Short-Acting Narcotic Analgesics Review
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Federal Schedule	Manufacturer	Indication(s)
benzhydrocodone/ acetaminophen* (Apadaz®)[1]	CII	KVK-Tech	Short-term (≤ 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
butorphanol nasal spray[2]	CIV	generic	Management of pain when the use of an opioid analgesic is appropriate
codeine sulfate[3]	CII	generic	Mild to moderately severe pain
codeine/acetaminophen[4]	CIII	generic	Mild to moderate pain
codeine/butalbital/ acetaminophen/caffeine (Fioricet® with codeine)[5]	CIII	generic, Actavis/Teva	Tension or muscle contraction headache
codeine/butalbital/aspirin/caffeine (Ascomp with codeine)[6,7]	CIII	generic, Breckenridge	Tension or muscle contraction headache
codeine/carisoprodol/aspirin†[8]	CIII	Ingenus	Moderate pain and muscle spasm associated with acute, painful musculoskeletal conditions
dihydrocodeine bitartrate/ acetaminophen/caffeine (Dvorah, Trezix™)[9,10]	CIII	generic, Phlight, Wraser	Moderate to moderately severe pain
fentanyl buccal (Fentora®)[11]	CII	Cephalon, Mayne*	Breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain
fentanyl nasal spray (Lazanda®)[12]	CII	West	
fentanyl sublingual spray (Subsys®)[13]	CII	Insys/West	
fentanyl transmucosal oral lozenge (Actiq®)[14]	CII	generic, Teva	
hydrocodone/acetaminophen solution (Lortab®)[15]	CII	generic, Akorn	Moderate to moderately severe pain
hydrocodone/acetaminophen tablet‡[16,17]	CII	generic	
hydrocodone/ibuprofen[18]	CII	generic	Short-term management of acute pain
hydromorphone (Dilaudid®)[19]	CII	generic, Rhodes	Management of pain in patients where an opioid analgesic is appropriate
levorphanol[20]	CII	generic	Moderate to severe pain
meperidine§[21,22]	CII	generic	Moderate to severe pain
morphine immediate release[23]	CII	generic	Moderate to severe acute and chronic pain
morphine immediate release‖[24,25]	CII	Hikma	Moderate to severe acute pain in adults; Moderate to severe acute pain in pediatrics ≥ 2 years of age (oral solution) or weighing ≥ 50 kg (tablets)
oxycodone immediate release (Oxaydo®¶)[26]	CII	Egalet/Zyla	Moderate to severe acute and chronic pain

FDA-Approved Indications (continued)

Drug	Federal Schedule	Manufacturer	Indication(s)
oxycodone immediate release (Roxicodone®)[27,28]	CII	generic, Mallinckrodt	Moderate to severe pain in adults
oxycodone/acetaminophen (Endocet®, Nalocet®, Percocet®, Primlev™, Prolate®)[29,30,31,32,33]	CII	generic, Qualitest/Par, Forte Bio-Pharma, Endo, Akrimax, Forte Bio-Pharma/FH2 Pharma	Moderate to severe pain
oxycodone/aspirin[34,35]	CII	generic	Moderate to severe pain
oxymorphone immediate release[36]	CII	generic	Moderate to severe acute pain
pentazocine/naloxone[37]	CIV	generic	Moderate to severe pain
tapentadol (Nucynta®)[38]	CII	Collegium	Relief of moderate to severe acute pain
tramadol (Ultram®)[**39]	CIV	generic, Janssen	Management of moderate to moderately severe pain in adults
tramadol (Qdolo™)[‖40]	CIV	Athena	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
tramadol/acetaminophen (Ultracet®)[††41]	CIV	generic, Janssen	Short-term (≤ 5 days) treatment of acute pain
tramadol/celecoxib (Seglentis®)[‖42]	CIV	Kowa	Management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate

*An authorized generic (AG) is available.

† Ingenus has discontinued codeine/carisoprodol/aspirin tablets as of September 1, 2020; product may remain on the market until supply has been depleted.[43]

‡ Previously available as the branded generic Norco® and branded generic Lorcet®, both of which have been discontinued.

§ Meperidine should only be used for the acute treatment of moderate to severe pain. It should not be used for the treatment of chronic pain. Prolonged use can increase the risk of toxicity (e.g., seizures) from the accumulation of the metabolite, normeperidine.

¶ Product name changed from Oxecta™ to Oxaydo® in 2015.[44]

‖ Approved under the abbreviated 505(b)(2) New Drug Application (NDA) pathway, which allows at least some data for approval to come from studies not conducted by or for the applicant.[45]

** Janssen announced the discontinuation of Ultram tablets in April 2020; the United States (US) Food and Drug Administration (FDA) is recommending product remain on the formularies until September 30, 2022, when the last batch expires. Product may be available until supply is depleted.[46]

†† Janssen announced the discontinuation of Ultracet in April 2020; the FDA is recommending product remain on formularies until October 31, 2022, when the last batch expires. Product may remain available until supply is depleted.[47]

Sufentanil (Dsuvia®) is a 30 mcg sublingual tablet indicated for use in adults in a certified medically supervised healthcare setting (e.g., hospitals, surgical centers, emergency departments) for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[48] It should not be used for home use, in children, or for ≥ 72 hours. It should only be administered by a healthcare professional (HCP), only be used in patients with no

alternative who are expected to tolerate the opioid, and discontinued before leaving the certified medically supervised healthcare setting. Dsuvia use will not be addressed in this therapeutic class review.

OVERVIEW

Pain is often undertreated, and pain management is greatly misunderstood. Different management techniques are utilized for acute and chronic pain. Historically, it has been cited that up to 73% of hospitalized medical patients receiving opiates were found in severe or moderate distress despite their analgesic regimen.[49] Caregivers' misconceptions regarding opiate doses, duration of analgesic effect, and fear of addiction were partly responsible for this undertreatment in both hospital and ambulatory care settings.[50] Despite strategies to improve pain control in the past few decades, the American Pain Society (APS) reports that over 80% of surgical patients experience acute postoperative pain, of which about 75% report the severity as moderate, severe, or extreme, and less than half of surgical patients report adequate postoperative pain relief.[51] In contrast, inappropriate use of opioid analgesics is thought to have contributed to the national crisis of opioid-related morbidity, mortality, and misuse.[52] Balancing use of opioid analgesics in the treatment of pain while mitigating the risks associated with medications in this class remains a challenge.

Treatment Guidelines

The World Health Organization's (WHO) guidelines for cancer pain management recommend a 3-stepped approach with consideration for the type of pain and response to therapy.[53] If pain occurs, WHO recommends prompt oral administration of drugs in the following order: non-opioids (acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs]); then, as necessary, mild opioids (codeine); then strong opioids, until the patient is free of pain. These agents can be used alone or in combination to achieve or maintain effective and safe pain management; any opioid can be considered for pain relief in the maintenance setting. Analgesics should be given around the clock, rather than on-demand. Psychosocial care and adjuvant therapies (e.g., corticosteroids, antidepressants, anticonvulsants, bisphosphonates) should also be considered as part of a comprehensive care plan.

For survivors of cancer, the American Society of Clinical Oncology (ASCO) provides guidelines on the use of pain medication in this population, including opioid analgesics in those who do not respond to more conservative management options; however, they do not recommend the use of one opioid over another.[54] Similarly, in 2022, the National Comprehensive Cancer Network (NCCN) updated their guidelines on the treatment of cancer pain in adults. The NCCN also does not specify the use of one specific opioid over another for all patients; however, they recommend against the use of meperidine (due to central nervous system [CNS] toxicity) and mixed agonist-antagonists (limited usefulness) for cancer pain.[55] Also, the NCCN recommends that the same opioid be used when both a short-acting and long-acting opioid are appropriate, when available. Extensive dosing, adverse effect management, and assessment guidance are also provided.

In 2016, the APS published a guideline on the management of postoperative pain.[56] These guidelines recommend oral over intravenous opioid analgesics in patients who are able to use the oral route. Intramuscular opioids are not recommended. The APS also recommends multimodal pain control, including non-pharmacologic and other medications, such as acetaminophen or NSAIDs, gabapentin, or pregabalin; however, one opioid agent is not recommended over another.

In the 2009 Management of Persistent Pain in Older Persons guideline, the American Geriatric Society (AGS) advises that in the elderly, even pain that is causing severe impairment may not be spontaneously revealed for a variety of personal, cultural, or psychological reasons.[57] Older persons may under-report pain, but there are also inherent difficulties in recognizing pain experienced by patients with cognitive impairment. Nevertheless, all patients with moderate to severe pain, pain-related functional impairment, or diminished quality of life due to pain should be considered for opioid therapy and should be reassessed for ongoing attainment of therapeutic goals, adverse effects, and safe and responsible medication use. Tramadol has opioid activity with apparently low abuse potential and is reportedly about as effective and safe as codeine or hydrocodone; however, tramadol has the additional risk of seizures if used in high doses or in predisposed patients.

In 2016, the Centers for Disease Control and Prevention (CDC) released guidelines for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care.[58] The guidelines prefer nonpharmacologic and non-opioid pharmacologic therapy for chronic pain, and recommend a full individualized assessment, including risk evaluation and realistic treatment goal setting, prior to prescribing opioids for chronic pain. If opioids are deemed appropriate for a patient's chronic pain, the CDC recommends initial treatment with immediate release opioids instead of extended-release opioids, which should be prescribed at the lowest effective dose. The CDC further specifies that doses of ≥ 50 morphine milligram equivalents (MME)/day should prompt reassessment of the opioid therapy benefits and risks for the patient and use of ≥ 90 MME/day should be avoided without justification. Long-term opioid use often begins with acute pain treatment; thus, immediate release opioids should be used for acute pain at the lowest effective dose, and the quantity should not exceed the expected duration of pain severe enough to require opioids (typically 3 days and with > 7 days rarely needed). The CDC advises reassessment within 1 to 4 weeks to determine benefits, harms, and appropriate dosing and continued follow up at least every 3 months as the balance of benefits and risks of opioid therapy may change over time. At these visits, efforts should be made to optimize other therapies and taper or discontinue opioids as able. In order to decrease risks, the guidelines recommend avoiding concurrent use of benzodiazepines when possible and employing risk management strategies, such as offering naloxone in high-risk individuals (e.g., history of overdose, history of substance abuse, doses ≥ 50 MME/day, concurrent benzodiazepine use). Likewise, they recommend urine drug testing at baseline and annually with long-term use and review of state prescription drug monitoring programs (PDMPs) at baseline and every 3 months. Prescribers should also offer treatment for opioid use disorder (e.g., buprenorphine or methadone in combination with behavioral therapies). In 2019, the CDC issued a media statement advising against misapplication of their 2016 Guideline for Prescribing Opioids for Chronic Pain.[59] Areas of misapplication include use in populations outside the scope of the guidelines; instituting hard limits on dosages; abruptly tapering or discontinuing opioid therapy; and medication-assisted treatment for opioid use disorder. For patients already on long-term opioid therapy at high doses, the CDC advises to maximize non-opioid treatment, empathetically review risks associated with continuing high-dose opioids, collaborate with patient to taper dose, taper dose slowly at an individualized pace, and closely monitor to mitigate overdose risk. In February 2022, the CDC posted a Federal Register notice on the Proposed 2022 CDC Clinical Practice Guideline for Prescribing Opioids. The 2022 proposed guidance updates and expands on the 2016 version and is open for public comment until April 2022.[60]

In 2017, the American College of Physicians (ACP) updated their guidelines on noninvasive treatments for acute, subacute, and chronic low back pain.[61] The guidelines recommend nonpharmacologic

treatment in most patients with acute or subacute low back pain (e.g., superficial heat, massage, acupuncture, spinal manipulation). In cases when a pharmacologic treatment is preferred, an NSAID or skeletal muscle relaxant is recommended. For the treatment of chronic low back pain, nonpharmacologic treatment is also preferred. Those with an inadequate response to nonpharmacologic therapy may be treated with an NSAID as first-line pharmacologic therapy and tramadol or duloxetine as second-line therapy. The guidelines state that opioids should only be considered in those who have failed these prior therapies and if the benefits outweigh the risks on an individualized basis.

In 2020, the ACP and the American Academy of Family Physicians (AAFP) published guidelines for the management of outpatient acute pain from non-low back, musculoskeletal injuries in adults.[62] They recommend that patients should be treated with topical NSAIDs with or without menthol gel as first-line therapy to decrease or relieve symptoms and to improve physical functioning and treatment satisfaction (strong recommendation; moderate-certainty evidence). It is suggested that clinicians treat patients with oral NSAIDs to reduce or relieve symptoms and to improve physical function or with oral acetaminophen to reduce pain (conditional recommendation; moderate-certainty evidence). Additionally, they suggest that clinicians treat patients with specific acupressure for reduction of pain and improvement of physical functioning. The ACP and AAFP also suggest transcutaneous electrical nerve stimulation to reduce pain (conditional recommendation; low-certainty evidence). Lastly, guidelines suggest against treating non-low back, musculoskeletal injury acute pain with opioids, including tramadol (conditional recommendation; low-certainty evidence).

Also in 2017, the American Society of Interventional Pain Physicians (ASIPP) updated opioid prescribing guidelines for the management of patients with chronic, non-cancer pain.[63] ASIPP recommends that medical necessity of opioids should be established based on average moderate to severe pain (≥ 4 on a 0-to-10-point scale) and/or disability. Regarding specific products, ASIPP recommends initiation of opioids at low doses with short-acting agents and appropriate monitoring. They consider daily opioid doses of ≤ 40 MME as low-dose, 41 to 90 MME as moderate-dose, and ≥ 91 MME as high-dose. The ASIPP recommends methadone only after failure of other opioid therapy, advise to avoid use of long-acting opioids during opioid initiation, and recommends long-acting or high-dose opioids only in special circumstances in which there is severe, intractable pain. The ASIPP states there is similar effectiveness for long-acting and short-acting opioids, but there are greater risks to long-acting opioids. However, one specific short-acting opioid is not preferred over another. The ASIPP also recommends that all patients should be screened for opioid abuse and that providers should use urine drug testing and prescription drug monitoring programs to monitor for abuse.

Additionally, the Human Immunodeficiency Virus (HIV) Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA) issued guidelines in 2017 for managing chronic pain in people living with HIV.[64] These guidelines cover musculoskeletal, arthritic, and neuropathic pain types (non-cancer pain). It is recommended that all persons living with HIV be screened for chronic pain and if positive for pain, multidisciplinary treatment focused on nondrug therapies should be offered, followed by non-opioid drug therapy (e.g., gabapentin [preferred], serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, or pregabalin). Other options include capsaicin, medical cannabis (in select patients), and alpha lipoic acid. These guidelines recommend against use of lamotrigine and opioids as first-line treatments.

In 2017, the American Association of Oral and Maxillofacial Surgeons (AAOMS) issued a White Paper regarding opioid prescribing for acute and postoperative pain management.[65] NSAIDs are recommended over opioids as first-line therapy to manage acute and postoperative pain. If an opioid is needed, the lowest dose for the shortest duration should be used and extended-release formulations should be avoided.

For postpartum pain, the American College of Obstetricians and Gynecologists (ACOG) recommends a stepwise multimodal approach to include the use of standard oral and parenteral pain medications, such as acetaminophen, NSAIDs, and opioids for postoperative cesarean pain.[66] For vaginal birth, a stepwise multimodal approach starting with an NSAID or acetaminophen and escalating, if needed, to an opioid is recommended. ACOG states that if a codeine-containing medication is selected, duration of therapy and newborn signs of toxicity should be reviewed with the family. If an opioid is required, the duration should be limited to the shortest course expected to be adequate for managing acute pain.

The Institute for Clinical and Economic Review (ICER) published a final report on abuse-deterrent formulation (ADF) opioids.[67] At the time of evaluation, evidence showing a reduction in abuse risk with abuse-deterrent formulations compared to non-abuse-deterrent formulations risk was insufficient. Roxybond (oxycodone) is the only immediate release opioid to have been FDA approved as an abuse-deterrent *formulation*; however, this product has since been discontinued.

In order to help curb the potentially fatal effects of opioid overdoses, the Department of Health and Human Services (HHS) released guidelines recommending that naloxone should be prescribed to individuals who are at risk for opioid overdose, including individuals on relatively higher doses of opioid (≥ 50 MME/day), those with select respiratory comorbidities (e.g. sleep apnea, chronic obstructive pulmonary disease [COPD]), patients who are taking other medications which enhance opioid complications (e.g., benzodiazepines), or who have other non-opioid substance abuse disorders or mental health disorders.[68] In October 2019, the DHHS published a new guideline for clinicians on dosage reduction or discontinuation of long-term opioid analgesics.[69] This guidance discusses the risks of opioid taper and advises that opioids should not be quickly tapered or discontinued abruptly due to the potential for opioid withdrawal which can result in acute withdrawal symptoms, pain exacerbation, psychological distress, and suicidal ideation in patients who are physiologically dependent. Except for life-threatening circumstances (e.g., impending overdose), it is not recommended to abruptly reduce an opioid dose or discontinue an opioid. Guidance details situations when it may be appropriate to taper to a reduced dosage (e.g., pain improvement, patient request, no clinically meaningful improvement in pain or function with opioids, increasing doses without improvements in pain, signs of opioid misuse, side effects impacting function or quality of life, risks for an impending overdose/serious event, concurrent medications or comorbidities increasing the risk for adverse events, extended treatment period without clear benefits versus harms). Other key recommendations include: referring patients with serious mental illness, high suicide risk, or suicidal ideation to a behavioral health provider prior to taper; assessing patients for opioid use disorder if they show signs of opioid misuse and offering medication-assisted treatment if appropriate; advising patients of risks for overdose if they abruptly return to their higher dose; tapering by 5% to 20% every 4 weeks is common, but longer tapering schedules may be required; and considering transition to buprenorphine for patients on high doses and unable to taper.

Opioid Regulation

Over the years, various products within this class have been removed from the market, reformulated, or rescheduled based on abuse potential. In 2009, FDA advisory committee recommended that all propoxyphene-containing products be removed from the market based on their low benefit-to-risk ratio, and this was enforced in 2010.[70]

In 2011, the FDA announced the limitation of prescription acetaminophen combinations, including fixed-dose combinations with opioids, to a maximum of 325 mg acetaminophen per dosage unit. The FDA issued reminders for providers to stop prescribing/dispensing prescription combination products that contain more than acetaminophen 325 mg per tablet, capsule, or other dosage unit. These products are no longer considered safe by FDA and have been withdrawn from the market.[71]

In early December 2013, the FDA submitted a formal recommendation to the HHS to move hydrocodone combination products from Schedule III to Schedule II controlled substances. The Drug Enforcement Agency (DEA) made its final decision regarding appropriate scheduling of hydrocodone-containing productions, resulting in the reclassification of hydrocodone combination products from Schedule III to Schedule II controlled substances, which took effect on October 6, 2014.[72]

Soon after its approval in the US in 1995, diversion and abuse of tramadol were reported. This led to the addition of warnings regarding the abuse potential of tramadol to the product labeling by the FDA. Tolerance, dependence, and addiction to tramadol have been demonstrated and abrupt discontinuation of the drug can result in withdrawal symptoms. Effective August 18, 2014, tramadol-containing products were placed into Schedule IV of the Controlled Substance Act.[73]

In April 2015, the FDA issued final guidance on the evaluation and labeling of abuse-deterrent opioids for industry.[74] The only agent within this therapeutic class at the time with abuse-deterrent *properties* was Oxaydo, and its labeling includes data from an abuse-deterrence study.[75,76] The clinical significance of decreased "drug-liking" evaluated in the study is not established. However, this product is *not* recognized as an abuse-deterrent *formulation* by the FDA. The FDA has published information on abuse deterrence studies to guide new product development and evaluate generic formulations.[77] Since this guidance, oxycodone (Roxybond) is the only product in this class to have received FDA approval as an abuse-deterrent *formulation*; however, it has since been discontinued.

In response to opioid abuse, the FDA announced an action plan in 2016.[78] The action plan includes an evaluation of risks and benefits of opioid analgesics, using experts to determine abuse-deterrence, and improving access to abuse-deterrent formulations and medication-assisted treatment options. In March 2016, the FDA announced that all immediate-release opioid pain medications would now require a new boxed warning about the serious risks of misuse, abuse, addiction, overdose, and death.[79] Labeling for these products has been updated accordingly.

In April 2017, the FDA announced the restricted use of codeine and tramadol medicines in children because these medications carry serious risks, including slowed or difficult breathing and death.[80] These risks are greater in children younger than 12 years and, thus, should not be used in this pediatric population. These medicines should also be limited in some older children. The FDA also recommended against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants. In April 2019, the FDA released a drug safety communication regarding harm due to sudden discontinuation of opioid pain medications; the FDA also required labeling changes to these products addressing how to safely reduce the dose in patients dependent on opioids. Other labeling

updates as part of this safety communication included information on risk of central sleep apnea, drug interactions (serotonin syndrome), and proper storage and disposal.[81]

The FDA continues to evaluate and issue guidance on the use and development of opioids.[82] Part of the FDA's efforts include commissioning the National Academy of Sciences, Engineering, Medicine (NASEM) to develop a consensus report on "Framing Opioid Prescribing Guidelines for Acute Pain." This report was released in December 2019 and provides a framework for assessing opioid prescribing in order to develop a clinical practice guideline and determine areas of future research. The analysis also includes an evaluation of current opioid prescribing guidelines with identification of areas for additional research.[83] Similarly, the DEA has announced reductions in the quantity of Schedule II opioid prescriptions that may be manufactured in anticipation of a decline in need.[84,85,86,87,88]

In July 2020, the FDA released a MedWatch safety alert and drug safety communication for opioid pain relievers and opioid use disorder agents.[89] The FDA recommends that HCPs discuss the availability of naloxone with all patients at the time of prescribing or renewing opioid therapy. Furthermore, the FDA is requiring updated prescribing information for all opioid analgesics to add recommendations regarding naloxone. In addition, the FDA states that HCP should consider prescribing naloxone for patients who are not prescribed an opioid or OUD therapy if they are at a higher risk of opioid overdose (e.g., current/prior diagnosis of OUD or prior opioid overdose). The FDA also recommends providers consider naloxone when a patient has household members (e.g., children, close contacts) who may be at risk for accidental ingestion or opioid overdose.

In December 2020, the FDA announced an update on the steps being taken to address the opioid crisis, particularly regarding the Risk Evaluation and Mitigation Strategies (REMS).[90] Other efforts include reducing unnecessary exposure to prescription opioids and preventing new addiction; support for treating opioid use disorder, assisting in the development of new pain treatments, and addressing contributors to the illegal importation/sale of opioids. Details on the REMS program updates can be found in the REMS section of this therapeutic class review.

PHARMACOLOGY[91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117]

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

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

Butorphanol and pentazocine are mixed agonist-antagonist agents. They are both weak antagonists at μ-receptors and agonists at kappa-receptors. Due to their action at the kappa-receptors, these agents may produce dysphoric effects and increased blood pressure and heart rate in some individuals. Due to

their opioid antagonist properties, there is a ceiling on the analgesic effects of pentazocine and butorphanol.

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

Aspirin and NSAIDs, including celecoxib, work by blocking cyclooxygenase (COX)-1 and COX-2, which prevent the synthesis of various prostaglandins. These prostaglandins are partially responsible for the development of pain and inflammation. Celecoxib's inhibitory effects on prostaglandin synthesis is primarily due to inhibiting COX-2.

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

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

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

PHARMACOKINETICS[118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144]

Drug	Half-Life (hr)	T_{max} (hr)	Excretion
Opioid Component			
benzhydrocodone*	4.33 – 4.53	1.25 – 2.5	renally eliminated
butorphanol nasal spray	4.7 – 6.6 (parent) 18 (metabolite)	0.6 – 1	extensively metabolized and excreted in urine and feces
codeine sulfate	3 – 4 (parent) 2 (metabolite – morphine)	No data available	primarily eliminated in urine
dihydrocodeine[145]	3.3 – 4.5	No data available	metabolized to active dihydromorphine and renally eliminated
fentanyl buccal (Fentora)	2.63 – 11.7	0.5 – 0.75	>90% metabolized and renally eliminated
fentanyl nasal spray (Lazanda)	15.0 – 24.9	0.25 – 0.35	primarily (>90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites
fentanyl sublingual spray (Subsys)	5.25 – 11.99	0.67 – 1.25	primarily (>90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites
fentanyl transmucosal oral lozenge (Actiq)	3.2 – 6.4	0.33 – 0.67	>90% metabolized and renally eliminated
hydrocodone	3.8	1.3 – 3	hydrocodone and metabolites renally eliminated
hydromorphone (Dilaudid)	2.3	0.73	highly metabolized
levorphanol	11 – 16	1	extensively metabolized and renally eliminated
meperidine	3 – 4 (parent) 15 – 30 (metabolite)	2	highly metabolized and renally eliminated
morphine immediate release	adults: 2 – 15 pediatrics: 1.8 – 18.6	adults: 0.5 pediatrics: nr	extensively metabolized and renally eliminated
oxycodone	3 – 4.8	1.2 – 2	primarily metabolized and renally eliminated
oxymorphone immediate release	7.3 – 9.4	No data available	highly metabolized and eliminated in urine and feces
pentazocine	0.5 – 4	3.6	extensively metabolized and renally eliminated
tapentadol (Nucynta)	4	1.25	highly metabolized eliminated in urine
tramadol	6.5 – 9 (parent) 6.7 – 7.2 (metabolite)	1.9 – 3 (parent) 2.5 – 4 (metabolite)	primarily metabolized and renally eliminated

T_{max} = time to maximum serum concentration

* Benzhydrocodone is a prodrug of hydrocodone (converted to active hydrocodone by enzymes in the intestinal tract). The fixed-dose combination product benzhydrocodone/acetaminophen (Apadaz) met bioequivalence criteria for hydrocodone overall exposure (AUC) and maximum serum concentration (C_{max}) to other immediate release hydrocodone combination products. A dose of 6.12 mg benzhydrocodone is equivalent to 4.54 mg hydrocodone or 7.5 mg hydrocodone bitartrate.

Pharmacokinetics (continued)

Drug	Half-Life (hr)	T_{max} (hr)	Excretion
Non-opioid Component			
acetaminophen	1 – 3	1.2 – 3	highly metabolized and renally eliminated
aspirin	0.25 – 0.3	2 – 3 (low dose) 15 – 30 (high dose)	highly metabolized and renally eliminated
butalbital	35	No data available	highly metabolized and renally eliminated
caffeine[146]	No data available	3	highly metabolized and renally eliminated
carisoprodol	2	1.5 – 2	highly metabolized and renally eliminated
celecoxib	13	1.5	highly metabolized
ibuprofen	1.8 – 2.6	1.6 – 3.1	highly metabolized and renally eliminated
naloxone	2 – 3	1 – 3	highly metabolized and renally eliminated

nr = not reported; T_{max} = time to maximum serum concentration

CONTRAINDICATIONS/WARNINGS[147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173]

All immediate release opioid pain medications contain a boxed warning regarding serious risks of misuse, abuse, addiction, overdose, and death.[174] Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. These should only be used in combination when alternative treatment options are inadequate and doses and duration should be limited. Accidental ingestion, especially by children can result in a fatal overdose. Patients and caregivers should be counseled on recognizing respiratory depression and getting emergency medical care immediately for known or suspected overdoses, even if naloxone is administered. Additionally, the availability of naloxone for emergency treatment of opioid overdose should be discussed with the patient/caregiver when these agents are started or when the prescriptions are renewed. Prescribing naloxone should be based on the patient's risk factors for overdose (e.g., concurrent CNS depressants [benzodiazepines, skeletal muscle relaxants], history of opioid use disorder, prior opioid overdose). Consideration should also be given for prescribing naloxone if the potential exists for household members (e.g., children, close contacts) to accidentally ingest the opioid leading to overdose.

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

In general, opioids are contraindicated in patients who have acute or severe bronchial asthma or hypercarbia or situations of significant respiratory depression (in the absence of resuscitative equipment or monitors). Opioids can also lead to central sleep apnea (CSA) in a dose-dependent manner as well as sleep-related hypoxemia; a reduction in dosage may be warranted for patients with CSA. Opioids are also contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Agents containing butorphanol, hydrocodone, levorphanol, meperidine, and

pentazocine do not list these conditions as contraindications, but warnings to use with caution if any of these respiratory or gastrointestinal conditions are present.

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

Opioids should be used with caution in patients with renal or hepatic impairment and dosage adjustments may be warranted depending on the specific agent and degree of impairment. Oxymorphone is contraindicated in patients with moderate or severe hepatic impairment. In addition, several agents in this class contain acetaminophen, which has been associated with cases of acute liver failure; most cases were associated with daily doses > 4,000 mg. In 2009, an FDA advisory committee recommended increased restrictions on acetaminophen use in an effort to curb overdoses that can cause liver failure and/or death.[175] In 2011, the FDA asked manufacturers of prescription acetaminophen combination products to limit the maximum amount of acetaminophen in these products to 325 mg per tablet, capsule, or other dosage unit by January 1, 2014.[176]

Monoamine oxidase inhibitors (MAOI) can markedly potentiate the action of opioid agents; therefore, opioid use is not recommended in patients currently taking MAOIs or within the previous 14 days. Caution should be observed in administering pentazocine to patients who are currently receiving MAOIs or who have received an MAOI within the preceding 14 days, due to potential CNS excitation and/or hypertension from catecholamines. In addition, all opioids contain a warning regarding serotonin syndrome when used concomitantly with any serotonergic drug (e.g., MAO inhibitors, selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRI], tricyclic antidepressants [TCAs], triptans, linezolid, lithium). Serotonin syndrome typically occurs within several hours to a few days following use.[177]

Opioids may induce or aggravate seizures in some clinical settings, particularly in patients with a history of seizure disorders.

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

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

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

Other warnings instruct prescribers to be aware of the abuse potential of these products, the possibility of hypoventilation, the dangers if used in pediatric patients, and the increased risk of respiratory depression when used with cytochrome P450 3A4 (CYP3A4) inhibitors. Impairment of physical and/or mental abilities, increased seizure risk, use of caution when performing hazardous tasks, respiratory depression, abuse potential, and increased sedation when used with other CNS depressants are also associated with opioid use. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Monitor for decreased bowel motility.

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

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH) and cortisol. All opioids carry a warning for adrenal insufficiency; if an opioid causes adrenal insufficiency, treat with corticosteroids and withdraw the opiate as appropriate.[178] Also, thyroid stimulating hormone may be stimulated or inhibited by opioids. Patients with adrenal insufficiency, thyroid disease (e.g., hypothyroidism), or myxedema may not be appropriate candidates for codeine administration.

Opioid analgesics may cause tolerance and/or physical dependence with chronic use; therefore, it is important that these agents not be abruptly discontinued in physically dependent patients. Withdrawal symptoms as well as return of pain may occur if these agents are discontinued abruptly; gradually taper the opioid dosage at the time of discontinuation to minimize the risk for withdrawal symptoms.

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome.

Opioids may affect the ability to drive a vehicle or operate machinery; patients should not drive/operate machinery until it is known how the medication may impact their mental or physical abilities.

Hydrocodone/ibuprofen and tramadol/celecoxib are contraindicated in the treatment of peri-operative pain in the coronary artery bypass graft (CABG) setting. The boxed warning for NSAID-containing products cite the increased risk for adverse events seen with NSAID use, such as serious cardiovascular thrombotic events, myocardial infarction, stroke, and gastrointestinal adverse events, all of which can be fatal.

Tramadol (Qdolo, Ultram) and tramadol/acetaminophen (Ultracet) are contraindicated in any situation where opioids are contraindicated including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally-acting analgesics, opioids, or psychotropic drugs. Tramadol may worsen CNS and respiratory depression in patients taking any of these agents. Withdrawal symptoms may occur if tramadol is discontinued abruptly. Clinical experience suggests that withdrawal symptoms may be avoided by tapering tramadol at the time of discontinuation. Additionally, tramadol-containing products carry a warning for suicide risk and should not be prescribed to patients who are suicidal or addiction-prone.

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

Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine. Similar events have occurred with tramadol and in at least 1 instance the pediatric patient was an ultra-rapid metabolizer of tramadol. As a result, codeine-

containing products and tramadol-containing products are contraindicated for post-operative pain management in all pediatric patients (< 18 years) undergoing tonsillectomy and/or adenoidectomy.

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

Meperidine should be used with caution in patients with atrial flutter or other supraventricular tachycardias due to a possible vagolytic action that may produce a significant increase in ventricular response rate. In addition, the undiluted solution may have a slight topical anesthetic effect on mucous membranes.

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

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

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

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

Carisoprodol is contraindicated in patients with carbamate hypersensitivity and porphyria. Rarely, the initial dose of carisoprodol has been followed by idiosyncratic reactions within minutes or hours, including extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion, and disorientation.

Aspirin is contraindicated in patients with known allergy to NSAID products and in patients with the syndromes of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma). Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye syndrome. Patients who consume 3 or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin. Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding. Aspirin also carries the potential for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which can be fatal or life-threatening.

Rarely, acetaminophen has caused serious skin reactions (e.g., acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)), which can be fatal. In addition, there have been postmarketing cases of hypersensitivity and anaphylaxis in patients using acetaminophen. An acetaminophen-containing agent should be discontinued at the first appearance of skin rash or other hypersensitivity.

Celecoxib, a component of Seglentis, is a sulfonamide and has been associated with anaphylaxis, including in patients with aspirin sensitive asthma. Tramadol/celecoxib (Seglentis) is contraindicated in patients with hypersensitivity to sulfonamides and NSAIDs. Celecoxib has also been associated with fluid retention, edema, new onset or worsening hypertension, renal toxicity (e.g., renal papillary necrosis), hepatotoxicity (e.g., fulminant hepatitis, liver necrosis, hepatic failure) and severe skin reactions (e.g., SJS, TEN, DRESS, AGEP). Additionally, as celecoxib can reduce inflammation, and potentially fever, it may decrease the ability to detect infections. Patients receiving long-term treatment with celecoxib-containing drugs should have hemoglobin or hematocrit evaluated if any signs or symptoms of anemia or blood loss occur.

Reports of hyponatremia as well as hypoglycemia have occurred with use of tramadol. Many hyponatremia cases have been severe (serum sodium < 120 mmol/L) and some of the hypoglycemia cases resulted in hospitalization. The majority of cases of hyponatremia were in females > 65 years old during the initial week of therapy; some of these cases occurred due to syndrome of inappropriate antidiuretic hormone secretion (SIADH). If signs/symptoms of hyponatremia occur (e.g., confusion, disorientation), start appropriate management (fluid restriction), and discontinue tramadol. Most cases of hypoglycemia occurred in those with risk factors (e.g., diabetes, renal insufficiency, elderly). If hypoglycemia is suspected, assess blood glucose and consider discontinuation of tramadol, if appropriate.

Risk Evaluation and Mitigation Strategy (REMS)[179]

Due to the risk of accidental exposure, misuse, abuse, addiction, and overdose related to transmucosal fentanyl formulations (fentanyl oral transmucosal [Actiq], fentanyl buccal [Fentora], fentanyl nasal spray [Lazanda], and fentanyl sublingual spray [Subsys]), these agents are only available through a restricted access program called Transmucosal Immediate Release Fentanyl (TIRF) REMS access program. These medications are also dispensed with medication guides. Outpatient healthcare providers (e.g., prescribers, pharmacies) must enroll in this program, and prescribers must complete training and be certified. Outpatient pharmacies are also required to be certified and must verify documentation of opioid tolerance with each prescription. Wholesalers and distributors also must enroll in order to distribute these products; however, they can only distribute to certified pharmacies. In addition, outpatients must be enrolled in the REMS program, be opioid-tolerant, and sign a Patient-Prescriber Agreement to ensure they understand the risks and benefits of therapy. In 2016, the FDA modified the TIRF REMS requirement to be consistent with the safety label changes that pertained to risks of misuse, abuse, addition, overdose, death, neonatal opioid withdrawal syndrome, serotonin syndrome with concomitant use of serotonergic drugs, adrenal insufficiency, androgen deficiency, and risks associated with concomitant use with benzodiazepines or other CNS depressants.[180]

In September 2017, the FDA determined that a REMS is necessary for immediate release (IR) opioid analgesics to ensure that the drug benefits outweigh the risks.[181] As a result, the FDA sent letters to manufacturers of immediate release opioid analgesic products informing them that products that are intended for outpatient setting use will be subject to the same REMS requirement as the extended-release (ER)/long-acting (LA) opioid analgesics. The REMS program requires additional educational content on pain management for healthcare professionals, which includes principles of acute and chronic pain management, non-pharmacologic treatments for pain, and pharmacologic treatments for pain (including both opioid and non-opioid medications). Additional information about the safe use of opioids must also be included. As product labeling is updated, these revisions to the REMS program will

be incorporated, including a description of the REMS to the boxed warning. As of September 2018, all immediate release opioids were added to the Opioid REMS program.

In December 2020, the FDA announced an update on the steps being taken to address the opioid crisis, particularly regarding the REMS.[182] The FDA is strengthening the REMS for TIRF products to ensure the benefits continue to outweigh the risks by finalizing modifications to the REMS program. Updates include the following requirements: 1) prescribers document a patient's opioid tolerance for each outpatient prescription; 2) outpatient pharmacies dispensing TIRF medicines document and verify the patient's opioid tolerance prior to dispensing; 3) inpatient pharmacies develop procedures for verification of opioid tolerance in patients requiring TIRF products during hospitalization; 4) a new patient registry, as well as other data sources, for monitoring accidental exposure, misuse, abuse, addiction, and overdose of these products. Additionally, efforts are also underway to assess the opioid analgesics (OA) REMS.

DRUG INTERACTIONS[183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209]

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

Monoamine oxidase inhibitors (MAOIs) may intensify the actions of opioid agents.

All opioids contain a warning regarding serotonin syndrome when used concomitantly with any serotonergic drug as described above.[210]

Patients taking cytochrome P450 enzyme (CYP450) inducers or inhibitors may demonstrate an altered response to codeine; therefore, analgesic activity should be monitored. Acyclovir may increase the plasma concentration of meperidine and normeperidine. Ritonavir may increase the plasma concentration of normeperidine. Phenytoin may increase the metabolism and clearance of meperidine. Caution should be used with concomitant use of meperidine with any of these agents.

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

Opioids can reduce the efficacy of diuretics; additional monitoring and dose adjustments may be required.

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

A dose reduction of hydrocodone or benzhydrocodone-containing products may be needed when combined with a CYP3A4 inhibitor; likewise, a dose adjustment may be needed for hydrocodone or benzhydrocodone-containing products when combined with a CYP3A4 inducer.

The concomitant use of benzhydrocodone and CYP3A4 inhibitors can increase the plasma concentration of hydrocodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of benzhydrocodone and CYP2D6 and CYP3A4 inhibitors.

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

Fentanyl and tramadol are mainly metabolized by the CYP450 enzyme pathway; co-administration of these agents with CYP450 enzyme inducers or inhibitors may adversely affect their metabolism. Patients taking carbamazepine, a CYP3A4 inducer, may have a significantly reduced analgesic effect of tramadol; concurrent administration of carbamazepine and tramadol is not recommended due to the increased tramadol metabolism by carbamazepine and due to the seizure risk associated with tramadol. Conversely, concurrent use of tramadol and CYP3A4 inhibitors (e.g., erythromycin, ketoconazole, ritonavir) can increase the plasma levels of tramadol and can lead to a higher amount of metabolism via CYP2D6 and higher levels of M1; patients should be monitored for serious adverse events (e.g., seizures serotonin syndrome), and adverse effects of opioid toxicity (e.g., respiratory depression). Similarly, concurrent use of tramadol and CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine, bupropion) may lead to an increase in the plasma level of tramadol and a decrease in the plasma concentration of M1 metabolite; if concurrent use of a CYP2D6 inhibitor is needed, monitor for adverse reactions (e.g., opioid withdrawal, seizures, serotonin syndrome) and when the CYP2D6 inhibitor is discontinued monitor for respiratory depression and sedation. In patients on warfarin, prothrombin time should be monitored and adjust the dosage of warfarin, as needed, as there have been reports of changes in warfarin effect with tramadol.

In vitro studies have shown that celecoxib, a component of tramadol/celecoxib (Seglentis) inhibits CYP2D6; therefore, potential exists for an interaction with drugs metabolized by CYP2D6 (e.g., atomoxetine) leading to increased exposure and toxicity of the CYP2D6 substrate. In addition, coadministration of celecoxib with CYP2C9 inhibitor (e.g., fluconazole) or inducers (e.g., rifampin) increase or decrease, respectively, the exposure of celecoxib.

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

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

Use of NSAIDs is associated with interactions with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta blockers, loop and thiazide diuretics, methotrexate, lithium, anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), and selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). Concurrent use of NSAIDs and analgesic doses of aspirin does not result in greater efficacy than the NSAID alone and is associated with a significantly increased incidence of GI adverse reactions compared to use of the NSAID alone. Additionally, the combination increase the risk for bleeding.

Ibuprofen has been shown to reduce the natriuretic effect of furosemide and thiazides in some patients. Ibuprofen also has been shown to reduce renal lithium clearance and elevate plasma lithium concentration.

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

Aspirin may inhibit the uricosuric effects of uricosuric agents.

Concomitant use of celecoxib and cyclosporine may increase nephrotoxic effects of cyclosporine. Concurrent use of celecoxib with pemetrexed may increase myelosuppression, and renal and GI toxicities. Concomitant use of celecoxib and corticosteroids may enhance the risk of GI ulceration or bleeding. Concurrent use of celecoxib with digoxin has been reported to raise the digoxin serum level and prolong its half-life; monitor serum digoxin levels and for signs of digoxin toxicity. Concurrent use of celecoxib with other NSAIDs or salicylates (e.g., diflunisal, salsalate) raises the potential for GI toxicity, and does not substantially increase efficacy.

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

Additive CNS depression may occur with carisoprodol-containing products when combined with other CNS depressants.

ADVERSE EFFECTS[211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237]

Drug	Asthenia	Constipation	Dizziness	Dyspnea	Headache	Nausea	Rash	Somnolence	Vomiting
benzhydrocodone/ acetaminophen (Apadaz)	1 – 5	12	7.5	1 – 5	6	21.5	nr	18.5	13
butorphanol nasal spray	> 1	> 1	19	> 1	> 1	≤ 13	> 1	43	≤ 13
codeine sulfate	nr	reported	reported	nr	reported	reported	reported	reported	reported
codeine/acetaminophen	nr	reported	reported	reported	nr	reported	reported	nr	reported
codeine/butalbital/ acetaminophen/caffeine (Fioricet with codeine)	nr	reported	reported	nr	reported	reported	reported	reported	reported
codeine/butalbital/aspirin/caffeine (Ascomp with codeine)	nr	nr	reported	nr	nr	reported	reported	reported	reported
codeine/carisoprodol/ aspirin	reported	nr	reported	nr	reported	reported	reported	reported	reported
dihydrocodeine bitartrate/ acetaminophen/caffeine (Dvorah, Trezix)	nr	reported	reported	nr	reported	reported	nr	reported	reported
fentanyl buccal (Fentora)	11	12	13 – 19	9	9 – 10	17 – 29	< 1	7 – 9	5 – 20
fentanyl nasal spray (Lazanda)	≥ 1	1 – 10	≥ 1	≥ 1	≥ 1	4 – 9	nr	≥ 1	7 – 13
fentanyl sublingual spray (Subsys)	9.7	5 – 10.4	7.2	10.4	≥ 1	10.4 – 13.1	nr	9.5	10.3 – 16
fentanyl transmucosal oral lozenge (Actiq)	9 – 38	4 – 20	16 – 17	4 – 22	6 – 20	23 – 45	2 – 8	15 – 17	12 – 31
hydrocodone/acetaminophen solution (Lortab)	nr	reported	reported	reported	nr	reported	reported	reported	reported
hydrocodone/acetaminophen tablet	nr	reported	reported	reported	nr	reported	reported	reported	reported

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

Adverse Effects (continued)

Drug	Asthenia	Constipation	Dizziness	Dyspnea	Headache	Nausea	Rash	Somnolence	Vomiting
hydrocodone/ibuprofen	3 – 9	22	14	< 3	27	21	< 1	22	3 – 9
hydromorphone (Dilaudid)	reported	reported	reported	reported	reported	reported	reported	reported	reported
levorphanol	nr	nr	reported	nr	nr	reported	reported	nr	reported
meperidine	reported	reported	reported	nr	reported	reported	reported	nr	reported
morphine immediate release	nr	reported	reported	nr	reported	reported	reported	reported	reported
oxycodone immediate release (Oxaydo)	reported	reported	reported	reported	reported	reported	reported	reported	reported
oxycodone immediate release (Roxicodone)	≥ 3	≥ 3	≥ 3	< 3	≥ 3	≥ 3	< 3	≥ 3	≥ 3
oxycodone/acetaminophen (Endocet, Nalocet, Percocet, Primlev)	reported	reported	reported	reported	reported	reported	reported	reported	reported
oxycodone/aspirin	reported	reported	reported	reported	reported	reported	reported	reported	reported
oxymorphone immediate release	< 1	4	7	< 1	7	19	< 1	9	9
pentazocine/naloxone	reported	reported	reported	nr	reported	reported	reported	reported	reported
tapentadol (Nucynta)	nr	8	24	< 1	reported	30	1	15	18
tramadol (Qdolo, Ultram)	6 – 12	24 – 46	26 – 33	< 1	18 – 32	24 – 40	1 – < 5	16 – 25	9 – 17
tramadol/acetaminophen (Ultracet)	> 1	6	3	< 1	> 1	3	> 1	6	> 1
tramadol/celecoxib (Seglentis)	nr	reported	16.9	nr	11.5	30.1	reported	8.2	15.8

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

Opioids have been associated with a decrease in sex hormone levels. Laboratory assessment is recommended in patients who report low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.[238]

The safety profile of morphine sulfate immediate release tablets and oral solution in pediatrics is similar to that seen in adults. Among 81 patients 2 to 17 years of age experiencing acute pain, the most common adverse effects reported during initial treatment were nausea (17%), vomiting (10%), constipation (6%), reduced oxygen saturation (5%), and flatulence (5%).

SPECIAL POPULATIONS[239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265]

Pediatrics

Fentanyl buccal (Fentora), fentanyl nasal spray (Lazanda), fentanyl sublingual spray (Subsys), tapentadol (Nucynta), and tramadol/celecoxib (Seglentis) are indicated for patients 18 years of age or older. Fentanyl transmucosal (Actiq) is approved for patients 16 years old or older. Tramadol-containing products (Qdolo, Ultram, Ultracet, Seglentis) are contraindicated in all children less than 12 years old and also in children less than 18 years old for post-operative management following tonsillectomy and/or adenoidectomy. Additionally, use should be avoided in pediatric patients 12 to 17 years who have other risk factors (e.g., obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease) that may increase the likelihood for respiratory depression unless the benefits are determined to be greater than the risks. Hydrocodone/ibuprofen has no established safety and efficacy in patients less than 16 years of age. The safety and efficacy of pentazocine-containing products and codeine/carisoprodol/aspirin in children under 12 years of age have not been established. Hydrocodone/acetaminophen (Lortab elixir only) has not been studied in patients younger than 2 years old. Hydrocodone/acetaminophen has not been adequately studied in pediatric patients. Immediate release morphine sulfate 15 mg and 30 mg tablets and 10 mg/5 mL and 20 mg/5 mL oral solution are approved for use in select pediatric patients ≥ 2 years of age; 15 mg and 30 mg tablets are not recommended in pediatric patients weighing < 50 kg. Safety and efficacy of morphine sulfate oral solution are not established in pediatrics 2 to 17 years of age for chronic pain or in patients < 2 years old. Although the safety and pharmacokinetics of oxycodone oral solution were assessed in an open-label clinical study in 89 pediatric patients 2 years old to < 17 years old with postoperative pain, definitive conclusion were not made due to insufficient data. The safety and efficacy of the remaining products in this review, including morphine sulfate oral solution 20 mg/mL, have not been established in the pediatric population.

The FDA has restricted the use of codeine and tramadol medicines in children due to the increased risk of slowed or difficult breathing and death in patients less than 12 years of age.[266] Single-ingredient codeine and all tramadol-containing products are approved only for use in adults.

Pregnancy

The products listed in this review assigned a pregnancy category are Pregnancy Category C. Gradually, labeling for products in this class are being updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). The labeling for codeine/butalbital/aspirin/caffeine (Ascomp with codeine), fentanyl (Actiq, Fentora, Lazanda, Subsys), hydrocodone/acetaminophen (Lortab), hydromorphone (Dilaudid), meperidine, oxycodone (Oxaydo, Roxicodone), oxymorphone, tapentadol (Nucynta), tramadol (Qdolo, Ultram), and tramadol/acetaminophen (Ultracet) have been updated in compliance with the PLLR. The labeling for codeine/butalbital/aspirin/caffeine, oxycodone/aspirin, and tramadol/celecoxib (Seglentis) state that use of NSAIDs in the third trimester should be avoided in pregnant women starting at 30 weeks gestation to prevent premature closing of the fetal ductus arteriosus; additionally, use of NSAIDs at about 20 weeks gestation or later can lead to fetal renal dysfunction, resulting in oligohydramnios and potentially neonatal renal impairment. The labeling for codeine/butalbital/aspirin/caffeine also states, along with the labeling for the other updated labels,

that data are insufficient to inform of a drug-associated risk for major birth defects and miscarriage. Previously, oxycodone single-ingredient products (Roxicodone, Oxaydo) were Category B, while the others were Category C. Benzhydrocodone/acetaminophen (Apadaz), in compliance with the PLLR, was not assigned a Pregnancy Category on approval. There are no available clinical data on hydrocodone or benzhydrocodone use during pregnancy to inform of drug-associated risks.

Prolonged use of opioids during pregnancy may lead to neonatal opioid withdrawal syndrome.

In 2017, the FDA recommended against using single-ingredient codeine and all tramadol-containing products in breastfeeding mothers due to potential harm to the infant.[267]

Use of oral acetaminophen during pregnancy has not been associated with major congenital malformations.

Prolonged use of opioids may reduce fertility in males and females of reproductive potential. In addition, based on the mechanism of action, NSAID use may delay or prevent rupture of ovarian follicles leading to reversible infertility.

Geriatrics

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

Plasma levels of oxymorphone may be seen up to 40% higher in elderly patients over age 65 years than seen in younger patients.

The elderly are at greater risk for NSAID-related serious cardiovascular, GI, and renal adverse effects.

Hepatic and Renal Impairment

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

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

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

A decreased dosing frequency to every 12 hours and lower maximum daily dose are recommended for tramadol for patients with creatinine clearance (CrCl) < 30 mL/minute. A dose reduction is also recommended in patients with severe hepatic impairment.

Due to the celecoxib component, use of tramadol/celecoxib (Seglentis) is not recommended in patients with severe renal impairment; similarly, use of tramadol/celecoxib is not recommended in patients with moderate or severe hepatic impairment.

Other

Some individuals may be ultra-rapid metabolizers of codeine and tramadol due to a specific cytochrome P450 2D6 (CYP2D6) phenotype and may convert codeine and tramadol into their active metabolite more rapidly and completely resulting in higher than expected serum levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.

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

Since tramadol/celecoxib (Seglentis) is not available in lower strengths of celecoxib, it is not recommended in patients who are poor CYP2C9 metabolizers, in whom reduced doses are recommended.

Cardiac Disease

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

DOSAGES[268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296]

Drug	Starting Dose	Dosing Instructions	Available Strengths
benzhydrocodone/ acetaminophen (Apadaz)	1 to 2 tablets every 4 to 6 hours as needed for pain	Do not exceed 12 tablets in a 24-hour period (6.12 mg benzhydrocodone = 4.54 mg hydrocodone = 7.5 mg hydrocodone bitartrate)	Tablets: 4.08/325 mg, 6.12/325 mg, 8.16/325 mg
butorphanol nasal spray	1 spray into 1 or both nostrils; may repeat after 3 to 4 hours	If 1 spray is administered and adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given The initial 2-dose sequence may be repeated in 3 to 4 hours, as required, after the second dose of the sequence	Solution: 10 mg/mL
codeine sulfate	15 mg to 60 mg every 4 to 6 hours, as needed	Do not exceed 360 mg in 24 hours	Tablets: 15 mg, 30 mg, 60 mg
codeine/ acetaminophen	Tablet: 1 to 2 tablets every 4 hours, as needed Elixir: 15 mL every 4 hours	Do not exceed codeine 60 mg per dose and 360 mg per day or acetaminophen 4 g per day	Tablets: 15/300 mg, 30/300 mg, and 60/300 mg Elixir: 12/120 mg per 5 mL
codeine/butalbital/ acetaminophen/ caffeine (Fioricet with codeine)	1 to 2 capsules every 4 hours as needed for pain	Do not exceed 6 capsules per day	Capsule: 30/50/300/40 mg
codeine/butalbital/ aspirin/caffeine (Ascomp with codeine)	1 to 2 capsules every 4 hours as needed for pain	Do not exceed 6 capsules per day	Capsule: 30/50/325/40 mg
codeine/carisoprodol/ aspirin	1 to 2 tablets, 4 times daily	Do not exceed 8 tablets per day	Tablet: 16/200/325 mg

Dosages (continued)

Drug	Starting Dose	Dosing Instructions	Available Strengths
dihydrocodeine bitartrate/ acetaminophen/ caffeine (Dvorah, Trezix)	2 tablets or capsules every 4 hours, as needed	Do not exceed 10 capsules per 24 hours	Tablet (Dvorah): 16/325/30 mg Capsule (Trezix): 16/320.5/30 mg
fentanyl buccal (Fentora)	100 mcg, as needed	Until the appropriate dose is reached, patients may find it necessary to take an additional dose during a single episode of breakthrough pain not relieved in 30 minutes; one tablet of the same dose may be taken; if pain is not relieved, patients must wait 4 hours before treating another episode of breakthrough pain If treatment of several consecutive breakthrough cancer pain episodes requires more than 1 unit per episode, an increase in dose to the next higher available strength should be considered If patient is currently on fentanyl transmucosal lozenges (Actiq), see prescribing information for additional dosing recommendations	Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg
fentanyl nasal spray (Lazanda)	100 mcg, as needed	Individually titrate to an effective dose, from 100 mcg to 200 mcg to 400 mcg, and up to a maximum of 800 mcg, which provides adequate analgesia with tolerable side effects Dose is a single spray into 1 nostril, a single spray into each nostril (2 sprays), or 2 sprays into each nostril (4 sprays); no more than 4 doses per 24 hours Wait at least 2 hours before treating another episode of breakthrough pain with fentanyl nasal spray	Nasal sprays: 100 mcg, 300 mcg, 400 mcg
fentanyl sublingual spray (Subsys)	100 mcg, as needed	Titrated as tolerated to an effective dose One dose of Subsys should be used per breakthrough pain episode; in cases where the pain may not be relieved within 30 minutes of the dose, 1 additional dose of the same strength may be used for that breakthrough episode At least 4 hours must elapse prior to initiating treatment for another episode of pain Maintenance dosing should not exceed 4 doses per 24 hours Dose increase should be considered when several consecutive attempts to control breakthrough pain have failed	Sublingual sprays: 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,200 mcg, 1,600 mcg

Dosages (continued)

Drug	Starting Dose	Dosing Instructions	Available Strengths
fentanyl transmucosal oral lozenge (Actiq)	200 mcg, as needed	Until the appropriate dose is reached, patients may find it necessary to take an additional dose during a single episode; patients must wait at least 4 hours before treating another episode of breakthrough pain If treatment of several consecutive breakthrough cancer pain episodes requires more than 1 unit per episode, an increase in dose to the next higher available strength should be considered	Transmucosal oral lozenges: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,200 mcg, 1,600 mcg
hydrocodone/ acetaminophen solution (Lortab)	15 mL every 4 to 6 hours	Not to exceed 90 mL in 24 hours See dosing chart in prescribing information for initial doses for children	Solution: 7.5/325 mg per 15 mL, 10/300 mg per 15 mL (Lortab), 10/325 mg per 15 mL
hydrocodone/ acetaminophen tablet	1 to 2 tablets every 4 to 6 hours	Not to exceed 6 tablets or capsules in 24 hours; for tablets or capsules that contain 8 mg hydrocodone, may take up to 8 tablets per 24 hours For tablets that contain 7.5 mg or 10 mg hydrocodone, take 1 tablet or capsule every 4 to 6 hours	Tablets: 2.5/325 mg, 5/300 mg, 5/325 mg, 7.5/300 mg, 7.5/325 mg, 10/325 mg
hydrocodone/ ibuprofen	1 tablet every 4 to 6 hours	Not to exceed a maximum of 5 tablets in 24 hours	Tablets: 5/200 mg, 7.5/200 mg, 10/200 mg
hydromorphone (Dilaudid)	Tablets: 2 to 8 mg every 4 to 6 hours Liquid: 2.5 to 10 mg every 3 to 6 hours	Dose should be adjusted so that at least 3 to 4 hours of pain relief may be achieved Dose should be increased, as needed, according to patient's response	Tablets: 2 mg, 4 mg, 8 mg Liquid: 5 mg/5 mL Suppository: 3 mg
levorphanol	2 mg every 6 to 8 hours	Total oral daily doses of more than 6 mg to 12 mg in 24 hours are generally not recommended as starting doses	Tablet: 2 mg, 3 mg
meperidine	Adult: 50 to 150 mg every 3 to 4 hours Pediatric: 1.1 to 1.8 mg/kg every 3 to 4 hours	Not for chronic use	Tablets: 50 mg Solution: 50 mg/5 mL
morphine immediate release	Tablets: 15 mg to 30 mg every 4 hours, as needed Solution: 10 mg to 20 mg every 4 hours, as needed	The dose should be titrated based upon the individual patient's response 100 mg/5 mL oral solution is for use *only* in opioid-tolerant adults	Tablets: 15 mg, 30 mg Solution: 10 mg/5 mL, 20 mg/5 mL, 100 mg/5 mL Suppository: 5 mg, 10 mg, 20 mg, 30 mg

Dosages (continued)

Drug	Starting Dose	Dosing Instructions	Available Strengths
morphine immediate release (Hikma)	Tablets: *Adults and pediatrics weighing ≥ 50 kg* - 15 mg to 30 mg every 4 hours, as needed Solution: *Adults* - 10 mg to 20 mg every 4 hours, as needed *Pediatrics ≥ 2 years of age* - 0.15 to 0.3 mg/kg orally every 4 hours as needed	Tablets: Do not exceed 30 mg as initial dose in pediatrics Solution: In pediatric patients ≥ 2 years of age, use only the 10 mg/5 mL and 20 mg/5 mL concentrations (see prescribing information of the oral solution for accurate dose calculation and measurement) Do not exceed 20 mg as initial dose in pediatrics The dose should be titrated based upon the individual patient's response 100 mg/5 mL oral solution is for use *only* in opioid-tolerant adults	Tablets: 15 mg, 30 mg Solution: 10 mg/5 mL, 20 mg/5 mL, 100 mg/5 mL
oxycodone immediate release (Oxaydo)	Opioid-naïve: 5 mg to 15 mg every 4 to 6 hours, as needed	The dose must be swallowed whole and is not amenable to crushing and dissolution Do not use for administration via nasogastric, gastric, or other feeding tubes as it may cause obstruction of the feeding tube	Tablets: 5 mg, 7.5 mg (contains abuse-deterrent *properties*; resistant to crushing, chewing, snorting, and injection related abuse)
oxycodone immediate release (Roxicodone)	5 mg to 15 mg every 4 to 6 hours, as needed	The dose should be titrated based upon the individual patient's response	Capsule: 5 mg (generic only) Tablets: 5 mg, 10 mg (generic only), 15 mg, 20 mg (generic only), 30 mg Solution: 5 mg/5 mL, 20 mg/mL (generic only for both)
oxycodone/ acetaminophen (Endocet, Nalocet, Percocet, Primlev, Prolate)	1 to 2 tablets or capsules every 6 hours	Do not exceed oxycodone 60 mg or acetaminophen 4 g per day in adults Children: < 45 kg body weight – do not exceed 90 mg/kg per day based on the acetaminophen component > 45 kg body weight – do not exceed 4 g per day based on the acetaminophen component	Tablets: 2.5/300 mg (Nalocet), 2.5/325 mg (Percocet), 5/300 mg (Primlev, Prolate), 5/325 mg (Endocet, Percocet), 7.5/300 mg (Primlev, Prolate), 7.5/325 mg (Endocet, Percocet), 10/300 mg (Primlev, Prolate), 10/325mg (Endocet, Percocet) Solution: 10/300 mg/5 mL (Prolate)
oxycodone/aspirin	1 tablet every 6 hours	The maximum daily dose of aspirin should not exceed 4 grams or 12 tablets	Tablet: 4.8355/325 mg
oxymorphone immediate release	10 mg to 20 mg every 4 to 6 hours	Administer on an empty stomach, at least 1 hour prior to or 2 hours after eating 5 mg dose is available for patients with renal or hepatic impairment and for geriatric patients	Tablet: 5 mg, 10 mg
pentazocine/naloxone	1 to 2 tablets every 3 or 4 hours	Do not exceed 600 mg pentazocine per day	Tablet: 50/0.5 mg

Dosages (continued)

Drug	Starting Dose	Dosing Instructions	Available Strengths
tapentadol (Nucynta)	1 tablet every 4 hours	Doses greater than 700 mg on the first day and doses of greater than 600 mg on subsequent days are not recommended	Tablets: 50 mg, 75 mg, 100 mg
tramadol (Qdolo, Ultram)	50 mg to 100 mg every 4 to 6 hours	Initiate at 25 mg per day; titrate in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times daily), then the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times daily) After titration, tramadol 50 mg to 100 mg can be administered as needed for pain relief every 4 to 6 hours (not to exceed 400 mg per day)	Tablets (Ultram): 50 mg, 100 mg (generic only) Oral solution (Qdolo): 5 mg/mL
tramadol/ acetaminophen (Ultracet)	2 tablets every 4 to 6 hours	Not to exceed a maximum of 8 tablets in 24 hours For the short-term (≤ 5 days) management of acute pain The elimination half-life of tramadol is increased in patients with severe renal impairment (CrCl < 30 mL/min), cirrhosis of the liver, or over 75 years; therefore, the dosing interval should be extended in this population	Tablets: 37.5/325 mg
tramadol/celecoxib (Seglentis)	2 tablets every 12 hours as needed	Do not exceed 2 tablets every 12 hours Do not administer with other tramadol or celecoxib containing products	Tablet: 44/56 mg tramadol/celecoxib

For elderly patients over 75 years old, total tramadol dose should not exceed 300 mg per day. Tramadol should be given every 12 hours for patients with creatinine clearance (CrCl) < 30 mL/minute with a maximum dose of 200 mg per day. Patients with severe hepatic impairment should receive tramadol 50 mg every 12 hours. For the tramadol oral solution (Qdolo) patients should use a calibrated oral syringe or other oral dosing device with milliliter units to measure the correct amount of prescribed medication (rather than household teaspoons or tablespoons), and prescriptions should include both the total dose in milligrams and the total dose in volume to prevent dosing errors.

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

Label revisions to fentanyl nasal spray (Lazanda) dosage and administration provide an alternate titration strategy and modifications to the approved REMS. This is part of the Transmucosal Immediate release Fentanyl (TIRF) REMS Access Program.

The only agent within this therapeutic class with abuse-deterrent *properties* is Oxaydo; Oxaydo contains sodium lauryl sulfate, inducing nasal passage irritation when crushed or snorted, and polyethylene oxide, forming a viscous mixture entrapping the opioid component to impede solvent extraction for intravenous abuse.[297,298] However, Oxaydo is not recognized as an abuse-deterrent *formulation* by the FDA. Though no longer available, Roxybond is the only short-acting opioid to

receive FDA approval as an abuse-deterrent *formulation*; the product utilized both physical and chemical barriers.[299,300]

Opioids should be stored securely, out of sight and reach of children, in a location not accessible to other individuals.[301] Once the medication is expired or no longer being used it should be disposed of properly through a drug take-back program, if available or in another appropriate manner as determined by the FDA: www.fda.gov/drugdisposal.

Opioid Morphine Equivalent Conversions[302]

The below table is intended to provide an estimate of overall opioid exposure; it should not be used for dosing determinations (e.g., converting a patient from one opioid to another). Conversion factors may vary based on individual pharmacokinetics and duration of use (e.g., opioid-naïve versus chronic dosing). The same conversion is used for immediate- and extended-release oral products with the same opioid component unless otherwise specified. This table includes medications that are not reviewed in this class review for reference purposes. Likewise, some medications are not included in this table due to limited data. While previously assigned a morphine milligram equivalents (MME) conversion factor, the CDC has since removed buprenorphine's MME assignment and nalbuphine has been removed from the list.

Opioid	MME Conversion Factor
butorphanol	7
codeine	0.15
dihydrocodeine	0.25
fentanyl buccal, SL tablet, or lozenge*	0.13
fentanyl film or oral spray*	0.18
fentanyl nasal spray*	0.16
fentanyl patch†	7.2
hydrocodone	1
hydromorphone	4
levorphanol tartrate	11
meperidine	0.1
methadone	3
morphine	1
opium	1
oxycodone	1.5
oxymorphone	3
pentazocine	0.37
tapentadol	0.4
tramadol	0.1

* Multiply conversion factor by the number of micrograms in the dose.

† Based on total micrograms exposure over 24 hours and assumes 1 mg parenteral fentanyl = 100 mg oral morphine (e.g., 25 mcg/hr patch = 180 MME over 3 days = 60 MME/day).

CLINICAL TRIALS

Search Strategies

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

The following agents have demonstrated efficacy in placebo-controlled trials: fentanyl buccal tablet (Fentora), fentanyl nasal spray (Lazanda), and fentanyl sublingual spray (Subsys).[303,304,305,306,307] Tramadol oral solution (Qdolo) was approved under the abbreviated 505(b)(2) NDA pathway, which allows at least some data for approval to come from studies not conducted by or for the applicant.[308] As a result, no new clinical trials were conducted for approval of this formulation.

butorphanol nasal spray versus butalbital compound/codeine

In a double-blind, parallel-group study, patients with migraine (n=321) were randomly assigned to receive either butorphanol nasal spray 1 mg followed in 1 hour by an optional second 1 mg dose or butalbital compound with codeine administered orally (1 capsule containing butalbital 50 mg, caffeine 40 mg, aspirin 325 mg, and codeine phosphate 30 mg).[309] Patients were instructed to self-administer medication when migraine pain reached intensity of moderate or severe and to record study-related events in a diary for 24 hours post-treatment. Efficacy analyses were performed on data from 275 patients who received study medication and returned a patient diary. During the first 2 hours after treatment, butorphanol was more effective than butalbital compound/codeine in treating migraine pain as measured by pain intensity difference scores, percentage of responders (pain decreased to mild or none), percentage of pain-free patients, and degree of pain relief, with a more rapid time to onset of 15 minutes. A similar percentage of patients in the 2 groups used rescue medication during the first 4 hours, after which more butorphanol-treated than butalbital compound/codeine-treated patients used rescue medication. Butorphanol-treated patients had more side effects, less improvement in digestive symptoms, and less improvement in functional ability than butalbital compound/codeine-treated patients.

fentanyl transmucosal oral lozenge (Actiq) versus morphine immediate release (IR)

In a randomized, double-blind, cross-over trial with 134 adult ambulatory cancer patients, fentanyl transmucosal oral lozenge and morphine sulfate immediate release (MSIR) were compared for the management of breakthrough pain.[310] Enrolled patients were stabilized on a fixed schedule opioid

regimen of either morphine sulfate or transdermal fentanyl and an effective MSIR dose of 15 mg to 60 mg up to 4 times daily for breakthrough pain. In an open-label fashion, fentanyl transmucosal oral lozenge was administered to establish the effective dose for breakthrough pain for 69% of patients. Double-blind randomization occurred and then a set of capsules and oral transmucosal delivery systems (1 placebo unit per set being either capsule or transmucosal unit) were administered for each breakthrough pain dosing. During the blinded study, fentanyl transmucosal oral lozenge was significantly better than MSIR for pain intensity reduction, pain relief, and pain intensity differences. Patients favored the fentanyl transmucosal oral lozenge for breakthrough pain based on global performance.

oxymorphone IR versus oxycodone IR

In a double-blind, parallel-group study, oxymorphone IR was compared with placebo for efficacy and with oxycodone IR and placebo for safety in patients with acute moderate to severe post-surgical pain.[311] Three hundred patients received oxymorphone IR 10 mg, 20 mg, or 30 mg; oxycodone IR 10 mg; or placebo. All oxymorphone IR doses were superior to placebo for providing pain relief for 8 hours ($p<0.05$), each with a significant analgesic dose response compared to placebo ($p<0.001$). All oxymorphone IR groups maintained analgesia for 48 hours. The median dosing interval was over 9.5 hours for oxymorphone IR 30 mg. Opioid-related adverse events were similar among groups, and were generally mild or moderate; the overall safety profile was comparable to that of oxycodone IR.

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

In a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group trial, 456 women experiencing moderate to severe pain between 14 and 48 hours after surgery were randomized to receive a single dose of oxycodone/ibuprofen (no longer commercially available), ibuprofen, oxycodone, or placebo.[312] Combination treatment was associated with significantly better scores for total pain relief 6 hours after dosing and sum of pain intensity differences 6 hours after dosing compared with ibuprofen alone ($p<0.02$ and $p<0.015$, respectively), oxycodone alone ($p<0.009$ and $p<0.001$), or placebo (both $p<0.001$). Fewer patients receiving combination treatment required rescue medication, and the time to use of rescue medication was significantly longer in the combination treatment group compared with the other groups ($p<0.05$). The onset of pain relief occurred within 15 minutes of dosing with all regimens. Nausea was the most frequently reported adverse event in all groups, highest with placebo and followed by oxycodone, ibuprofen, and combination treatment.

In a multicenter, double-blind, double-dummy, parallel-group investigation, 498 patients with moderate to severe pain within 5 hours after extraction of 2 or more impacted third molars were randomized to single doses of oxycodone/ibuprofen 5/400 mg (no longer available), ibuprofen 400 mg, oxycodone 5 mg, or placebo.[313] Combination therapy was associated with greater analgesia than ibuprofen alone, oxycodone alone, or placebo, as measured by the sum of pain intensity difference over 6 hours ($p<0.001$ versus oxycodone or placebo, $p=0.002$ versus ibuprofen) and total pain relief through 6 hours ($p<0.001$ versus oxycodone or placebo, $p=0.012$ versus ibuprofen). Combination therapy was well tolerated, and pharmacokinetic evaluation implied no interaction between oxycodone and ibuprofen.

oxymorphone versus oxycodone IR versus placebo

A multicenter, randomized, double-blind, active- and placebo-controlled, parallel-group study was conducted in men and women aged 18 years and older undergoing abdominal surgery.[314] Patients were randomized to receive oxymorphone 10 mg or 20 mg, oxycodone 15 mg, or placebo every 4 to 6 hours. The study included single-dose and 48-hour efficacy assessments. The primary efficacy endpoint was the median time to study discontinuation for all causes. Three hundred thirty-one patients were included in the study. The median time to study discontinuation was significantly longer for all active treatments compared with placebo (oxymorphone 10 mg, 17.9 hours; oxymorphone 20 mg, 20.3 hours; oxycodone 15 mg, 24.1 hours; placebo, 4.8 hours; $p<0.006$). Oxymorphone 20 mg was significantly more effective than placebo over the 6-hour single-dose evaluation ($p<0.05$). With multiple dosing, all active-treatment groups had significantly lower least squares mean current and average pain intensities compared with placebo ($p<0.004$ and $p<0.005$, respectively). Discontinuations due to treatment-emergent adverse events did not differ significantly among the groups.

tapentadol (Nucynta) versus morphine IR

Patients (n=400) undergoing molar extraction were randomized to receive single doses of tapentadol 25 mg, 50 mg, 75 mg, 100 mg, or 200 mg, morphine sulfate 60 mg, ibuprofen 400 mg, or placebo.[315] Mean total pain relief over 8 hours (TOTPAR-8) was the primary endpoint. Secondary endpoints included mean total pain relief over 4 hours (TOTPAR-4) and onset of analgesia. Of all measured endpoints, only mean TOTPAR-4 was higher (and onset of action appeared more rapid) for tapentadol 200 mg than morphine sulfate 60 mg. Pain relief scores with morphine sulfate 60 mg were between those of tapentadol 100 mg and 200 mg. The incidence of nausea and vomiting appeared to be lower with all doses of tapentadol compared with morphine sulfate 60 mg but was not statistically significant.

tapentadol (Nucynta) versus oxycodone (Roxicodone)

A 10-day, phase 3, randomized, double-blind, active- and placebo-controlled study compared the efficacy and tolerability of tapentadol, oxycodone, and placebo in 666 patients with uncontrolled osteoarthritis pain who were candidates for primary replacement of the hip or knee as a result of end-stage degenerative joint disease.[316] Patients received tapentadol 50 mg or 75 mg, oxycodone 10 mg, or placebo every 4 to 6 hours while awake. The primary endpoint was the SPID over 5 days. Pre-specified noninferiority comparisons with oxycodone were performed with respect to efficacy and tolerability. Five-day SPID was significantly lower in those treated with tapentadol or oxycodone (all $p<0.001$). Tapentadol 50 mg and 75 mg and oxycodone 10 mg were associated with significant reductions in pain intensity compared with placebo based on 2- and 10-day SPID, as well (all $p<0.001$). The efficacy of tapentadol 50 mg and 75 mg was noninferior to that of oxycodone 10 mg; however, the incidence of nausea, vomiting, and constipation was significantly lower for both doses of tapentadol compared with oxycodone ($p<0.001$).

tramadol/acetaminophen (Ultracet) versus tramadol (Ultram)

A total of 456 patients with moderate to severe pain within 5 hours of extraction of 2 or more third molars were randomized to receive 2 identical encapsulated tablets containing tramadol/acetaminophen 37.5/325 mg, tramadol 50 mg, or placebo.[317] Tramadol/acetaminophen was superior to tramadol ($p<0.001$) or placebo ($p<0.001$) on all efficacy measures, including total pain relief

over 6 hours, sum of pain intensity differences, and sum of both. The most common adverse events with active treatment were nausea, dizziness, and vomiting, which occurred more frequently in the tramadol group than in the tramadol/acetaminophen group.

tramadol/acetaminophen (Ultracet) versus codeine/acetaminophen

A randomized, double-blind, parallel-group, active-control, double-dummy trial compared the efficacy and tolerability of tramadol/acetaminophen 37.5/325 mg tablets with codeine/acetaminophen capsules 30/300 mg in 462 patients with chronic nonmalignant low back pain, osteoarthritis, or both.[318] Pain intensity was assessed hourly for 6 hours each week over a 4-week period. Pain relief and changes in pain intensity were comparable in both groups throughout the study. Equivalent mean doses and maximum daily doses used in each group were similar. The overall incidence of adverse events was comparable, with more patients in the codeine/acetaminophen group reporting somnolence (24% versus 17%, p=0.05) and constipation (21% versus 11%, p<0.01) than the tramadol/acetaminophen group.

A multicenter, randomized, double-blind, active- and placebo-controlled trial evaluated tramadol plus acetaminophen for orthopedic and abdominal post-surgical pain.[319] Patients with moderate pain or greater were randomized to an initial 2 tablets of 37.5 mg tramadol plus 325 mg acetaminophen (n=98), codeine 30 mg plus acetaminophen 300 mg (n=109), or placebo (n=98). Thereafter, they received 1 to 2 tablets every 4 to 6 hours, as needed for pain, for 6 days. Tramadol plus acetaminophen was superior to placebo for total pain relief, sum of pain intensity differences, and sum of pain relief and pain intensity differences (p≤0.015). For average daily pain relief, average daily pain intensity, and overall medication assessment, tramadol plus acetaminophen was superior to placebo (p≤0.038); codeine plus acetaminophen did not separate from tramadol plus acetaminophen in any criteria. Discontinuation because of adverse events occurred in 8.2% of tramadol plus acetaminophen, 10.1% of codeine plus acetaminophen, and 3% of placebo patients. Except for constipation and vomiting being more prevalent in codeine plus acetaminophen patients, adverse events were similar for active treatments.

A 4-week, randomized, double-blind, parallel-group, multicenter trial compared tramadol/acetaminophen 37.5/325 mg with codeine/acetaminophen 30/300 mg for the management of chronic nonmalignant low back pain, osteoarthritis pain, or both in 462 adults.[320] Pain relief (scale, 0 = none to 4 = complete) and pain intensity (scale, 0 = none to 3 = severe) were measured after 30 minutes and then hourly for 6 hours after the first daily dose each week. Pain relief and changes in pain intensity were comparable from day 1 and lasted for at least 6 hours. Total pain relief scores and sum of pain intensity differences were also comparable throughout. Overall assessments of safety and efficacy by patients and investigators were similar for the 2 treatment groups.

tramadol/acetaminophen (Ultracet) versus hydrocodone/acetaminophen (Vicodin, no longer commercially available)

In a single-center, double-blind, parallel-group, placebo- and active-controlled study in adults with at least moderate pain after extraction of 2 or more impacted third molars, patients were randomized to receive 1 to 2 tramadol/acetaminophen 37.5/325 mg tablets, 1 hydrocodone/acetaminophen 10/650 mg tablet, or placebo.[321] Two hundred adults took part in the study. The median time to onset of pain relief was approximately 34 minutes with tramadol/acetaminophen tablets and 25.4 minutes with hydrocodone/acetaminophen. Although the median time to onset of pain relief was shorter with

hydrocodone/acetaminophen, 2 tramadol/acetaminophen tablets had comparable efficacy to hydrocodone/acetaminophen. The median time to re-medication with a supplemental analgesic agent was 169 minutes in the tramadol/acetaminophen group and 204 minutes in the hydrocodone/acetaminophen group; however, the duration of pain relief was not significantly different between the groups. The overall incidence of adverse events was lower with tramadol/acetaminophen (0%) than with hydrocodone/acetaminophen (4%) or placebo (10%).

tramadol/celecoxib (Seglentis) versus tramadol (Ultram) versus celecoxib (Celebrex®)

A double-blind, double-dummy, parallel group study assessed the efficacy of tramadol/celecoxib compared to its individual components in 637 adults with acute post-operative pain following unilateral bunionectomy with osteotomy.[322] Patients were randomized 2:2:2:1 to tramadol/celecoxib 200 mg every 12 hours, tramadol 50 mg every 6 hours, celecoxib 100 mg every 12 hours, or placebo. Mean baseline pain was 6.7 on the NPRS intensity scale. Rescue mediation (acetaminophen and oxycodone) was permitted. Compared to the other groups, tramadol/celecoxib demonstrated a statistically significantly lower pain level as based on the primary endpoint measure of mean time-weighted summed pain intensity difference over 48 hours (SPID48).

opioids versus non-opioids for chronic back, hip, or knee pain

A 12 month, randomized trial compared the efficacy of opioids to non-opioids in Veterans Affairs patients with moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use (n=240).[323] In each group (opioid or non-opioid), the intervention was assigned a 3-step prescribing strategy, which could be adjusted within the treatment group based on patient response. In the opioid group, step 1 was immediate release hydrocodone/acetaminophen, morphine, or oxycodone, step 2 was sustained action morphine or oxycodone, and step 3 was transdermal fentanyl. Opioids were titrated to a maximum daily dose of 100 mg morphine equivalent. In the non-opioid group, step 1 was acetaminophen or an NSAID, step 2 was adjuvant oral medications (e.g., amitriptyline, nortriptyline, gabapentin) or topical analgesics, and step 3 was pregabalin, duloxetine, or tramadol. The primary outcome was pain-related function, as measured by the Brief Pain Inventory (BPI; range, 0 to 10) over 12 months, which were similar between the 2 groups (3.4 for opioids and 3.3 for non-opioids; treatment different, 0.1 [95% CI, -0.5 to 0.7]). The key secondary outcome was pain intensity, as measured by the BPI severity scale (range, 0 to 10), and was found to be better in the non-opioid group over 12 months (score of 4 in the opioid group versus 3.5 for the non-opioid group; treatment difference, 0.5 [95% CI, 0 to 1]). Adverse effects related to medications were higher at 12 months in the opioid group compared to the non-opioid group (1.8 versus 0.9, respectively; difference, 0.9 [95% CI, 0.3 to 1.5]).

META-ANALYSES

Meta-analyses evaluating single-agents within this class have been published, but meta-analyses comparing agents within this class are limited.[324,325,326,327,328,329,330,331] In addition, some meta-analyses do not differentiate short-acting and long-acting opioids.

A few meta-analyses have compared agents within this class in patients with breakthrough or general cancer pain. One meta-analysis of 10 randomized clinical trials for breakthrough cancer pain compared various forms of fentanyl (e.g., nasal spray, sublingual tablets, buccal film, transmucosal) to morphine sulfate immediate release in pain intensity difference compared to placebo up to 60 minutes following

intake.[332] Most fentanyl formulations, excluding sublingual tablets, resulting in a greater pain intensity difference compared to placebo at 15 minutes following intake while all fentanyl formulations showed a difference at 30 minutes. However, morphine sulfate did not demonstrate a difference in pain intensity until 45 minutes. Likewise, only nasal fentanyl spray produced a clinically meaningful difference (pain intensity change ≥ 2) at 15 minutes. An earlier meta-analysis of 5 trials found similar results.[333]

A meta-analysis of 14 studies (n=3,521) assessed various analgesic combinations (e.g., acetaminophen with codeine [various strength combinations], acetaminophen with hydrocodone [various strength combinations], non-opioids, codeine/butalbital/aspirin/caffeine, oxycodone with ibuprofen, and ibuprofen with codeine) for postoperative pain following third-molar surgery.[334] Of all combinations, ibuprofen 400 mg in combination with oxycodone 5 mg had superior efficacy in sum of pain intensity at 6 hours scores (6.44; range of all agents, 1.46 to 6.44) and total pain relief at 6 hours scores (9.31; range of all agents, 3.24 to 10.3).

A Cochrane review of 35 other Cochrane reviews (approximately 45,000 participants in approximately 350 studies) evaluated single-dose analgesics for acute postoperative pain in adults, including non-opioid analgesics and dental surgeries.[335] The primary outcome assessed was at least 50% pain relief over 4 to 6 hours compared to placebo. The authors calculated number-needed-to-treat (NNT) in reliable studies to achieve this primary outcome calculated for all agents and ranged from 1.5 to 20 among all agents. NNTs of agents in this class were 2.2 (95% CI, 2.3 to 3.3), 3.9 (95% CI, 3.3 to 4.7), 2.7 (95% CI, 2.4 to 3.1), and 1.8 (95% CI, 1.6 to 2.2), for codeine 60 mg with acetaminophen 800 mg to 1,000 mg, codeine 60 mg, codeine 60 mg with acetaminophen 600 mg to 650 mg, oxycodone/acetaminophen 10/650 mg, and oxycodone/acetaminophen 10/1,000 mg, respectively.

SUMMARY

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

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

Oxaydo is an immediate release opioid analgesic with abuse-deterrent *properties* intended to discourage abuse of the medication. These preventative measures offer no analgesic advantage over existing products. While it is acknowledged that diversion and misuse of opioids may be commonplace, patients should be evaluated to determine whether such preventative measures are required. However, Oxaydo is not recognized as an abuse-deterrent *formulation* by the FDA. The only agent within this therapeutic class considered an abuse-deterrent *formulation* by the FDA is previously available Roxybond; which utilized both physical and chemical barriers.

Clinical guidelines do not recommend one opioid agent over another.

All agents within this class are considered controlled substances and contain a boxed warning regarding serious risks of misuse, abuse, addiction, overdose, and death as well as risks when combined with other central nervous system depressants; benzhydrocodone, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, oxycodone, oxymorphone, and tapentadol containing products and codeine tablets are Schedule II controlled substances; codeine and dihydrocodeine combination products are Schedule III; and butorphanol, pentazocine, and tramadol containing products are Schedule IV.

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