shivering; reduce rigors from amphotericin B	Oral, I.M., SubQ: 50-150 mg every 3-4 hours as needed	Yes

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Morphine (Astramorph; AVINza; Duramorph; Infumorph 200; Infumorph 500; Kadian; MS Contin, DepoDur)	C-II	Injection (IV, IM, SubQ, IT), Oral, Rectal	Oral capsule, extended release: 10mg, 20 mg, 30 mg, 40 mg, 45 mg, 50 mg, 60 mg, 70 mg, 75 mg, 80 mg, 90 mg, 100 mg, 120 mg, 130 mg, 150 mg, 200 mg Intramuscular device: 10 mg/0.7 mL Injection solution: 0.5 mg/mL; 1 mg/mL; 4 mg/mL; 5 mg/mL; 8 mg/mL; 10 mg/mL; 15 mg/mL; 25 mg/mL; 50 mg/mL; 150 mg/30 mL; 200 mg/20mL (Available in preservative-free formulations) Injection solution, liposomal: 10 mg/mL; 15 mg/1.5 mL Oral solution: 10 mg/5 mL; 20 mg/5 mL; 20 mg/mL; 100 mg/5 mL Rectal suppository: 5 mg; 10 mg; 20 mg; 30 mg Oral tablet: 15 mg, 30 mg Oral tablet; extended release: 15 mg, 30 mg, 60 mg, 100 mg, 200 mg	Relief of moderate-to-severe acute and chronic pain; relief of pain of myocardial infarction; relief of dyspnea of acute left ventricular failure and pulmonary edema; preanesthetic medication Infumorph: Used in continuous microinfusion devices for intrathecal or epidural administration in treatment of intractable chronic pain Extended release products: Moderate-to-severe pain when continuous, around-the-clock opioid analgesia is needed for an extended period of time	N/A	Oral: 10-30 mg every 4 hours as needed IM: 5-15 mg every 4 hours as needed; *IM no longer recommended IV, IT: 0.1-5 mg every 3-4 hours; in myocardial infarction- 2-8 mg every 5-15 minutes; continuous infusion: 0.8-10 mg/hour (up to 80 mg/hour) Rectal: 10-20 mg every 3-4 hours	Yes
Opium Tincture	C-II	Oral	Oral tincture: 10 mg/mL (1%)	Treatment of diarrhea in adults	N/A	6 mg of undiluted opium tincture (10 mg/mL) 4 times daily	Yes

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Oxycodone (Oxecta, Roxicodone)	C-II	Oral	Oral capsule: 5 mg Oral concentrate: 20 mg/mL Oral solution: 5 mg/5 mL Oral tablet: 5 mg, 10 mg, 15 mg, 20 mg, 30 mg Oral tablet Abuse-Deterrent: 5 mg, 7.5 mg *Also available in a long-acting oral tablet formulation: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg	Management of moderate-to-severe pain, normally used in combination with non-opioid analgesics	N/A	Initial: 5-15 mg every 4-6 hours as needed; dosing range: 5-20 mg per dose	Product Dependent
Oxycodone and Acetaminophen (Endocet; Magnacet; Percocet; Primlev; Roxicet; Roxicet)	C-II	Oral	Oral caplet: Oxycodone hydrochloride 5 mg and acetaminophen 500 mg Oral capsule: Oxycodone hydrochloride 5 mg and acetaminophen 500 mg Oral solution: Oxycodone hydrochloride 5 mg and acetaminophen 325 mg per 5 mL Oral tablet: Oxycodone hydrochloride 2.5 mg and acetaminophen 325 mg; 5/300 mg; 5/325 mg; 5/400 mg; 7.5/300 mg; 7.5/325 mg; 7.5/500 mg; 10/300 mg; 10/325 mg; 10/400 mg; 10/650 mg	Management of moderate to moderately-severe pain	N/A	Initial dose, based on oxycodone content: 2.5-10 mg every 6 hours as needed. Titrate according to pain severity and individual response. Do not exceed acetaminophen 4 g daily.	Yes: Excludes caplet and solution
Oxycodone and Aspirin (Endodan®; Percodan®)	C-II	Oral	Oral tablet: Oxycodone hydrochloride 4.8355 mg and aspirin 325 mg	Management of moderate- to moderately-severe pain	N/A	One tablet every 6 hours as needed for pain; maximum aspirin dose should not exceed 4 g/day.	Yes

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Oxycodone and Ibuprofen	C-II	Oral	Oral tablet: Oxycodone hydrochloride 5 mg and ibuprofen 400 mg	Short-term (≤7 days) management of acute, moderate-to-severe pain	N/A	Take 1 tablet as needed (maximum: 4 tablets/24 hours)	Yes
Oxymorphone (Opana; Opana ER)	C-II	Injection (IM, IV), Oral	Injection solution (IM, IV): 1 mg/mL Oral tablet: 5 mg, 10 mg Oral tablet, extended release: 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg (available in an abuse-deterrent formulation)	Parenteral: Management of moderate-to-severe acute pain; analgesia during labor; preoperative medication; anesthesia support; relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to acute left ventricular failure Oral: Management of moderate-to-severe acute pain Oral, extended release: Management of moderate-to-severe pain in patients requiring around-the-clock opioid treatment for an extended period of time	N/A	IM, SubQ: 1-1.5 mg; may repeat every 4-6 hours as needed IV: 0.5 mg Acute pain: 5-10 mg every 4-6 hours as needed Chronic pain (Opana® ER): 5-40 mg every 12 hours	Product dependent
Paregoric	C-III	Oral	Oral tincture: 2 mg/5 mL	Treatment of diarrhea	N/A	5-10 mL 1-4 times daily Children: 0.25-0.5 mL/kg 1-4 times daily	Yes
Pentazocine and Naloxone	C-IV	Oral	Oral tablet: pentazocine 50 mg and naloxone 0.5 mg	Relief of moderate-to-severe pain; indicated for oral use only	N/A	Pentazocine 50 mg every 3-4 hours; may increase to 100 mg/dose if needed, but should not exceed 600 mg/day (maximum: 12 tablets/day)	Yes

Product	Schedule	Route of Administration	Available Doses	Labeled Uses	Unlabeled Uses	Dose Range (mg), Adults	Generic Available
Tapentadol (Nucynta; Nucynta ER)	C-II	Oral	Oral tablet: 50 mg, 75 mg, 100 mg Oral tablet, Extended Release: 50 mg, 100 mg, 150, mg, 200 mg, 250 mg Nucynta Oral Solution: FDA approved October 2012; anticipated availability currently unknown.	Immediate release: Relief of moderate-to-severe acute pain Extended Release: Relief of moderate-to-severe chronic pain or neuropathic pain associated with diabetic peripheral neuropathy (DPN)	N/A	Acute moderate-severe pain: 50-100 mg every 4-6 hours as needed (maximum: 600 mg daily) Chronic moderate-severe pain: 50 mg twice daily (max dose: 500 mg daily);Titrate in increments of 50 mg no more frequently than twice daily every 3 days to effective dose	No
Tramadol (ConZip; Ultram; Ultram ER)	C-IV	Oral	Oral capsule, variable release: 100 mg (25 mg immediate release/75 mg extended release); 150 mg (37.5 mg immediate release/112.5 mg extended release); 200 mg (50 mg immediate release/150 mg extended release); 300 mg (50 mg immediate release/250 mg extended release) Oral tablet: 50 mg Oral tablet, extended release: 100 mg, 200 mg, 300 mg	Relief of moderate to moderately-severe pain	N/A	Immediate release: 50-100 mg every 4-6 hours (not to exceed 400 mg/day) Extended release: 100-300 mg once daily	Yes

Table 3. Rapid-Onset Fentanyl Products[3, 4]

Medication	Initial Dosage & Strengths	Max use	Daily Dose Example (4x initial)
Buccal tablets (fentanyl citrate; Fentora)	100 mcg 0.1mg to 0.8mg	2 doses per breakthrough pain episode every 4 hours	400mcg QD
Oral transmucosal lozenge (fentanyl citrate; Actiq)	200mcg 0.2mg to 1.6mg	Not >2/episode ≤4 units/day	800mcg QD
Buccal film (Onsolis)	200mcg 0.2mg to 1.2mg	4 applications per day	800mcg QD
Sublingual tablets (Abstral)	100 mcg under the tongue 0.1mg to 0.8mg	2 doses/episode ≤4 breakthrough episodes/day	400mcg QD
Intranasal spray (Lazanda)	100 mcg (1 spray to 1 nostril) 0.1mg & 0.4mg	≤4 episodes of breakthrough pain	400mcg QD
Sublingual spray (Subsys)	100 mcg under the tongue 0.1mg to 0.8mg	2 doses/episode ≤4 breakthrough episodes/day	400mcg QD

Pharmacology

The opioid analgesics bind to specific receptors within and outside the central nervous system (CNS).[1, 2] Three opioid receptors are indicated in the mechanism of opioid analgesia: mu, delta, and kappa. The mu receptor is considered the most important and its activation produces both analgesic and euphoric effects. Mu receptors are found within the CNS and peripherally in areas and tracts associated with pain perception, sensory nerves, mast cells, and in the gastrointestinal (GI) tract.[1, 2] The activation is highly variable and the response seen between patients and the various opioids therefore vary. Factors such as renal and hepatic function, age and genetic factors also affect an individual's response to opioids.[15, 16]

Opioids are classified as full agonists, partial agonists, or mixed agonist-antagonists. Full agonists' effectiveness with increasing doses is not limited by a ceiling and they will not reverse or antagonize the effects of other full agonists given simultaneously. Morphine, hydromorphone, codeine, oxycodone, oxymorphone, hydrocodone, methadone, levorphanol, and fentanyl are classified as full agonists. Partial agonists (such as buprenorphine) are subject to a ceiling effect and are less effective analgesics than full agonists at opioid receptors. Mixed agonist-antagonists block or are neutral at one opioid receptor while activating a different opioid receptor and their analgesic effectiveness is also limited by a dose-related ceiling effect. Examples include pentazocine (Talwin), butorphanol tartrate (Stadol), dezocine (Dalgan), and nalbuphine hydrochloride (Nubain). They are contraindicated for use in patients receiving an opioid agonist because they may precipitate a withdrawal syndrome and increase pain.[17]

Morphine is the opioid agent against which all analgesics are compared.[1, 2] Morphine is obtained from opium or extracted from poppy straw. Many semisynthetic morphine derivatives are produced by modifications to the parent morphine structure. For example, codeine is methylmorphine and oxycodone and naloxone are 14-OH compounds. Each of the opioid agents and morphine derivatives can vary in potency. Equianalgesic dosing recommendations are available and allow for conversion between agents. The individual effects of opioid analgesics can vary from patient to patient and careful monitoring is required during conversion between agents to ensure the response is appropriate.

Table 4. Pharmacokinetics of the Short-Acting Opioid Agents[3, 4, 18]

Agents	Bioavailability	Onset of Action	Half-life	Distribution	Metabolism	Excretion
Buprenorphine Products	I.M.: 70%; Sublingual tablet: 29%; Transdermal patch: ~15% Absorption: I.M., SubQ: 30% to 40%	IM: Within 15 minutes Peak effect: IM: ~1 hour; Transdermal patch: Steady state achieved by day 3 Duration: I.M.: ≥6 hours	I.V.: 2.2-3 hours Sublingual tablet: ~37 hours Transdermal patch: ~26 hours	97-187 L/kg	Primarily hepatic via N-dealkylation by CYP3A4 to norbuprenorphine (active metabolite), and to a lesser extent via glucuronidation by UGT1A1 and 2B7 to buprenorphine 3-O-glucuronide; the major metabolite, norbuprenorphine, also undergoes glucuronidation via UGT1A3; extensive first-pass effect Protein binding: High (~96%, primarily to alpha- and beta globulin)	Feces (~70%); urine (27% to 30%)
Butorphanol	Nasal: 60% to 70%	I.M. and nasal: ≤15 minutes; I.V.: Within a few minutes Peak effect: I.M., I.V.: 0.5-1 hour; Nasal: 1-2 hours Duration: I.M., I.V.: 3-4 hours; Nasal: 4-5 hours	~2-9 hours; Hydroxybutorphanol ~18 hours	305-901 L	Hepatic to major metabolite, hydroxybutorphanol Protein binding: ~80%	Primarily urine (70% to 80%; ~5% unchanged); feces (15%)
Codeine Products	53%	0.5-1 hour Peek effect: 1-1.5 hours Duration: 4-6 hours	~3 hours	~3-6 L/kg	Hepatic via UGT2B7 and UGT2B4 to codeine-6-glucuronide, via CYP2D6 to morphine (active), and via CYP3A4 to norcodeine. Morphine is further metabolized via glucuronidation to morphine-3-glucuronide and morphine-6-glucuronide (active). Protein binding: ~7% to 25%	Urine (~90%, ~10% of the total dose as unchanged drug); feces
Dihydrocodeine Products	~20%	10-30 minutes Duration: 4-6 hours	3.8 hours	1.1-1.3 L/kg	Hepatic; substantial first-pass metabolism. Metabolite of hydrocodone with an active metabolite of dihydromorphone.	Primarily urine (highly variable)

Agents	Bioavailability	Onset of Action	Half-life	Distribution	Metabolism	Excretion
Fentanyl Products	Buccal film: 71% Buccal tablet: 65% Lozenge: ~50% Sublingual spray: 76% Sublingual tablet: 54%	IM: 7-8 minutes IV: Almost immediate Transdermal: 6 hours Transmucosal: 5-15 minutes Duration: IM: 1-2 hours; I.V.: 0.5-1 hour; Transdermal may last 72-96 hours	I.V.: 2-4 hours Transdermal patch: 20-27 hours Transmucosal products: 3-14 hours Nasal spray: 15-25 hours	4-6 L/kg; Highly lipophilic, redistributes into muscle and fat	Hepatic, primarily via CYP3A4 Protein binding: 80% to 85%	Urine 75% (primarily as metabolites, <7% to 10% as unchanged drug); feces ~9%
Hydrocodone Products		10-20 minutes Duration: 4-8 hours	3.3-4.4 hours	3.4-4.1 L/kg	Hepatic; O-demethylation via primarily CYP2D6 to hydromorphone (major, active metabolite with ~10- to 33-fold higher or as much as a >100-fold higher binding affinity for the mu-opioid receptor than hydrocodone); N-demethylation via CYP3A4 to norhydrocodone (major metabolite); and ~40% of metabolism/clearance occurs via other non-CYP pathways, including 6-ketosteroid reduction to 6-alpha-hydrocol and 6-beta-hydrocol, and other elimination pathways	Urine (26% of single dose in 72 hours, with ~12% as unchanged drug, 5% as norhydrocodone, 4% as conjugated hydrocodone, 3% as 6-hydrocodol, and 0.21% as conjugated 6-hydromorphol

Agents	Bioavailability	Onset of Action	Half-life	Distribution	Metabolism	Excretion
Hydromorphone	62%	Immediate release: Oral: 15-30 minutes; Peak effect: 30-60 minutes I.V.: 5 minutes; Peak effect: 10-20 minutes Extended release: 6 hours; Peak effect: ~9 hours Duration: Immediate release: Oral, I.V.: 3-4 hours Extended release: ~13 hours	Immediate release: 2-3 hours Extended release: ~11 hours	4 L/kg	Hepatic via glucuronidation; to inactive metabolites Protein binding: ~8% to 19%	Urine (primarily as glucuronide conjugates)
Levorphanol	~70%	10-60 minutes Duration: 4-8 hours	11-16 hours	10-13 L/kg	Hepatic via glucuronidation Protein binding: ~40%	Urine (as inactive metabolite)
Meperidine	~50% to 60%; increased with liver disease	Oral, SubQ: 10-15 minutes; I.V.: ~5 minutes Peak effect: SubQ.: ~1 hour; Oral: 2 hours Duration: Oral, SubQ.: 2-4 hours	Adults: 2.5-4 hours, Liver disease: 7-11 hours Normeperidine (active metabolite): 15-30 hours; can accumulate with high doses (>600 mg/day) or with decreased renal function	~4 L/kg	Hepatic; hydrolyzed to meperidinic acid (inactive) or undergoes N-demethylation to normeperidine (active; has 1/2 the analgesic effect and 2-3 times the CNS effects of meperidine) Protein binding: 65% to 75%	Urine (as metabolites)

Agents	Bioavailability	Onset of Action	Half-life	Distribution	Metabolism	Excretion
Morphine Products	17% to 33%	Oral (immediate release): ~30 minutes; I.V.: 5-10 minutes Duration: Immediate release: 4 hours Extended release: 8-24 hours	Immediate release forms: 2-4 hours; Avinza® ~24 hours; Kadian®:11-13 hours	1-6 L/kg; binds to opioid receptors in the CNS and periphery (eg, GI tract)	Hepatic via conjugation with glucuronic acid primarily to morphine-6-glucuronide (active analgesic) morphine-3-glucuronide (inactive as analgesic); minor metabolites include morphine-3-6-diglucuronide; other minor metabolites include normorphine (active) and morphine 3-ethereal sulfate Protein binding: 20% to 35%	Urine (primarily as morphine-3-glucuronide, ~2% to 12% excreted unchanged); feces (~7% to 10%)
Opium Tincture	Variable	15–30 minutes Duration: 4-5 hours	36 hours	~2-4 hours	Hepatic	Urine (primarily as morphine glucuronide conjugates and unchanged drug - morphine, codeine, papaverine, etc)
Oxycodone Products	60% to 87%	10-15 minutes Peak effect: 0.5-1 hour Duration: 3-6 hours	2-4 hours	2.6 L/kg	Hepatically via CYP3A4 to noroxycodone (has weak analgesic), noroxymorphone, and alpha- and beta-noroxycodol. CYP2D6 mediated metabolism produces oxymorphone (has analgesic activity; low plasma concentrations), alpha- and beta-oxymorphol. Protein binding: ~45%	Urine (~19% as parent; >64% as metabolites)
Oxymorphone	~10%	Parenteral: 5-10 minutes Duration: Parenteral: 3-6 hours	Oral: Immediate release: 7-9 hours; Extended release: 9-11 hours	IV: 1.94-4.22 L/kg	Hepatic via glucuronidation to active and inactive metabolites Protein binding: 10% to 12%	Urine (<1% as unchanged drug); feces

Agents	Bioavailability	Onset of Action	Half-life	Distribution	Metabolism	Excretion
Tapentadol	~32%	20-40 minutes Duration: 4-6 hours	Immediate release: ~4 hours; Long acting formulations: ~5-6 hours	IV: 442-638 L	Extensive metabolism, including first pass metabolism; metabolized primarily via phase 2 glucuronidation to glucuronides (major metabolite: tapentadol-O-glucuronide); minimal phase 1 oxidative metabolism; also metabolized to a lesser degree by CYP2C9, CYP2C19, and CYP2D6; all metabolites pharmacologically inactive Protein binding: ~20%	Urine (99%: 70% conjugated metabolites; 3% unchanged drug)
Tramadol	Immediate release: 75%; Extended release: Ultram® ER: 85% to 90%	Immediate release: ~1 hour Duration: 9 hours	Tramadol: ~6-8 hours; Active metabolite: 7-9 hours; Zytram® XL: ~16 hours; Durela™, Ralivia™, Tridural™: ~5-9 hours	2.5-3 L/kg	Extensively hepatic via demethylation (mediated by CYP3A4 and CYP2B6), glucuronidation, and sulfation; has pharmacologically active metabolite formed by CYP2D6 (M1; O-desmethyl tramadol) Protein binding, plasma: ~20%	Urine (30% as unchanged drug; 60% as metabolites)

Methods

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2014), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE within the preceding 15 years, evaluating efficacy of short-acting opioid agents in the treatment of pain disorders with reduction of symptoms as the endpoint are included. Trials evaluating the opioid analgesics as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded. The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as pharmacokinetics[19-25], pharmacodynamics[19], pharmacoeconomics[26], utilization[27, 28], cognitive effects[29], or driving ability.[30]
- Individual trials comparing the opioid agents in dose-finding and placebo-controlled studies or in healthy volunteers.[20-25, 31-49]
- Individual clinical trials evaluating opioid agents or formulations not currently available in the US or clinical trials without access to the full article.[50-59]

Clinical Efficacy

Clinical experience with the short-acting and rapid-onset opioid agents in treating patients with pain is examined in a number of review, experimental, and observational trials. The appendix summarizes all of the available comparative clinical evidence available for the short-acting and rapid-onset opioid agents.

- **How do the short-acting opioid agents compare with each other for reducing pain symptoms?**

The clinical evidence available for the short-acting opioid agents is extensive. The majority of comparative evidence evaluated in this report comes from 6 systematic review trials involving 170 clinical trials and over 27,000 patients. Morphine is evaluated in each of the six systematic reviews, hydromorphone and oxycodone are evaluated in 4 of the systematic reviews and one systematic review is a more comprehensive evaluation of other opioid agents (codeine, fentanyl, methadone, tramadol).

Overall the evidence evaluating oral morphine demonstrates efficacy in the treatment of pain. For cancer pain, morphine is considered the gold standard for treatment of moderate to severe pain. One large systematic review of 54 studies reported morphine is effective for cancer pain but is associated with some adverse effects, including constipation, nausea and vomiting.[33]

Overall, hydromorphone demonstrates efficacy as a potent analgesic in two large systematic reviews evaluating the efficacy of hydromorphone and morphine.[60, 61] Both agents were found to be equally efficacious in the treatment of pain disorders with similar rates of adverse events.[60, 61] One small meta-analysis of eight studies[62] suggests hydromorphone (494 patients) provides improved clinical analgesia compared to morphine (510 patients, $p = 0.012$). However, the effect-size was small (Cohen's $d = 0.266$) and disappeared when one study was removed. No differences in adverse effects were reported between treatment groups. Felden et al[62] notes safety in renal failure or during acute analgesia titration may also be benefits to support using hydromorphone versus morphine. A final meta-analysis of 13 randomized controlled trials demonstrates efficacy and tolerability of hydromorphone for moderate to severe cancer pain as an alternative to morphine and oxycodone but fails to demonstrates superiority or inferiority for hydromorphone therapy compared to morphine therapy.[63]

Evidence evaluating oxycodone demonstrates similar rates of safety and efficacy compared to either morphine or hydromorphone. Oxycodone, therefore, can be recommended as an alternative to morphine or hydromorphone for cancer-related pain.[64] A systematic review of 15 clinical trials[65] evaluating oral opioid analgesics in the treatment of severe cancer pain demonstrated fair evidence for the efficacy of transdermal fentanyl and poor evidence for morphine, tramadol, oxycodone, methadone, and codeine.[65] The authors concluded more, larger-scale studies are required for evaluation of the opioid analgesics in the treatment of cancer-related pain.

Eight randomized, controlled trials were identified for evaluation of the short-acting opioid agents in the treatment of pain disorders. Five trials evaluated the efficacy of oxycodone, four trials evaluated the efficacy of hydrocodone, three trials evaluated the efficacy of codeine, and oxymorphone, tramadol, and tapentadol were evaluated in 1-2 trials. Overall, evidence from these comparative clinical trials suggests similar rates of efficacy when the agents are dosed with equipotent doses.

Three trials compared the efficacy of hydrocodone to oxycodone.[66-68] Palangio et al[68] evaluated the efficacy of a single dose of hydrocodone 7.5 mg/ibuprofen or oxycodone 5 mg/acetaminophen in the treatment of obstetric/gynecological pain in 180 patients. Both treatments were effective in reducing pain scores compared to placebo. Hydrocodone/ibuprofen produced greater analgesic efficacy at 5-8 hours post dose compared to oxycodone/acetaminophen ($p < 0.05$). No differences in adverse events were reported between treatment groups. Litkowski et al[66] evaluated the efficacy of a single dose of hydrocodone 7.5 mg/acetaminophen, oxycodone 5 mg/acetaminophen, and oxycodone 5 mg/ibuprofen in the treatment of dental pain in 249 patients. Pain relief and pain intensity reduction scores were greater in the oxycodone/ibuprofen treatment group compared to the other treatment groups ($p < 0.001$). In addition, nausea and vomiting was reported less frequently in the oxycodone/ibuprofen group compared to the other treatment groups ($p < 0.05$). Marco et al[67] preformed an evaluation of 73 patients over the age of 12 with a fracture randomized to receive hydrocodone 5 mg/acetaminophen or oxycodone 5 mg/ acetaminophen. No differences in safety or efficacy were reported

between treatment groups. In this small trial, constipation was reported more frequently in the hydrocodone treatment group (21%) compared to the oxycodone treatment group (0%). Overall, this limited evidence evaluating hydrocodone and oxycodone suggests improved analgesic efficacy when the agent is combined with ibuprofen.

The efficacy of oxycodone was evaluated in two additional trials, one comparing oxycodone to oxymorphone and one comparing oxycodone to tapentadol.[69, 70] Aqua et al[69] evaluated the efficacy of oxycodone 15 mg and oxymorphone 10 mg or 20 mg in the treatment of pain following abdominal surgery in men and woman over the age of 18. Both agents were more efficacious than placebo in reducing pain intensity but no differences in safety or efficacy were reported between the active treatment groups. Hartrick et al[70] evaluated the efficacy of oxycodone 10 mg and tapentadol 50 mg or 75 mg in 659 patients with end-stage joint disease. Again, both agents were more efficacious than placebo in reducing pain intensity and no differences in safety or efficacy were reported between the active treatment groups.

Three trials evaluated the efficacy of codeine, two trials compared codeine to tramadol and one compared codeine to hydrocodone.[71-73] Mullican et al[71] evaluated the efficacy of codeine 30 mg/acetaminophen and tramadol 37.5 mg/acetaminophen in the treatment of low back or osteoarthritis pain in 462 adult patients. Smith et al[73] evaluated the efficacy of codeine 30 mg/acetaminophen and tramadol 37.5 mg/acetaminophen in the treatment of orthopedic, abdominal or post-surgical pain in 305 adult patients. Rodreguez et al[72] evaluated the efficacy of codeine 30 mg/acetaminophen and hydrocodone 5 mg/acetaminophen in the treatment of chronic cancer pain in 121 adult patients. No differences in safety or efficacy were reported between codeine and tramadol or hydrocodone in any of the comparative clinical trials. One trial did report higher rates of constipation and somnolence with codeine when compared to tramadol ($p \leq 0.05$). Similar trends towards greater rates of constipation and nausea with codeine treatment were demonstrated in the other two trials. Overall, this limited evidence suggests codeine has similar rates of efficacy when compared to tramadol or hydrocodone but may be associated with higher rates of adverse events, particularly constipation.

- **How do the rapid-onset opioid agents compare with each other for reducing pain symptoms?**

Very limited comparative clinical evidence is available for the rapid-onset opioid agents. Just one trial was identified for evaluation. Mercadante et al[74] evaluated the efficacy of intranasal fentanyl spray (INFS) and oral transmucosal fentanyl citrate (OTFC) in the treatment of breakthrough cancer pain in 139 adult patients with cancer. Both agents were efficacious in producing pain relief. INFS produced a quicker onset of pain relief (11 minutes versus 16 minutes, $p < 0.05$) and was preferred by more patients ($p < 0.05$).

A body of evidence comparing the short-acting opioid agents to the rapid-onset agents is available. In summary, the systematic reviews and the RCTs comparing the

short-acting opioid agents to the rapid-onset agents demonstrate similar rates of efficacy. Some evidence suggests improved efficacy with the rapid-onset agents in select populations (unpredictable pain, short-duration of pain relief required). In general, the evidence does not provide sufficient conclusive evidence to support the use of new fentanyl products over the non-fentanyl comparators. The rapid-onset agents should only be considered when immediate release oral opioids (e.g. morphine, oxycodone) are either inadequate or unsuitable.[75 76 77]

- **Are there patient subgroups based on demographics (e.g., age, racial groups, gender) or comorbidities for which one of the short-acting opioid agents is more effective or associated with fewer adverse effects?**

Five patient populations may require special consideration when being treated with opioid analgesic agents: geriatric patients, pediatric patients, liver disease, opioid naïve patients, and patients with a history of drug and alcohol abuse.

Geriatric Patients

No well-designed specific studies evaluating opioid therapy in the elderly are available. Criteria which may be used for selecting analgesics in the elderly include: severity and type of pain, overall efficacy, overall side-effect profile, onset of action, duration of action, drug interactions, abuse potential, and practical issues, such as cost and availability of the drug. Comorbidities and functional status are also important factors when addressing pain in the elderly. Renal impairment is common in the elderly. All opioids except buprenorphine, demonstrate increased half-life in patients with renal dysfunction. Based on this, smaller opioid doses may be required in the elderly and treatment with buprenorphine may be preferred. Risk of adverse events in the elderly can be serious. Opioids with a good tolerability profile and that are safe in overdose should be preferred. Slow dose titration is important to reduce risk of adverse events.[78]

Pediatric Patients

Infants and children may require treatment with an opioid. However, caution should be used when opioid agents are used in the patient population due to differences in pharmacokinetic and pharmacodynamic properties and risk of adverse events.[3, 4] One clinical trial evaluating the treatment of pain in children 6 to 17 years old found ibuprofen may be a safer and more efficacious treatment option compared to acetaminophen or codeine.[79] Codeine is a commonly used medication in pediatrics, as it is viewed as a safer option than morphine due to its weaker association with respiratory depression. However, codeine is associated with a lack of predictable dose response. Tramadol may also be an effective treatment option as more pediatric pharmacokinetic information becomes available.[80, 81] Intranasally administered fentanyl (INF) may be considered an alternate route of delivery for pain relief in children. Available studies show similar or improved pain scores when compared with other opioids and administration methods.[82] In neonates, opioid use should be reserved for treatment of severe postoperative pain or use in intensive care units, using continuous infusions rather than intermittent boluses.[83]

Liver and Renal Disease

All of the opioid agents are metabolized by the liver and should be used with caution in patients with hepatic disease. Increased bioavailability after oral administration and cumulative effects may occur in this patient population. The pharmacokinetics of morphine, codeine, dihydrocodeine, meperidine, and propoxyphene may also be altered in patients with renal disease. The active metabolites of morphine and codeine may accumulate in this patient population with repeated dosing and symptoms of opioid overdose may result. Repeated doses of meperidine in patients with renal impairment may cause tremor and seizures and repeated doses of propoxyphene may lead to cardiac toxicity.[1, 3, 4]

Opioid Naïve Patients

Opioid-naïve patients are at increased risk for adverse events (respiratory depression and death) from inappropriate use of opioid pain medication. Identification of opioid-tolerant patients is complicated by interindividual variability in opioid responsiveness. It is recommended that patients be monitored during initial dosing and titration with rapid-onset opioids. Threshold levels were established to ensure patients are opioid-tolerant before rapid-onset opioids are taken. Patients considered opioid tolerant are those who are taking around-the-clock medicine, for one week or longer of one of the following agents: 60 mg/d oral morphine, ≥25 mcg/hr of transdermal fentanyl, ≥30 mg of oral oxycodone daily, ≥8 mg of oral hydromorphone daily, ≥25 mg oral oxymorphone daily or an equianalgesic dose of another opioid. [9]

Patients with a History of Drug/Alcohol Abuse

There is limited evidence available comparing the opioid analgesics in patients with a history of drug/alcohol abuse. The therapeutic management of pain in patients with addiction problems requires careful and ongoing assessments as well as a tailored management plans. Tools for clinicians treating pain in patients with a history of abuse include: strict contracts, judicious medication selection, frequent follow-ups and urine toxicology screenings.[84]

Adverse Drug Reactions

- **How does the safety of the short-acting opioid agents compare with each other?**

Opioid analgesic agents have been used for centuries and are the most commonly used pharmacologic agents for the treatment of moderate to severe pain.[1, 2] The most common adverse effects associated with the opioid analgesics include nausea, vomiting, sedation, pruritus and constipation.[3, 4] More serious adverse events which are frequently reported with opioid use include: respiratory depression, urinary retention, hypotension and delirium. Clinical trials demonstrate no differences in rates of serious adverse events when morphine and morphine-like agents are dosed with equianalgesic dosing schemes. However, differences in potency, multiple physicians, poly pharmacy, complicated medication regimens, and lack of education and communication between providers and

patients are common risk factors which increase the rate of opioid-related serious adverse effects.[1, 2]

Deaths related to misuse of prescription drugs is a growing problem. Prescription drug-related deaths exceed deaths resulting from automobile crashes in the US and are the number one cause of unintentional death. [85] According to the National Vital Statistics System Mortality File, opioid analgesics were involved in more than 40% of all drug poisoning deaths in 2008. In Utah, drug overdose deaths began to increase substantially in 2001 and the increase has continued through 2007.[86] In 2005, Utah had the highest rates in the nation of reported nonmedical use of pain relievers and increase in prescription opioid-related deaths."[87] Utah also ranks fourth in the nation for drug overdose.[88] The CDC stated in a recent report that unintentional drug overdose death rates in the United States have increased five-fold since 1990 and has been driven by increased use of opioid analgesics.[87] Hydromorphone, morphine, oxymorphone, oxycodone, fentanyl and methadone are potent schedule II controlled opioid agonists that have the highest potential for abuse and risk of producing respiratory depression.[89] Emergency department visits for fentanyl products have gone up by 105% from 2004 to 2008. It is also clear that preventative measures are needed and we have a responsibility to help prescribers and other healthcare professionals understand this increasing problem and to identify and implement prevention strategies.[90]

Cautions reported on package inserts of opioid analgesic agents

- Abuse potential, high risk of addiction, misuse, or diversion
- Respiratory disorders and concomitant use of respiratory/CNS depressants
- Patients with hepatic or renal impairment. Lowest possible dose should be used
- Carefully monitor patients that are taking CYP 3A4 inhibitors and increase dose conservatively
- MAOI therapy within 14 days; severe and unpredictable potentiation of opioids by MAOI inhibitors has been reported
- Concomitant use with other CNS depressants
- Elderly or debilitated patients; higher risk of respiratory depression and other adverse events
- Fentanyl is contraindicated in the management of acute or postoperative pain and should not be used in opioid non-tolerant patients.

Summary

The opioid analgesic agents have been used for centuries and are the most commonly used pharmacologic agents for the treatment of moderate to severe pain. Opioid analgesics stimulate opiate receptors and produce pain relief without producing loss of consciousness. This report reviewed the efficacy of the short-acting and rapid-onset opioid agents in the treatment of pain disorders. Seventeen opioid agents were included in the review. Current American Pain Society guidelines recommend a short-acting opioid for the treatment of breakthrough pain and a long-acting opioid for the treatment of around-the-clock pain. The World Health Organization analgesic ladder addresses pain relief strategies at three levels. Non-opioid pain relievers are used at the lowest level, weak opioid agents (codeine) are used for moderate pain and strong opioid agents (morphine, hydromorphone, oxymorphone, methadone and fentanyl) are recommended for the highest level of pain. Patients may be switched from one opioid to another using equipotent dosing and careful monitoring during the conversion. Appropriate management of breakthrough pain is important as patients with breakthrough pain have a higher frequency of hospital admissions and higher estimated annual medical costs.

Clinical experience with the short-acting agents in treating patients with pain is extensive. The majority of comparative evidence evaluated in this report comes from 6 systematic review trials involving 170 clinical trials and over 27,000 patients. Morphine is evaluated in each of the six systematic reviews and hydromorphone and oxycodone are evaluated in 4 of the systematic reviews. Overall the evidence evaluating oral morphine demonstrates efficacy in the treatment of pain. For cancer pain, morphine is considered the gold standard for treatment of moderate to severe pain. Hydromorphone demonstrates efficacy as a potent analgesic with equal efficacy and similar rates of adverse events compared to morphine. In addition, eight randomized, controlled trials were identified for evaluation of the short-acting opioid agents in the treatment of pain disorders. Five trials evaluated the efficacy of oxycodone, four trials evaluated the efficacy of hydrocodone, and three trials evaluated the efficacy of codeine. Overall, evidence from these comparative clinical trials suggests similar rates of efficacy when the agents are dosed with equipotent doses.

Very limited comparative clinical evidence is available for the rapid-onset opioid agents. One trial reported intranasal fentanyl spray may produce quicker onset of analgesia than oral transmucosal fentanyl citrate in the treatment of breakthrough cancer pain in 139 adult patients. A larger body of evidence evaluating short-acting opioid agents and rapid-onset agents is available. In summary, the systematic reviews comparing the short-acting opioid agents to the rapid-onset agents do not provide sufficient conclusive evidence to support the use of new fentanyl products over the non-fentanyl comparators. The rapid-onset agents should only be considered when immediate release oral opioids are either inadequate or unsuitable. Currently, the rapid-onset fentanyl products are only approved for treatment of BTP in opioid-tolerant patients with cancer.

Five patient populations may require special consideration when being treated with opioid analgesic agents: geriatric patients, pediatric patients, liver disease, opioid naïve patients, and patients with a history of drug and alcohol abuse. In general, these patients may require

changes in dosing schemes, reductions in duration of therapy, judicious medication selections and frequent follow-ups.

The most common adverse effects associated with the opioid analgesics include nausea, vomiting, sedation, pruritus and constipation. Serious adverse effects frequently reported with opioid use include: respiratory depression, urinary retention, hypotension and delirium. Clinical trials demonstrate no differences in rates of serious adverse events when morphine and morphine-like agents are dosed with equianalgesic dosing schemes. Unintentional drug overdose death rates in the United States have increased five-fold since 1990 and this has been driven by increased use of opioid analgesics. Hydromorphone, morphine, oxymorphone, oxycodone, fentanyl and methadone are potent schedule II controlled opioid agonists that have the highest potential for abuse and risk of producing respiratory depression.

Overall, the opioid analgesic agents are effective treatment options for pain disorders. When compared at equianalgesic doses, the opioid agents demonstrate similar rates of safety and efficacy. The opioid analgesic products are available in many dosage forms, varying potencies and differing durations of action. Pain management must be individualized for each patient and include careful evaluation of patient history, age, comorbidities, type of pain, underlying diseases and concurrent medications.

References

1. Yaksh TL, Wallace MS. Chapter 18. Opioids, Analgesia, and Pain Management. In: Brunton LL, Chabner BA, Knollmann BC, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. New York: McGraw-Hill; 2011.

2. Rathmell JP, Fields HL. Chapter 11. Pain: Pathophysiology and Management. In: Long DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J, eds. *Harrisons Princliples of Internal Medicine*. 18 ed. New York: McGraw-Hill; 2012.

3. AHFS Drug Information, ed *AHFS 2014 Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists; 2014.

4. Lexi-Comp I, ed *Drug Information Handbook.* 21st ed. Hudson, OH: Lexi-Comp; 2014.

5. Millan MJ. The induction of pain: an integrative review. *Prog Neurobiol.* Jan 1999;57(1):1-164.

6. Riedel W, Neeck G. Nociception, pain, and antinociception: current concepts. *Z Rheumatol.* Dec 2001;60(6):404-415.

7. Schaible HG. Peripheral and central mechanisms of pain generation. *Handb Exp Pharmacol.* 2007(177):3-28.

8. Miaskowski C ea. Guideline for the Management of Cancer Pain in Adults and Children. Glenview (IL): American Pain Society (APS. 2005;Clinical practice guideline no.3:166.

9. Fine PGM, Brennan MJM, Miaskowski C.A. PhD R. Opioid-Based Management of Persistent and Breakthrough pain. *International Association for the Study of Pain 12th World Congress on Pain.* Vol Glasgow, Scotland: Pain Medicine News; 2008.

10. Lossignol DA, Dumitrescu C. Breakthrough pain: progress in management. *Curr Opin Oncol.* Jul;22(4):302-306.

11. van der Valk R, Webers CA, Schouten JS, Zeegers MP, Hendrikse F, Prins MH. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. *Ophthalmology.* Jul 2005;112(7):1177-1185.

12. Fine PG, Portenoy RK. Establishing "best practices" for opioid rotation: conclusions of an expert panel. *J Pain Symptom Manage.* Sep 2009;38(3):418-425.

13. Knotkova H, Fine PG, Portenoy RK. Opioid rotation: the science and the limitations of the equianalgesic dose table. *J Pain Symptom Manage.* Sep 2009;38(3):426-439.

14. Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *The journal of pain : official journal of the American Pain Society.* 2002;3(1):38-44.

15. Ross JR, Rutter D, Welsh K, et al. Clinical response to morphine in cancer patients and genetic variation in candidate genes. *Pharmacogenomics J.* 2005;5(5):324-336.

16. Pasternak GW. Molecular biology of opioid analgesia. *J Pain Symptom Manage.* May 2005;29(5 Suppl):S2-9.

17. (NIH). NCIatNIoH.

18. Rowell FJ, Seymour RA, Rawlins MD. Pharmacokinetics of intravenous and oral dihydrocodeine and its acid metabolites. *Eur J Clin Pharmacol.* 1983;25(3):419-424.

19. Ing Lorenzini K, Daali Y, Dayer P, Desmeules J. Pharmacokinetic-pharmacodynamic modelling of opioids in healthy human volunteers. a minireview. *Basic Clin Pharmacol Toxicol.* Mar;110(3):219-226.

20. Darwish M, Kirby M, Jiang JG. Effect of buccal dwell time on the pharmacokinetic profile of fentanyl buccal tablet. *Expert Opin Pharmacother.* Sep 2007;8(13):2011-2016.

21. Darwish M, Kirby M, Robertson P, Jr., Hellriegel E, Jiang JG. Comparison of equivalent doses of fentanyl buccal tablets and arteriovenous differences in fentanyl pharmacokinetics. *Clin Pharmacokinet.* 2006;45(8):843-850.

22. Darwish M, Tempero K, Kirby M, Thompson J. Relative bioavailability of the fentanyl effervescent buccal tablet (FEBT) 1,080 pg versus oral transmucosal fentanyl citrate 1,600 pg and dose proportionality of FEBT 270 to 1,300 microg: a single-dose, randomized, open-label, three-period study in healthy adult volunteers. *Clin Ther.* May 2006;28(5):715-724.

23. Fisher A, Watling M, Smith A, Knight A. Pharmacokinetic comparisons of three nasal fentanyl formulations; pectin, chitosan and chitosan-poloxamer 188. *Int J Clin Pharmacol Ther.* Feb;48(2):138-145.

24. Nave R, Schmitt H, Popper L. Faster absorption and higher systemic bioavailability of intranasal fentanyl spray compared to oral transmucosal fentanyl citrate in healthy subjects. *Drug Deliv.* Jun-Jul;20(5):216-223.

25. Saunders DL, Messina J, Darwish M, Xie F, Leary KJ, Cantilena LR. Assessment of the relative potency of fentanyl buccal tablet to intravenous morphine in healthy volunteers using a thermally induced hyperalgesia pain model. *J Clin Pharmacol.* Jun;52(6):870-879.

26. Kuo KL, Saokaew S, Stenehjem DD. The pharmacoeconomics of breakthrough cancer pain. *J Pain Palliat Care Pharmacother.* Jun;27(2):167-175.

27. Mitra R. The utilization of opiates in pain management: use or abuse. *Eur J Phys Rehabil Med.* Feb;49(1):93-96.

28. Wightman R, Perrone J, Portelli I, Nelson L. Likeability and abuse liability of commonly prescribed opioids. *J Med Toxicol.* Dec;8(4):335-340.

29. Hojsted J, Kurita GP, Kendall S, Lundorff L, de Mattos Pimenta CA, Sjogren P. Non-analgesic effects of opioids: the cognitive effects of opioids in chronic pain of malignant and non-malignant origin. An update. *Curr Pharm Des.*18(37):6116-6122.

30. Strand MC, Fjeld B, Arnestad M, Morland J. Can patients receiving opioid maintenance therapy safely drive? A systematic review of epidemiological and experimental studies on driving ability with a focus on concomitant methadone or buprenorphine administration. *Traffic Inj Prev.*14(1):26-38.

31. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev.*8:CD004959.

32. Basurto Ona X, Rigau Comas D, Urrutia G. Opioids for acute pancreatitis pain. *Cochrane Database Syst Rev.*7:CD009179.

33. Wiffen PJ, McQuay HJ. Oral morphine for cancer pain. *Cochrane Database Syst Rev.* 2007(4):CD003868.

34. Derry S, Derry CJ, Moore RA. Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults. *Cochrane Database Syst Rev.*6:CD010289.

35. Derry S, Moore RA, McQuay HJ. Single dose oral codeine, as a single agent, for acute postoperative pain in adults. *Cochrane Database Syst Rev.* (4):CD008099.

36. Haroutiunian S, McNicol ED, Lipman AG. Methadone for chronic non-cancer pain in adults. *Cochrane Database Syst Rev.*11:CD008025.

37. Ramiro S, Radner H, van der Heijde DM, Buchbinder R, Aletaha D, Landewe RB. Combination therapy for pain management in inflammatory arthritis: a Cochrane systematic review. *J Rheumatol Suppl.* Sep;90:47-55.

38. Whittle SL, Richards BL, van der Heijde DM, Buchbinder R. The efficacy and safety of opioids in inflammatory arthritis: a Cochrane systematic review. *J Rheumatol Suppl.* Sep;90:40-46.

39. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. *Cochrane Database Syst Rev.*8:CD006146.

40. Gimbel J, Ahdieh H. The efficacy and safety of oral immediate-release oxymorphone for postsurgical pain. *Anesth Analg.* Nov 2004;99(5):1472-1477; table of contents.

41. McNulty JP. Can levorphanol be used like methadone for intractable refractory pain? *J Palliat Med.* Apr 2007;10(2):293-296.

42. Corsinovi L, Martinelli E, Fonte G, et al. Efficacy of oxycodone/acetaminophen and codeine/acetaminophen vs. conventional therapy in elderly women with persistent, moderate to severe osteoarthritis-related pain. *Arch Gerontol Geriatr.* Nov-Dec 2009;49(3):378-382.

43. Goudas L, Carr DB, Bloch R, et al. Management of cancer pain. *Evid Rep Technol Assess (Summ).* Jan 2001(35):1-5.

44. Davies A, Finn A, Tagarro I. Intra- and interindividual variabilities in the pharmacokinetics of fentanyl buccal soluble film in healthy subjects: a cross-study analysis. *Clin Drug Investig.*31(5):317-324.

45. Finn AL, Vasisht N, Stark JG, Gever LN, Tagarro I. Dose proportionality and pharmacokinetics of fentanyl buccal soluble film in healthy subjects: a phase I, open-label, three-period, crossover study. *Clin Drug Investig.* Jan 1;32(1):63-71.

46. Kress HG, Oronska A, Kaczmarek Z, Kaasa S, Colberg T, Nolte T. Efficacy and tolerability of intranasal fentanyl spray 50 to 200 microg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. *Clin Ther.* Jun 2009;31(6):1177-1191.

47. Mystakidou K, Panagiotou I, Gouliamos A. Fentanyl nasal spray for the treatment of cancer pain. *Expert Opin Pharmacother.* Jul;12(10):1653-1659.

48. Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther.* Apr 2007;29(4):588-601.
49. Vasisht N, Gever LN, Tagarro I, Finn AL. Formulation selection and pharmacokinetic comparison of fentanyl buccal soluble film with oral transmucosal fentanyl citrate: a randomized, open-label, single-dose, crossover study. *Clin Drug Investig.* 2009;29(10):647-654.
50. Bekkering GE, Soares-Weiser K, Reid K, et al. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. *Curr Med Res Opin.* Jul;27(7):1477-1491.
51. Stegmann JU, Weber H, Steup A, Okamoto A, Upmalis D, Daniels S. The efficacy and tolerability of multiple-dose tapentadol immediate release for the relief of acute pain following orthopedic (bunionectomy) surgery. *Curr Med Res Opin.* Nov 2008;24(11):3185-3196.
52. Daniels S, Casson E, Stegmann JU, et al. A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Curr Med Res Opin.* Jun 2009;25(6):1551-1561.
53. Daniels SE, Upmalis D, Okamoto A, Lange C, Haeussler J. A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for postoperative (bunionectomy) pain. *Curr Med Res Opin.* Mar 2009;25(3):765-776.
54. Hale M, Upmalis D, Okamoto A, Lange C, Rauschkolb C. Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. *Curr Med Res Opin.* May 2009;25(5):1095-1104.
55. Etropolski M, Kelly K, Okamoto A, Rauschkolb C. Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. *Adv Ther.* May;28(5):401-417.
56. Vorsanger G, Xiang J, Okamoto A, Upmalis D, Moskovitz B. Evaluation of study discontinuations with tapentadol inmmediate release and oxycodone immediate release in patients with low back or osteoarthritis pain. *J Opioid Manag.* May-Jun;6(3):169-179.
57. Fricke JR, Jr., Hewitt DJ, Jordan DM, Fisher A, Rosenthal NR. A double-blind placebo-controlled comparison of tramadol/acetaminophen and tramadol in patients with postoperative dental pain. *Pain.* Jun 2004;109(3):250-257.
58. Fricke JR, Jr., Karim R, Jordan D, Rosenthal N. A double-blind, single-dose comparison of the analgesic efficacy of tramadol/acetaminophen combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery. *Clin Ther.* Jun 2002;24(6):953-968.
59. Wolff RF, Aune D, Truyers C, et al. Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. *Curr Med Res Opin.* May;28(5):833-845.
60. Quigley C. WITHDRAWN: Hydromorphone for acute and chronic pain. *Cochrane Database Syst Rev.*10:CD003447.
61. Quigley C. Hydromorphone for acute and chronic pain. *Cochrane Database Syst Rev.* 2002(1):CD003447.
62. Felden L, Walter C, Harder S, et al. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. *Br J Anaesth.* Sep;107(3):319-328.
63. Pigni A, Brunelli C, Caraceni A. The role of hydromorphone in cancer pain treatment: a systematic review. *Palliat Med.* Jul;25(5):471-477.
64. King SJ, Reid C, Forbes K, Hanks G. A systematic review of oxycodone in the management of cancer pain. *Palliat Med.* Jul;25(5):454-470.
65. Koyyalagunta D, Bruera E, Solanki DR, et al. A systematic review of randomized trials on the effectiveness of opioids for cancer pain. *Pain Physician.* Jul;15(3 Suppl):ES39-58.
66. Litkowski LJ, Christensen SE, Adamson DN, Van Dyke T, Han SH, Newman KB. Analgesic efficacy and tolerability of oxycodone 5 mg/ibuprofen 400 mg compared with those of oxycodone 5 mg/acetaminophen 325 mg and hydrocodone 7.5 mg/acetaminophen 500 mg in patients with moderate to severe postoperative pain: a randomized, double-blind, placebo-controlled, single-dose, parallel-group study in a dental pain model. *Clin Ther.* Apr 2005;27(4):418-429.
67. Marco CA, Plewa MC, Buderer N, Black C, Roberts A. Comparison of oxycodone and hydrocodone for the treatment of acute pain associated with fractures: a double-blind, randomized, controlled trial. *Acad Emerg Med.* Apr 2005;12(4):282-288.

68. Palangio M, Wideman GL, Keffer M, et al. Combination hydrocodone and ibuprofen versus combination oxycodone and acetaminophen in the treatment of postoperative obstetric or gynecologic pain. *Clin Ther.* May 2000;22(5):600-612.

69. Aqua K, Gimbel JS, Singla N, Ma T, Ahdieh H, Kerwin R. Efficacy and tolerability of oxymorphone immediate release for acute postoperative pain after abdominal surgery: a randomized, double-blind, active- and placebo-controlled, parallel-group trial. *Clin Ther.* Jun 2007;29(6):1000-1012.

70. Hartrick C, Van Hove I, Stegmann JU, Oh C, Upmalis D. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. *Clin Ther.* Feb 2009;31(2):260-271.

71. Mullican WS, Lacy JR, Group T-A-S. Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the management of chronic pain: a comparative trial. *Clin Ther.* Sep 2001;23(9):1429-1445.

72. Rodriguez RF, Castillo JM, Del Pilar Castillo M, et al. Codeine/acetaminophen and hydrocodone/acetaminophen combination tablets for the management of chronic cancer pain in adults: a 23-day, prospective, double-blind, randomized, parallel-group study. *Clin Ther.* Apr 2007;29(4):581-587.

73. Smith AB, Ravikumar TS, Kamin M, et al. Combination tramadol plus acetaminophen for postsurgical pain. *Am J Surg.* Apr 2004;187(4):521-527.

74. Mercadante S, Radbruch L, Davies A, et al. A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomised, crossover trial. *Curr Med Res Opin.* Nov 2009;25(11):2805-2815.

75. Zeppetella G, Ribeiro MD. Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database Syst Rev.* 2006(1):CD004311.

76. Zeppetella G. Opioids for the management of breakthrough cancer pain in adults: a systematic review undertaken as part of an EPCRC opioid guidelines project. *Palliat Med.* Jul 2011;25(5):516-524.

77. Elsner F, Zeppetella G, Porta-Sales J, Tagarro I. Newer generation fentanyl transmucosal products for breakthrough pain in opioid-tolerant cancer patients. *Clin Drug Investig.* 2011;31(9):605-618.

78. Pergolizzi J, Boger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract.* Jul-Aug 2008;8(4):287-313.

79. Clark E, Plint AC, Correll R, Gaboury I, Passi B. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics.* Mar 2007;119(3):460-467.

80. Duedahl TH, Hansen EH. A qualitative systematic review of morphine treatment in children with postoperative pain. *Paediatr Anaesth.* Aug 2007;17(8):756-774.

81. Harrop JE. Management of pain in childhood. *Arch Dis Child Educ Pract Ed.* Aug 2007;92(4):ep101-108.

82. Mudd S. Intranasal fentanyl for pain management in children: a systematic review of the literature. *J Pediatr Health Care.* Sep-Oct;25(5):316-322.

83. Simons SH, Anand KJ. Pain control: opioid dosing, population kinetics and side-effects. *Semin Fetal Neonatal Med.* Aug 2006;11(4):260-267.

84. Passik SD, Kirsh KL. Opioid therapy in patients with a history of substance abuse. *CNS Drugs.* 2004;18(1):13-25.

85. Sundwell DN RR, Erin Johnson. Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain. *Utah Department of Health.* Vol 2009.

86. Health UDo. Utah Health Status Update: Prescription Medication Overdose Deaths in Utah. 2008; http://health.utah.gov/opha/publications/hsu/08Nov_RxDrugDth.pdf. Accessed 15 March 2012.

87. CDC. Adult Use of Prescription Opioid Pain Medications - Utah, 2008. *MMWR.* February 19, 2010 2010;59(6):153-157.

88. ABC4. http://www.abc4.com/content/news/health/story/Prescription-drug-overdose-common-in-Utah/W1r6dHztDUeQdyVI1yHXXg.cspx. Accessed 23 March 2012.

89. DILAUDID® ORAL LIQUID and DILAUDID® TABLETS (hydromorphone hydrochloride) Product Label. 2007.

90. SAMHSA. http://www.oas.samhsa.gov/2k10/DAWN016/OpioidEdHTML.pdf. Accessed 22 March 2012.

91. Vissers D, Stam W, Nolte T, Lenre M, Jansen J. Efficacy of intranasal fentanyl spray versus other opioids for breakthrough pain in cancer. *Curr Med Res Opin.* May 2010;26(5):1037-1045.

Appendix: Evidence Tables

Evidence Table 1. Clinical Trials Evaluating the Efficacy of Short-Acting Opioid Agents in the Treatment of Pain Disorders

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Quigley et al, 2013[60, 61] Systematic Review of 48 randomized, controlled trials	3510	Treatment of both acute and chronic pain conditions in adults and children	Administration of hydromorphone compared with other opioids, bupivicaine and with itself, using different formulations	Analgesic efficacy Hydromorphone = Morphine Patient Preference Hydromorphone = Morphine	Hydromorphone = Morphine
King at el, 2011[64] Systematic Review of 29 trials (1 meta-analysis, 14 randomized controlled trials, 10 prospective observational studies and 4 case series)	16,284	Adult patients with moderate to severe cancer-related pain	Any formulation and route of oxycodone was considered, except intrathecal	Analgesic efficacy Oxycodone = Morphine Oxycodone = Hydromorphone	Oxycodone = Morphine Oxycodone = Hydromorphone
Felden et al, 2011[62] Meta-analysis of 11 controlled clinical studies (randomized, controlled trials and observational studies)	1215	Patients being treated with hydromorphone and/or morphine	Hydromorphone (494) Morphine (510)	Clinical analgesia Hydromorphone > Morphine (p = 0.012)	Hydromorphone = Morphine
Wiffen et al, 2007[33] Systematic Review of 54 randomized, controlled trials	3749	Adults and children with cancer pain	Oral Morphine (modified-release products and immediate-release products)	Analgesic efficacy • Morphine IR = Morphine immediate release • Morphine IR = Tramadol • Morphine IR = Oxycodone • Oral transmucosal fentanyl citrate > Morphine IR; p < 0.05	Nausea • Morphine IR > Oxycodone Hallucinations • Morphine IR > Oxycodone Treatment-related Discontinuation Rate • Morphine: 117/1893 (6%)
Pigni et al, 2010[63] Systematic review of 13 randomized controlled clinical trials	1208	Patients with moderate to severe cancer pain	Hydromorphone	Analgesic efficacy Hydromorphone = Morphine = Oxycodone	Variable Results

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Koyyalagunta et al, 2004[65] Systematic review of 15 randomized and non-randomized clinical trials	1583	Patients with moderate to severe cancer pain	Codeine Fentanyl (transmucosal) Methadone Morphine Oxycodone Tramadol	Fentanyl ≥ Codeine = Methadone = Morphine = Oxycodone = Tramadol	Overall AEs No differences between treatment groups Constipation Fentanyl ≥ Codeine = Methadone = Morphine = Oxycodone = Tramadol Overall Tolerability Fentanyl ≥ Codeine = Methadone = Morphine = Oxycodone = Tramadol
Aqua et al, 2007[69] Randomized, Double-Blind, Multicenter, Active- and Placebo-Controlled, Parallel-Group Trial	331	Men and women aged ≥18 years who discontinued short-acting parenteral opioids and developed moderate or severe pain within 30 hours after abdominal surgery	Oxycodone IR 15 mg (n = 83) Oxymorphone IR 10 (n = 82) or 20 mg (n = 81) Placebo (n = 85) Duration: Every 4 to 6 hours for up to 48 hours	Trial Discontinuation Rate Oxymorphone = Oxycodone >
Placebo Pain Intensity Scores Oxymorphone = Oxycodone >
Placebo	Adverse Event Related Discontinuation Rate: • Oxymorphone 10 mg: 8.5% (7/82) • Oxymorphone 20 mg: 17.3% (14/81) • Oxycodone: 13.3% (11.83) • Placebo: 12.9% (11/85) Frequency of Treatment-Related Adverse Events Reported: • Oxymorphone 10 mg: 46.3% (37/82) • Oxymorphone 20 mg: 51.9% (42/81) • Oxycodone: 54.2% (45/83) • Placebo: 34.1% (29/85)

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Mullican et al, 2001[71] Randomized, double blind, parallel-group, active-control, doubledummy, multicenter trial	462	Adult patients with chronic nonmalignant low back pain, osteoarthritis (OA) pain, or both	Codeine/APAP 30 mg/300 mg (n = 153) Tramadol/APAP 37.5 mg/325 mg (n = 309)	Total Pain Relief Scores: • codeine/APAP: 11.4 • tramadol/APAP: 11.9 Sum of Pain Intensity Differences • codeine/APAP: 3.3 • tramadol/APAP: 3.8 Assessments of efficacy by patients • codeine/apap = tramadol/apap Assessments of efficacy by patients • codeine/apap = tramadol/apap	Overall AE Rate: • codeine/apap = tramadol/apap Somnolence • codeine/APAP: 24% (37/153) • tramadol/APAP: 17% (54/309); p = 0.05 Constipation • codeine/APAP: 21% (32/153) • tramadol/APAP: 11% (35/309); p < 0.01 Headache • codeine/APAP: 7% (11/153) • tramadol/APAP: 11% (34/309); p = 0.08
Litkowski et al, 2005[66] Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Parallel-Group Study	249	Patients with moderate to severe postoperative dental pain	Hydrocodone 7.5 mg/Acetaminophen 500 mg (n = 63) Oxycodone 5 mg/Acetaminophen 325 mg (n = 61) Oxycodone 5 mg/lbuprofen 400 mg (n = 62) Placebo (n = 63)	Analgesia (Pain Relief Scores) • Hydrocodone/APAP: 8.36 • Oxycodone/APAP: 9.53 • Oxycodone/Ibuprofen: 14.98 • Placebo: 5.05 p < 0.001 for all agents compared to Oxycodone/Ibuprofen Sum of Pain Intensity Differences • Hydrocodone/APAP: 3.32 • Oxycodone/APAP: 3.58 • Oxycodone/Ibuprofen: 7.78 • Placebo: 0.69 p < 0.001 for all agents compared to Oxycodone/Ibuprofen	Nausea • Hydrocodone/APAP: 10 (15.9%) • Oxycodone/APAP: 14 (23%) • Oxycodone/Ibuprofen: 4 (6.5%); p < 0.05 compared to Oxycodone/apap • Placebo: 2 (3.2%) Vomiting • Hydrocodone/APAP: 5 (7.9%) • Oxycodone/APAP: 11 (18%) • Oxycodone/Ibuprofen: 2 (3.2%); p < 0.05 compared to Oxycodone/apap • Placebo: 1 (1.6%)
Palangio at al, 2000[68] Randomized, double-blind, parallel-group, single-dose, active-comparator, placebo-controlled study	180	Patients with moderate to severe postoperative obstetric or gynecologic pain	Hydrocodone 7.5mg/ibuprofen 200 mg (n = 61) Oxycodone 5 mg/acetaminophen 325 mg (n = 59) Placebo (n = 60)	Mean pain relief scores at hours 5, 6, 8 post-dose Hydrocodone/Ibuprofen > Oxycodone/APAP; p < 0.05 Mean pain intensity difference scores at hours 5-8 post-dose Hydrocodone/Ibuprofen > Oxycodone/APAP; p < 0.05	Adverse Event Rates • Hydrocodone/Ibuprofen: 11 (18%) • Oxycodone/APAP: 7 (11.9%) • Placebo: 6 (10%)

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Hartrick et al, 2009[70] Randomized, Double-Blind, Active- and Placebo-Controlled Study	659	Patients who were candidates for joint replacement surgery due to end-stage joint disease	Oxycodone IR 10 mg (n = 172) Placebo (n = 169) Tapentadol IR 50 mg (n = 157) Tapentadol IR 75 mg (n = 168)	Sum of pain intensity difference Tapentadol (50 mg, 75 mg) = Oxycodone > Placebo	Nausea/ Vomiting (Odds Ratio) • Tapentadol 50 vs Oxycodone: 0.21 (95% CI,0.128-0.339) • Tapentadol 75 vs Oxycodone: 0.32 (95% CI, 0.204-0.501) Constipation (Odds Ratio) • Tapentadol 50 vs Oxycodone: 0.13 (95% CI,0.057-0.302) • Tapentadol 75 vs Oxycodone: 0.20 (95% CI, 0.098-0.398) Discontinuation Rate • Tapentadol 50: 18% (28/157) • Tapentadol 75: 26% (43/168) • Oxycodone: 35% (60/172) • Placebo: 10% (17/169)
Rodreguez et al, 2007[72] Randomized, Double-blind, Parallel-Group Study	121	Adults with Chronic Cancer Pain	Codeine 30 mg/Acetaminophen 500 mg (n = 59) Hydrocodone 5 mg/Acetaminophen 500 mg (n = 62)	Response Rate to Initial Dosage • Codeine/APAP: 58% • Hydrocodone/APAP: 56% Response Rate to Double-Dosage • Codeine/APAP: 8% • Hydrocodone/APAP: 15% Rate of Lack of Pain Relief • Codeine/APAP: 34% • Hydrocodone/APAP: 29%	Constipation • Codeine/APAP: 36% • Hydrocodone/APAP: 29% Dizziness • Codeine/APAP: 24% • Hydrocodone/APAP: 19% Vomiting • Codeine/APAP: 24% • Hydrocodone/APAP: 16% Dry mouth • Codeine/APAP: 15% • Hydrocodone/APAP: 18%
Smith et al, 2004[73] Randomized, multicenter, double-blind, active- and placebo-controlled trial	305	Patients with orthopedic (n = 153) and abdominal (n = 152) postsurgical pain	Codeine 30 mg/APAP 300 mg (n = 109) Placebo (n = 98) Tramadol 37.5 mg/325 mg APAP (n = 98)	Analgesic Efficacy: Tramadol/APAP = Codeine/APAP > Placebo	Overall Rate of AEs: Tramadol/APAP = Codeine/APAP Constipation: • Codeine/APAP: 10.1% • Tramadol/APAP: 4.1% Vomiting • Codeine/APAP: 14.7% • Tramadol/APAP: 9.2%

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Marco et al, 2005[67] Randomized, Double-blind, Controlled Trial	73	Patients over the age of 12 years with fractures	Hydrocodone 5 mg with acetaminophen (n = 32) Oxycodone 5 mg with acetaminophen (n = 35)	Hydrocodone = Oxycodone	Overall Rate of AEs: Hydrocodone = Oxycodone Constipation: • Hydrocodone: 21% • Oxycodone: 0%
Zepetella et al, 2006[75] Systematic review of 4 randomized controlled trials	393	Patients with cancer who require treatment for break-through pain	Opioid Analgesics	Fentanyl (transmucosal) ≥ Morphine ≥ Placebo	Fentanyl = Morphine
Vissers D et al. 2010[91] Systematic review of 6 randomized controlled trials	594	Adult patients with cancer with breakthrough pain	Fentanyl (Intranasal) Other opioid analgesics	Intranasal Fentanyl ≥ Fentanyl Buccal Tablets Intranasal Fentanyl ≥ Oral Transmucosal Fentanyl Intranasal Fentanyl ≥ Oral Morphine	Not Reported

Evidence Table 1. Clinical Trials Evaluating the Efficacy of Rapid-Onset Opioid Agents in the Treatment of Pain Disorders

Reference / Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Mercadante et al, 2009 Randomized, multicenter, open-label, crossover trial	139	Adult cancer patients receiving stable background opioid treatment and experiencing BTP episodes	Intranasal fentanyl spray (INFS) Oral transmucosal fentanyl citrate (OTFC)	Onset of pain relief: INFS > OTFC, $p < 0.05$ Patient Preference: INFS > OTFC, $p < 0.05$	INFS = OTFC