Long-Acting Narcotic Analgesics
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Schedule	Indication(s)
buprenorphine (Belbuca®)[1]	Alvogen, Biodelivery Sciences	CIII	▪ Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
buprenorphine (Butrans®)[2]	generic, Purdue	CIII	
fentanyl transdermal[3,4]	generic	CII	
hydrocodone extended-release (Hysingla® ER)[5]	Alvogen, Purdue	CII	
hydrocodone extended-release (Zohydro® ER)[6]	generic, Pernix	CII	
hydromorphone extended-release[7,8]	generic	CII	
methadone (Diskets®, Methadose™)[9,10]	generic, West-Ward/Hikma, Mallinckrodt	CII	▪ Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate; ▪ Detoxification and maintenance treatment of opioid addiction
morphine sulfate extended-release[11,12]	generic*†	CII	▪ Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
morphine sulfate extended-release (MS Contin®)[13]	generic, Rhodes	CII	
oxycodone extended-release (Oxycontin®)[14]	generic‡, Purdue	CII	
oxycodone extended-release (Xtampza ER®)[15]	Collegium	CII	
oxymorphone extended-release§[16,17]	generic	CII	

* Allergan has discontinued manufacture of Kadian® non-abuse-deterrent extended-release morphine sulfate capsules; generic products, approved with Kadian as the reference product, are still available.

† Pfizer has discontinued manufacture of Avinza® non-abuse-deterrent extended-release morphine sulfate capsules. Generic products, approved with Avinza as the reference product, are still available.

‡ Authorized generic.

§ In July 2017, Endo announced that they will voluntarily remove Opana® ER (oxymorphone ER) from the market in response to a request from the Food and Drug Administration (FDA) who determined that the product's risks outweigh its benefits.[18,19] Although Opana ER had abuse-deterrent *properties* following its reformulation in 2012, it was not considered an abuse-deterrent *formulation* by the FDA. In addition, oxymorphone extended-release products were approved based on the original formulation of Opana ER (originally approved in 2006), which did not contain abuse-deterrent properties.

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FDA-Approved Indications (continued)

Drug	Manufacturer	Schedule	▪ Indication(s)
tapentadol extended-release (Nucynta® ER)[20]	Collegium	CII	▪ Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate ▪ Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
tramadol extended release (Conzip®)[21]	Trigen‡, Vertical	CIV	▪ Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
tramadol extended release¶ [22,23]	generic	CIV	

‡ Authorized generic.

¶ Generics were approved to the reference product of either Ryzolt® (previously manufactured by Purdue Pharma) or Ultram® ER (previously manufactured by Janssen).

Ionsys®, a fentanyl iontophoretic transdermal system for pain management in hospitalized patients only, will not be addressed in this Therapeutic Class Review.

OVERVIEW

Pain of multiple etiologies remains a substantial problem for many patients presenting in the clinical setting.[24] Pain management must be individualized for each of these patients. There are many opioid analgesic products available, differing in specific opioid, dosage form, abuse-deterrent properties, and duration of action. In this review, the terms "narcotic" and "opioid" are used interchangeably.

Data from 2019 demonstrated that approximately 20.4% of adults report chronic pain in the United States (US).[25] Historically, data have suggested that pain may be undertreated, but newer estimates imply that opioid treatment for pain may be overutilized.[26] An estimated 20% of patients who presented to outpatient providers with noncancer pain or pain-related diagnoses, whether acute or chronic, received an opioid prescription.[27] Caregivers' misconceptions regarding opiate doses, duration of analgesic effect, and fear of addiction may be responsible for the historical undertreatment of pain, and some of the historical increase in opioid use is thought to be related to prescribers worrying they are undertreating their patients' pain.[28,29] Unfortunately, approximately 49,860 people died from overdoses related to opioid pain medications in the US in 2019.[30] Likewise, drug-related deaths have tripled from 1999 to 2017.[31] Opioid related overdose deaths in 2017 were higher among males (20.4%) in comparison to females (9.4%). In 2018, 15% of the US population received ≥ 1 opioid prescription. Annually from 2012, there has been a continued decreased in opioid prescribing. Likewise, the yearly rate for high-dose opioid prescriptions has decreased by 66.1% from 2006 to 2018. Regardless, persistent pain that is uncontrolled may have clinical, psychological, and social consequences; thus, it is critical to weigh the risks and benefits of opioid use and reevaluate patients routinely for appropriate dose, duration, and treatment choice, including both pharmacologic and nonpharmacologic modalities.

Different management techniques are utilized for acute and chronic pain. When properly used, long-acting opioids decrease administration frequency, decrease the incidence of adverse effects, and

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increase periods of consistent pain control. While definitions vary, chronic pain is generally defined as pain lasting > 3 months or past the time required for normal tissue healing. It has various etiologies, including injury, inflammation, and underlying medical conditions.[32]

Treatment Guidelines

The World Health Organization's (WHO) guidelines for cancer pain management for adults recommend a 3-stepped approach with consideration for the type of pain and response to therapy.[33] 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.

In 2016, the American Society of Clinical Oncology (ASCO) published guidelines for chronic pain management in adult cancer survivors.[34] For pharmacologic treatment, systemic non-opioid analgesics and adjuvant analgesics are suggested for chronic pain and to improve function. They state that opioids may be used in patients who do not respond to more conservative management.

Similarly, the National Comprehensive Cancer Network (NCCN) published guidelines on the treatment of cancer pain in adults in 2022 specific to pain scale ratings.[35] On a scale of 0 to 10, the pain scale rating of 1 to 3 is mild pain, 4 to 6 is moderate pain, and ≥ 7 is severe pain. The recommendation in opioid-naïve patients with mild pain is non-opioid and adjuvant therapies unless contraindications due to adverse effects, drug interactions, or comorbidities are present. For moderate/severe pain, NCCN recommends adding a short-acting opioid as needed to non-opioids/adjuvant therapies. Consideration for treatment in the hospital or hospice setting for patient-specific goals is recommended for any severe pain/pain crisis. NCCN defines opioid-tolerant patients as those who chronically receive opioids on a daily basis. The FDA considers tolerance as receiving at least 25 mcg/hr fentanyl patch, at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer. The NCCN recommendation for opioid-tolerant patients is the same as opioid-naïve patients, except that they specify titrating short-acting opioid dose by 30% to 50% or more for patients with moderate to severe pain. Recommendations for both opioid-naïve and opioid-tolerant patients include opioid rotation if dose-limiting adverse effects are noted. Long-acting opioids should be considered if ≥ 4 daily doses of short-acting opioid are consistently needed. NCCN recommends against the use of meperidine (due to central nervous system [CNS] toxicity from normeperidine metabolite) and mixed agonist-antagonists (e.g., pentazocine, nalbuphine, butorphanol due to limited usefulness) for cancer pain. Also, NCCN recommends providing a short-acting opioid for breakthrough pain when using methadone as a long-acting opioid. NCCN also provides extensive guidance on dosing, adverse effect management, and pain assessment.

A position statement released by the American Academy of Neurology (AAN) in 2018 states that the risks of opioids outweigh their benefits for treating most chronic conditions.[36] AAN states that there is insufficient evidence to support the efficacy of opioid therapy for the treatment of chronic pain and note this to be especially true of neuropathic pain. Furthermore, the AAN mentions that clear evidence has

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demonstrated that opioids can worsen migraine. However, AAN states opioids may be considered for weakness, pain, or other symptoms at the end of life as a component of palliative care.

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.[37] These CDC guidelines on opioid prescribing are not intended to deny opioid therapy for pain management in patients with chronic pain, sickle cell disease, undergoing cancer treatment, and cancer survivors with chronic pain; rather, the guidelines aim to ensure that clinicians and patients consider all safe and effective treatment options. These guidelines include 12 recommendations: 3 regarding when to initiate or continue opioids for chronic pain; 4 regarding opioid selection, dosage, duration, follow-up, and discontinuation; and 5 regarding assessing risk and addressing harms of opioid abuse.[38] The guidelines prefer nonpharmacologic and nonopioid pharmacologic therapy for chronic pain, and recommend a full individual 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, they recommend initial treatment with immediate-release opioids instead of extended-release opioids, which should be prescribed at the lowest effective dose. They further specify that doses of ≥ 50 morphine milligram equivalents (MME)/day should prompt reassessment of the individual's benefits and risks and use of ≥ 90 MME/day should be avoided without justification. They state that long-term opioid use often begins with acute pain treatment; thus, opioids for acute pain should be immediate-release, 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). They recommend reassessment within 1 to 4 weeks to determine benefits, harms, and appropriate dosing and continued follow up at least every 3 months. At these visits, efforts should be made to optimize other therapies and taper or discontinue opioids as able and as risks outweigh the individual's benefits. In order to decrease risks, the guidelines recommend avoiding concurrent use of benzodiazepines when possible and 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 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 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.[39]

In 2017, the American College of Physicians (ACP) updated their guidelines on noninvasive treatments for acute, subacute, and chronic low back pain.[40] The guidelines recommend nonpharmacologic treatment (e.g., superficial heat, massage, acupuncture, spinal manipulation) in most patients with acute or subacute low back pain. 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 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.[41] They

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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).

In March 2020, the North American Spine Society (NASS) published evidence-based clinical guidelines on the diagnosis and treatment of low back pain. There is limited information provided regarding opioids in this setting as the opioid crisis occurred after the guideline development was already underway. However, it is suggested that use of opioid pain medications for treating low back pain be limited and restricted to a short duration (grade of recommendation: B). In contrast, non-selective NSAIDs are suggested for the treatment of low back pain (grade of recommendation: B).

In 2017, the American Society of Interventional Pain Physicians (ASIPP) updated opioid prescribing guidelines for the management of patients with chronic, non-cancer pain.[42] ASIPP recommends that medical necessity of opioids should be established based on an average moderate to severe (pain or disability level ≥ 4 on a 0 to 10-point scale). Regarding specific products, ASIPP recommends initiation of opioids at low doses with short-acting agents and appropriate monitoring. They consider daily doses of ≤ 40 morphine milligram equivalents (MME) as low dose, 41 to 90 MME as moderate dose, and ≥ 91 MME as high dose opioids. They recommend methadone only after failure of other opioid therapy and state long-acting opioids should be avoided during opioid initiation and recommend long-acting or high dose opioids only in special circumstances in which there is severe, intractable pain. They state there is similar effectiveness for long-acting and short-acting opioids, but there are greater risks of adverse events with long-acting opioids. However, they do not recommend 1 specific short-acting opioid over another. 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.

The HIV Medicine Association (HIVMA) of the Infectious Disease Society of America (IDSA) has issued the first comprehensive guidelines for managing chronic pain in people living with the human immunodeficiency virus (HIV) that covers musculoskeletal, arthritic, and neuropathic pain types (not cancer pain).[43] 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 drugs (gabapentin [preferred], serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, or pregabalin). Other options include capsaicin, medical cannabis (in select patients), and alpha lipoic acid. The guidelines recommend against use of lamotrigine and against opioids as first-line.

The American Association of Oral & Maxillofacial Surgeons (AAOMS) issued a White Paper regarding opioid prescribing for acute and postoperative pain management.[44] NSAIDs are recommended over opioids as first-line therapy to manage acute and post-operative pain. If an opioid is needed, the lowest dose for the shortest duration should be used and extended-release formulations avoided.

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The Institute for Clinical and Economic Review (ICER) has published a final report on abuse-deterrent formulation (ADF) opioids.[45] The group concluded that the evidence is adequate to suggest a reduced risk of abuse among individual patients prescribed Oxycontin compared to non-ADF opioids; however, evidence is not sufficient to show a reduced risk of abuse for individual patients being prescribed any other abuse-deterrent ER opioid assessed in the report (Hysingla ER, Xtampza ER).

In 2018, the Scientific and Medical Advisory Board of the Restless Legs Syndrome (RLS) Foundation published new guidance stating that opioid therapy is a mainstay of refractory RLS management and low total daily doses of opioids may be life-transforming for patients with refractory RLS.[46] Therapy should be started with a short-acting formulation to determine response, but long-acting opioids are preferred. Most commonly used agents are oxycodone and methadone, but tramadol, codeine, morphine, and hydrocodone can also be considered. Controlled-release medication should be used for evening dosage and short-acting drugs, if needed, during the day.

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 at risk for opioid overdose, including individuals who are on relatively higher doses of opioid (≥ 50 MME/day), those with select respiratory comorbidities (e.g., sleep apnea, chronic obstructive pulmonary disease [COPD]), take other medications which enhance opioid complications (e.g., benzodiazepines), or have other non-opioid substance abuse disorders or mental health disorders.[47] In October 2019, the HHS published a new guideline for clinicians on dosage reduction or discontinuation of long-term opioid analgesics.[48] 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 or discontinue opioid dosing. 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, although longer tapering schedules may be required; and considering transition to buprenorphine for patients on high doses and unable to taper.

Opioid Regulation

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 Food and Drug Administration (FDA). Tolerance, dependence, and addiction to tramadol have been demonstrated and abrupt discontinuation of the drug can result in withdrawal symptoms. Effective in August 2014, tramadol-containing products were placed into Schedule IV of the Controlled Substance Act.[49]

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In 2013, the FDA announced class-wide safety labeling changes and new post-market study requirements for all extended-release and long-acting (ER/LA) opioid analgesics intended to treat pain. [50] The updated indication states that ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.

In April 2015, the FDA released guidance to the industry regarding the development of opioid drug products with abuse-deterrent properties to limit the misuse, abuse, and potentially death associated with these products.[51] This guidance states that abuse-deterrent properties discourage abuse but may not fully prevent abuse. Examples of abuse-deterrent properties include physical/chemical barriers to prevent breakdown of the product, agonist/antagonist combinations, added aversive substances, unique drug delivery systems (e.g., depot injections, implants), or new molecular entities or prodrugs with novel effects (e.g., altered receptor binding or require enzymatic activation). In order for the FDA to approve a formulation as an abuse-deterrent formulation, an abuse-deterrent property is not sufficient; the manufacturer should demonstrate that the product deters abuse in studies. The types of studies the FDA requires are laboratory-based *in vitro* manipulation and extraction studies, pharmacokinetic studies, and clinical abuse potential studies, which commonly measure drug-liking by subjects without pain and with current addiction behaviors. The following agents have demonstrated abuse-deterrence in studies, thus meeting FDA requirements for abuse-deterrent formulations: Hysingla ER tablets, Oxycontin biconcave tablets, oxycodone ER (authorized generics of Oxycontin) tablets, and Xtampza ER capsules.[52,53,54] As a result, the labeling of these products includes information regarding abuse-deterrence, reflecting the FDA's approval of these products as abuse-deterrent formulations. The FDA also published information on abuse deterrence studies to guide new product development and evaluations of generic formulations.[55]

In February 2016, the FDA announced plans to reassess their approach to opioid medications with a focus on policies to reverse the epidemic of deaths associated with opioid use.[56] Select components of the action plan include the use of an expert advisory committee prior to the approval of an opioid without abuse-deterrent properties, the formation of a Pediatric Advisory Committee to review pediatric labeling for new products, an update of risk evaluation and mitigation strategy (REMS) requirements and improvement in access to abuse-deterrent formulations, naloxone, and other treatment options for patients with opioid-use disorders.

In April 2017, the FDA announced the restricted the use of codeine and tramadol medicines in children due to serious risks, including slowed or difficult breathing and death, which are a greater risk in children younger than 12 years.[57] These medications 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 September 2017, the FDA determined that a REMS is necessary for immediate-release (IR) opioid analgesics to ensure that the benefits outweigh the risks for this drugs.[58] As a result, the FDA sent letters to IR opioid analgesic manufacturers stating that these products that are intended for outpatient setting use will be subject to the same REMS requirement as the ER/LA opioid analgesics.

In October 2018, the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act was passed to reduce unnecessary opioid exposure, and lower the rate of new opioid addiction.[59] The provision requires the Drug Enforcement Administration

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(DEA) to provide drug manufacturers and distributors access to drug supply chain information from point of manufacture to point of sale.[60] This system, Automated Reports and Consolidated Orders System (ARCOS), helps drug manufacturers and distributors identify, report, and stop suspicious orders of opioids and reduce diversion rates. Additionally, the Act gave authority to the FDA to require manufacturers to develop disposal technologies to allow patients easier disposal of unused medications out of their homes.[61]

In April 2019, the FDA required label changes to guide prescribers on gradual, individualized tapering of opioid pain medications due to harm reported from sudden discontinuation.[62] The FDA was prompted to make these changes after receiving several reports of serious harm in patients physically dependent on opioid medications undergoing sudden discontinuation or rapid dose decrease. These effects include serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide. Withdrawal and uncontrolled pain from rapid dose decreases can lead patients to seek illicit substances to treat pain, which could be confused with abuse drug-seeking behaviors. Tapering schedules should be patient-specific based on multiple patient factors such as duration of therapy, type of pain treated, and physical and psychological patient attributes. The FDA suggests tapering by an increment of no more than 10% to 25% every 2 to 4 weeks.

In April 2019, the FDA announced as a part of their "Remove the Risk" campaign for removing and properly disposing of unused prescription opioids from the home, they were targeting females aged 35 to 64 years since the FDA considers them as common gatekeepers in the home for healthcare decisions and medication management.[63] The campaign involves a toolkit of materials for news media, healthcare providers, consumer groups, and other organizations.

The FDA continues to evaluate and issue guidance on the use and development of opioids.[64] 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.[65] 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.[66,67,68,69,70]

In July 2020, the FDA released a MedWatch safety alert and drug safety communication for opioid pain relievers and opioid use disorder agents.[71] The FDA recommends that healthcare professionals (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.

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PHARMACOLOGY[72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88]

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). Opioid agonists produce respiratory depression by direct action on the brain stem respiratory center. Buprenorphine (Belbuca, Butrans) differs in that it is a partial agonist/antagonist of opioid receptors.

Tapentadol (Nucynta ER) is a centrally-acting synthetic analgesic and exerts its analgesic effects without a pharmacologically active metabolite. The exact mechanism of action is unknown. Tapentadol also inhibits norepinephrine reuptake.

In addition to binding to the mu-opioid receptors, tramadol (Conzip, generic) exerts its effect through weak inhibition of norepinephrine and serotonin reuptake.

PHARMACOKINETICS[89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105]

Drug	Half-Life (hr)	Tmax (hr)	Excretion
buprenorphine (Belbuca)	27.6	3	69% metabolized and eliminated in feces and approximately 30% excreted in urine
buprenorphine (Butrans)	26	about 48-72	70% metabolized and eliminated in feces and approximately 27% excreted in urine
fentanyl transdermal	3–12	28.8–35.8	75% metabolized and renally eliminated
hydrocodone ER (Hysingla ER)	7–9	14–16	primarily metabolized and renally eliminated
hydrocodone ER (Zohydro ER)	8	5	highly metabolized; 26% eliminated in urine
hydromorphone ER	8–15	12–16	highly metabolized; 75% eliminated in urine
methadone (Diskets, Methadose)	8–59	1–7.5	highly metabolized; eliminated in urine and feces
morphine sulfate ER	2–15	8.6–10.3	90% metabolized and renally eliminated
morphine sulfate ER (MS Contin)	2–15	~ 1.5	90% metabolized and renally eliminated
oxycodone ER (Oxycontin)	4.5	1.6–3.2	primarily metabolized and renally eliminated
oxycodone ER (Xtampza ER)	~5.6	4–4.5	primarily metabolized and renally eliminated
oxymorphone ER	9.4–11.3	1–2	highly metabolized; eliminated in urine and feces
tapentadol ER (Nucynta ER)	5	3–6	97% metabolized and renally eliminated
tramadol ER (Conzip)	tramadol 10 metabolites 11	tramadol 5.9 metabolites 11	30% excreted as tramadol, 60% excreted as active metabolites in the urine
tramadol ER	tramadol 7.9 metabolites 8.8	tramadol 12 metabolites 15	30% excreted as tramadol, 60% excreted as active metabolites in the urine

hr = hours; Tmax = time to maximum serum concentration; nr = not reported

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CONTRAINDICATIONS/WARNINGS[106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122]

Contraindications

The agents in this review are contraindicated in patients with a known hypersensitivity to any component of the product. Hydromorphone is also contraindicated in patients with known hypersensitivity to sulfites. Oxymorphone ER is contraindicated in patients with a known hypersensitivity to morphine analogs, such as codeine.

Long-acting opioids are contraindicated in patients who are not opioid-tolerant; patients who have acute or severe bronchial asthma; situations of significant respiratory depression (in the absence of resuscitative equipment or monitors); and patients with known or suspected paralytic ileus.

In general, long-acting opioids are not indicated as an as-needed analgesic; for example, for use in the management of acute pain, mild pain, or intermittent pain, or in patients who require opioid analgesia for a short period of time in the management of post-operative pain, including use after outpatient or day surgeries (e.g., tonsillectomies).

Oxymorphone ER is contraindicated in patients with moderate and severe hepatic impairment.

Monoamine oxidase inhibitors (MAOIs) may intensify the actions of opioids; these long-acting opioids should not be taken in patients taking MAOIs or within 14 days of stopping MAOI treatment.

Tramadol ER (Conzip, generic) is contraindicated in patients who have acute intoxication with alcohol, hypnotics, centrally-acting analgesics, opioids, or psychotropic drugs, and situations where opioids may be contraindicated. In April 2017, the FDA released a Drug Safety Communication regarding the use of tramadol in pediatric patients and is requiring labeling revisions for these products.[123] Due to case reports of respiratory depression, some leading to death, the FDA required a new contraindication for the use of tramadol to treat pain following tonsillectomy and/or adenoidectomy in patients < 18 years old. An additional contraindication in children < 12 years old was also added. Notably, tramadol formulations within this class review are approved only in adults. Additional warnings were also required and are described below.

Warnings

Boxed Warnings

Buprenorphine transdermal (Belbuca, Butrans), methadone (Diskets, Methadose), fentanyl transdermal, morphine sulfate ER (MS Contin), hydrocodone ER (Hysingla ER, Zohydro ER), hydromorphone ER, morphine sulfate controlled-release (MS Contin), oxymorphone ER, oxycodone ER (Oxycontin), oxycodone ER (Xtampza ER), tapentadol ER (Nucynta ER), and tramadol ER (Conzip, generic) boxed warnings include: monitoring for signs of misuse, abuse, and addiction during therapy; fatal respiratory depression may occur, with the highest risk at initiation and with dose increases; and accidental exposure can result in the fatal overdose of the above medications in children. 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. Patients should be monitored closely for any signs and symptoms of respiratory depression and sedation.

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In August 2016, the FDA issued a Drug Safety Communication regarding the risk of death when combining opioid pain medications or cough medicine with benzodiazepines and other CNS depressants. The FDA required an additional boxed warning for all opioids describing this risk (as described above).[124]

The boxed warning for methadone (Diskets, Methadose) indicates that cardiac and respiratory deaths have been reported during initiation and conversion of pain patients to methadone treatment from other opioid agonists. Cases of QT interval prolongation and serious arrhythmia have also been observed.

Chronic maternal use of opioids during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome; infants may require treatment if exposed to opioids during gestation.

Respiratory depression is the chief hazard of opioid agonists. Serious or life-threatening hypoventilation may occur at any time during the use of long-acting opioids, especially during the initial 24 to 72 hours following initiation of therapy and following increases in dose. Respiratory depression is more likely to occur in elderly or debilitated patients, usually following large initial doses in non-tolerant patients or when opioids are given in conjunction with other agents that depress respiration, such as alcohol and other CNS depressants. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous. 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. 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.

When the patient no longer requires therapy with agents in this class, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically-dependent patient. These agents should not be abruptly discontinued in physically dependent patients; withdrawal syndrome, 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.

Patients should not consume alcohol or any products containing alcohol while taking because co-ingestion can result in fatal plasma morphine levels.

Oxycodone ER (OxyContin, Xtampza ER) also carry a boxed warning for drug interactions associated with cytochrome P450 3A4 inhibitor or inducer initiation or discontinuation potentially altering drug exposure which could lead to overdose.

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Other Warnings

Long-acting opioids may worsen increased intracranial pressure and obscure its signs. Patients with increased intracranial pressure, brain tumors, head injury, or impaired consciousness may be more susceptible. Patients at increased risk of hypotension and those in circulatory shock could experience worsened conditions with treatment. Orthostatic hypotension and syncope have also been reported with opioids. Patients at higher risk of hypotension include those with hypovolemia or those taking concurrent products that compromise vasomotor tone (e.g., phenothiazines, general anesthetics).

All agents in this review, except tramadol ER, may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsened symptoms.

All opioids contain a warning regarding serotonin syndrome when used concomitantly with any serotonergic drug (e.g., monoamine oxidase [MAO] inhibitors, selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRI], tricyclic antidepressants [TCAs], triptans, linezolid, lithium, or certain muscle relaxants [e.g., cyclobenzaprine, metaxalone]). Serotonin syndrome typically occurs within several hours to a few days following use.[125]

Monitor patients with a history of seizure disorders for worsened seizure control during therapy with buprenorphine, hydromorphone ER, morphine ER, morphine ER/naltrexone, oxycodone ER, oxymorphone ER, tapentadol ER, and tramadol ER since these agents can aggravate seizure disorder and may induce seizures in some clinical settings. This is not reported for fentanyl transdermal or hydrocodone ER medications.

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.[126]

Initiation of concurrent therapy with CYP3A4 inhibitors, or discontinuation of CYP3A4 inducers with buprenorphine, fentanyl transdermal, hydrocodone ER, and oxycodone ER, can result in a fatal opioid overdose.

All tablets or capsules of oral long-acting opioids, with the exception of oxycodone ER (Xtampza ER), should be swallowed whole. Taking broken, chewed, or crushed tablets or capsules can lead to a rapid release and absorption of a potentially fatal dose of most drugs in this class.

Buprenorphine and fentanyl patches are for transdermal use on intact skin only. Avoid exposure to direct heat while wearing the patch because an increased absorption of the drug can occur. Monitor patients who develop increased body temperature for opioid side effects and adjust dose if signs of respiratory or central nervous system depression are seen. Buprenorphine patches should not be used if the pouch seal is broken or the patch is cut, damaged, or changed in any way. Damaged or cut fentanyl patches should not be used.

Use of opioids with other CNS depressants may result in hypotension, sedation, respiratory depression, coma, or death.

Due to the risk of sedation with opioids, this may impair a patient's ability to drive or operate heavy machinery.

If urine testing for clinical management is needed, the assay should be assessed to ensure the sensitivity and specificity are appropriate.

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buprenorphine buccal (Belbuca) and buprenorphine transdermal (Butrans)

Avoid using buprenorphine in patients with long QT syndrome or a family history of the disease. Use caution in patients with hypokalemia, hypomagnesemia, or clinically-unstable cardiac disease. These patients should not exceed a dose of one 20 mcg/hr buprenorphine transdermal patch due to the risk of QTc prolongation.

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving sublingual buprenorphine for the treatment of opioid dependence. For patients with an increased risk of hepatotoxicity (e.g., history of excessive alcohol intake, liver disease), monitor liver enzyme levels before and periodically during treatment with buprenorphine. The risk of overdose may be greater in patients with moderate to severe hepatic impairment.

Cancer patients with oral mucositis may absorb buprenorphine buccal (Belbuca) more quickly than intended. A dose reduction is recommended in patients with known or suspected mucositis.

Rare cases of severe application site skin reactions have been reported with use of buprenorphine transdermal patches. Onset can occur within days to months after treatment starts. Discontinue therapy if this occurs.

Buprenorphine transdermal has not been studied for use in the management of addictive disorders.

fentanyl transdermal

In 2005 and again in 2007, the FDA issued safety communications that highlight important information on appropriate prescribing, dose selection, and the safe use of the fentanyl transdermal system (patch).[127] However, the FDA continues to receive reports of death and life-threatening adverse events related to fentanyl overdose that have occurred when the fentanyl patch was used to treat pain in opioid-naïve patients and when opioid-tolerant patients have applied more patches than prescribed, changed the patch too frequently, and exposed the patch to a heat source. Directions for prescribing and using the fentanyl patch must be followed exactly to prevent death or other serious side effects from fentanyl overdose.

Fentanyl may cause bradycardia; monitor patients with bradyarrhythmias.

hydrocodone bitartrate ER (Zohydro ER/Hysingla ER)

QTc prolongation has been observed with daily doses of hydrocodone ER 160 mg and should be considered when prescribing this agent in patients with congestive heart failure, bradyarrhythmias, electrolyte imbalances, or who are taking medications known to cause QTc prolongation. Avoid hydrocodone ER in patients with congenital long QT syndrome. A dose reduction or a change to an alternative analgesic should be made in patients who develop QTc prolongation.

Alcohol or alcohol-containing products should not be consumed while taking hydrocodone bitartrate ER as co-ingestion can result in fatal plasma hydrocodone levels.

oxycodone ER (Oxycontin)

A reformulation of oxycodone ER (Oxycontin) was approved in 2010 by the FDA, as well as the first reformulated generic version. These new formulations were designed to decrease the likelihood that this medication will be misused or abused, and result in overdose. The reformulation added tamper-resistant features aimed at preserving the controlled release of the active ingredient, oxycodone.[128] Any

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attempt to dissolve the tablets in liquid results in a gummy substance. The oxycodone ER 60 mg and 80 mg tablets (or a single dose > 40 mg) are to be used in opioid-tolerant patients only, since fatal respiratory depression may occur when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

oxycodone ER (Xtampza ER)

The risk of overdose may be greater in patients with moderate to severe hepatic impairment compared to patients with normal hepatic function; a lower starting dose is recommended in this population.

oxymorphone ER

In October 2012, the FDA issued a safety warning that thrombotic thrombocytopenic purpura appears to occur with the use of oxymorphone ER when it is abused and injected intravenously. TTP resulting in kidney failure requiring dialysis have been reported.[129] Oxymorphone ER should only be taken orally.

Endo has voluntarily removed Opana ER from the market, per FDA request.[130,131] Post marketing data illustrated that the reformulated Opana ER drew concerns that the benefits of the drug no longer outweighed the risks as there was a significant shift in the route of abuse of Opana ER from nasal to injection.

tramadol extended-release (Conzip, generic)

Tramadol extended-release formulations are for oral use only, should be swallowed whole, and should not be chewed, dissolved, split, or crushed.

The effects of concomitant use or discontinuation of drugs affecting cytochrome P450 should be taken into consideration in patients using tramadol.

Due to the risk of respiratory depression with tramadol in pediatric patients described above, the FDA has required an additional warning recommending against the use of tramadol in adolescents ages 12 to 18 years who are obese or have conditions which may increase the risk of serious breathing problems (e.g., obstructive sleep apnea, severe lung disease).[132] The FDA has also strengthened the warning regarding its use while breastfeeding; tramadol use by women while breastfeeding is not recommended as it may cause significant adverse reactions (e.g., excess sleepiness, difficulty feeding, breathing difficulty) in breastfed infants.

Tramadol ER should not be prescribed for patients who are suicidal or addiction-prone. Tramadol ER package labeling has been updated to recommend that clinicians perform an opioid addiction, abuse, and misuse risk assessment prior to prescribing tramadol ER. Patients with a personal or family history of substance abuse or mental illness are notably at an increased risk; however, such risk factors should not prevent a patient from receiving adequate pain management. Additionally, labeling includes recommendations for prescribers to discuss with patients the availability of naloxone when both initiating and renewing opioid therapy. Naloxone should be considered based on the patient's risk factors for opioid overdose (e.g., concurrent CNS depressant use, history of opioid use disorder, past opioid overdose) or if the patient lives with or has close contact with others at risk for accidental ingestion or overdose.

Reports of hyponatremia (serum sodium < 135 mmol/L) as well as hypoglycemia have occurred with use of tramadol. Many hyponatremia cases have been severe (serum sodium < 120 mmol/L) and some of

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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 (confusion, disorientation), start appropriate management (fluid restriction) and discontinue tramadol. Most cases of hypoglycemia occurred in those with risk factors (diabetes, renal insufficiency, elderly). If hypoglycemia is suspected, assess blood glucose and discontinuation of tramadol should be considered, if appropriate.

Risk Evaluation and Mitigation Strategy (REMS)[133]

In 2012, the revised REMS for extended-release (ER) and long-acting (LA) opioid medications was introduced. The FDA communicated that this class contains highly potent medications whose approved indication is to treat moderate-to-severe persistent pain for serious chronic conditions. In addition, misuse and abuse of these medications was addressed referencing a serious public health crisis of addiction, overdose, and death. The REMS introduced new safety measures (including dispensing of medication guides and prescriber training). 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. As a result, the FDA sent letters to IR opioid analgesic manufacturers informing them that their products that are intended for outpatient setting use will be subject to the same REMS requirement as the ER/LA opioid analgesics. In September 2018, the REMS program name was changed to the Opioid Analgesic REMS and now applies to immediate-release opioid analgesics for outpatient use as well.

Minor changes to this REMS program have occurred over the years. The current requirements of the REMS program include a medication guideline and healthcare provider training, including prescriber letters, blueprints for education points, patient counseling documents, and organization and licensing board education letters.

DRUG INTERACTIONS[134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150]

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

Mixed agonist/antagonist analgesics (e.g., pentazocine, nalbuphine, butorphanol) and partial agonists (buprenorphine) should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic. In these patients, the mixed agonist/antagonist or partial agonist may alter the analgesic effect or may precipitate withdrawal symptoms.

Monoamine oxidase inhibitors (MAOIs) may intensify the actions of fentanyl transdermal, hydrocodone ER, hydromorphone ER, morphine ER, morphine/naltrexone, tapentadol ER, and tramadol ER; these long-acting opioids should not be used in patients taking MAOIs or within 14 days of stopping MAOI treatment.

All opioids contain a warning regarding serotonin syndrome when used concomitantly with any serotonergic drug as described above.[151]

Concomitant use of diuretics and anticholinergics with opioids may reduce the efficacy of the diuretic and increase the risk of urinary retention respectively; monitor and adjust the doses as needed.

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Drugs that induce or inhibit cytochrome P450 3A4 enzymes may affect the metabolism of buprenorphine, fentanyl transdermal, hydrocodone ER, oxycodone ER, and tramadol ER. Initiation of concurrent therapy with CYP3A4 inhibitors, or discontinuation of CYP3A4 inducers with these agents, can increase the risk of serious adverse events. However, co-administration of the strong CYP3A4 inhibitor ketoconazole 200 mg with buprenorphine transdermal 10 mcg/hr did not result in changes in the buprenorphine pharmacokinetic profile. Concurrent use of a CYP3A4 inducer may result in a reduced analgesic effect.

Methadone is metabolized by several CYP isoforms, including CYP3A4, CYP2B6, CYP2C19, CYP2C9, and CYP2D6. As a result, use with inhibitors of these enzymes may require a decrease in methadone dose and inducers may result in decreased methadone efficacy. Methadone should be used cautiously in others taking concomitant medications that can affect cardiac conduction or electrolytes; monitoring of cardiac conduction is recommended.

Tramadol is metabolized by CYP2D6 to form an active metabolite. Concomitant administration of CYP2D6 inhibitors, such as quinidine, fluoxetine, paroxetine, and amitriptyline, may reduce metabolic clearance of tramadol increasing the risk for serious adverse events including seizures. Drugs that induce or inhibit cytochrome P450 3A4 enzymes may affect the metabolism of oxycodone ER; monitor and adjust dosage as required if concomitant use is warranted.

The use of buprenorphine, fentanyl transdermal, hydrocodone ER, hydromorphone ER, morphine ER, morphine ER/naltrexone, oxycodone ER, oxymorphone ER, or tapentadol ER with anticholinergic products may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. P-glycoprotein (P-gp) inhibitors, such as quinidine, may increase the exposure of morphine by 2-fold. Cimetidine can potentiate respiratory depression when given with oxymorphone or morphine. Morphine and oxycodone can reduce the effect of diuretics.

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ADVERSE EFFECTS[152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168]

Drug	Asthenia	Constipation	Dizziness	Dyspnea	Headache	Nausea	Rash	Somnolence	Vomiting
buprenorphine (Belbuca)	< 1	4–13 (3)	2–6 (1)	< 1	2–6 (3)	10–50 (7)	< 5	1–7 (< 1)	4–8 (< 1)
buprenorphine (Butrans)	1–5	3–13 (1–5)	2–15 (1–7)	≥ 1– < 5	5–16 (5–11)	13–23 (8–11)	3–9 (6)	2–13 (2–4)	4–9 (1)
fentanyl transdermal	> 10	> 10	3–10	3–10	3–10	> 10	> 1	> 10	> 10
hydrocodone ER (Hysingla ER)	≥ 1 – < 5	≥ 5	≥ 5	< 1	≥ 5	≥ 5	≥ 1– < 5	≥ 5	≥ 5
hydrocodone ER (Zohydro ER)	nr	8 (0)	2 (1)	1–10 (nr)	0 (1)	7 (3)	1–10 (nr)	1 (0)	7 (1)
hydromorphone ER	1–4 (4)	7–15 (4)	2–4 (1)	reported	5–8 (7)	9–12 (7)	reported	1–9 (0)	6 (4)
methadone (Diskets, Methadose)	reported	reported	reported	reported	reported	reported	reported	reported	reported
morphine sulfate ER	2	9	6	3	< 2	7	3	9	2
morphine sulfate ER (MS Contin)	reported	reported	reported	nr	reported	reported	reported	reported	reported
oxycodone ER (Oxycontin)	6 (nr)	23 (7)	13 (9)	1-5	7 (7)	23 (11)	1-5	23 (4)	12 (7)
oxycodone ER (Xtampza ER)	nr	5.2–13 (0.5)	1.6–5.7 (0)	< 1	6.2–13.9 (11.7)	10.9–16.6 (4.6)	1–5	< 1–8.8– (< 1)	4.1–6.4 (1.5)
oxymorphone ER	nr	27.6 (13.2)	17.8 (7.6)	1–10	12.2 (5.6)	33.1 (13.2)	nr	17.2 (2.2)	15.6 (4.1)
tapentadol ER (Nucynta ER)	2 (1)	17 (7)	17 (6)	1 (0)	15 (13)	21 (7)	1 (<1)	12 (4)	8 (3)
tramadol ER	3.5–6.5	12.2–29.7	15.9–28.2	1– < 5	11.5–15.8 (10.6)	15.1–26.2	nr	7.3–20.3 (1.7)	5–9.4
tramadol ER (Conzip)	3.5–8.6	9.3–21.3	9.6–13.6	nr	19.0–23.1	16.1–25.1	1-5	11.7–16.1	6.5–10.4
oxymorphone ER	nr	27.6 (13.2)	17.8 (7.6)	1–10	12.2 (5.6)	33.1 (13.2)	nr	17.2 (2.2)	15.6 (4.1)

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

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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.[169]

SPECIAL POPULATIONS[170,171,172,173,174,175,176,177,178,179,180,181,182,183,184, 185,186]

Pediatrics

Fentanyl transdermal is approved for use in patients as young as 2 years of age who are opioid-tolerant. Oxycodone ER (Oxycontin) is approved for use in opioid-tolerant pediatric patients ≥ 11 years of age who are already receiving and tolerating at least 20 mg oxycodone orally (or its equivalent).

Safety and efficacy of buprenorphine transdermal (Butrans), buprenorphine buccal (Belbuca), hydrocodone bitartrate ER (Hysingla ER, Zohydro ER), methadone (Diskets, Methadose), morphine sulfate ER (MS Contin), oxycodone ER (Xtampza ER), oxymorphone ER, tramadol ER (Conzip), and tapentadol ER (Nucynta ER) have not been established in patients younger than 18 years of age. Safety and efficacy of hydromorphone ER has not been established in patients younger than 17 years of age.

While not approved in this population, the FDA announced in April 2017 that they are requiring additional contraindications and warnings to the labeling of tramadol regarding its use in pediatric patients. This is a result of their investigation of case reports involving respiratory depression.[187]

Geriatrics

Elderly patients may be more sensitive to the opioid agonist effects than younger patients. Monitor geriatric patients closely for signs of sedation and respiratory depression, particularly when initiating opioid therapy and when given in conjunction with other drugs that depress respiration.

Administration of oxymorphone ER in elderly patients resulted in plasma levels that were 40% higher than those in younger subjects.

In clinical trials with buprenorphine buccal (Belbuca), adverse effects were higher in elderly patients than in younger adults.

In clinical trials with oxycodone ER (OxyContin) and oxycodone ER (Xtampza ER), oxycodone exposure was higher in elderly patients than in younger adults, but no unexpected or untoward adverse effects occurred. Use cautiously in this population.

Pregnancy

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. Opioids cross the placenta and may produce respiratory depression in neonates. Opioids are not for use in women during and immediately prior to labor, when shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions.

Based on the Pregnancy and Lactation Labeling Rule (PLLR), newer agents and agents with labeling changes have had their Pregnancy Category designation replaced with descriptive text. There are no available or adequate data with buprenorphine (Belbuca, Butrans), fentanyl transdermal, hydrocodone

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ER (Hysingla ER, Zohydro ER), hydromorphone ER, morphine sulfate ER (MS Contin), oxymorphone ER, tapentadol ER (Nucynta ER), and tramadol ER (Conzip) in pregnant women to inform of a drug-associated risk for major birth defects and miscarriage. Previously, most agents within this class were assigned Pregnancy Category C.

Previously, oxycodone ER (Oxycontin) was assigned a Pregnancy Category B designation, but this was also replaced with descriptive information. While animal studies did not reveal evidence of fetal harm, there are no adequate or well-controlled studies in pregnant women; animal studies are not always predictive of human response. Therefore, oxycodone ER should be used during pregnancy only if clearly required. There are no adequate and well-controlled studies of oxycodone ER (Xtampza ER) in pregnant women.

Methadone's Pregnancy Category C designation was also replaced based on the PLLR. There are no adequate and well-controlled studies in pregnant women; it should only be used when the benefit outweighs the potential risk. Methadone exposure can result in congenital oculomotor disorders (nystagmus, strabismus). In pregnant women who receive treatment with methadone, higher doses or administration of the daily dose in divided doses may be needed; pregnancy appears to result in significantly lower trough plasma concentrations, increased plasma clearance, and shorter half-life of methadone compared to observed following delivery. Women on high-dose methadone maintenance already nursing should be counseled to wean breast-feeding gradually to prevent neonatal abstinence syndrome.

Hepatic Impairment

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

Avoid use of fentanyl transdermal, tapentadol ER, and tramadol ER in patients with severe hepatic impairment. Reduce dose of tapentadol ER in patients with moderate hepatic impairment.

Initiate hydrocodone ER therapy at 50% of the usual starting dose in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression.

Hydromorphone ER should be initiated at 25% of the usual starting dose in patients with moderate hepatic impairment and closely monitor these patients for respiratory and central nervous system depression during initiation and dose titration. The pharmacokinetics of hydromorphone in severe hepatic impairment patients have not been studied.

Oxycodone ER should be initiated at 33% to 50% of the usual starting dose and carefully titrated in patients with hepatic impairment. An alternative analgesic is recommended in those requiring a dose of < 9 mg.

Buprenorphine transdermal (Butrans) has not been evaluated in patients with severe hepatic impairment. Since it is intended for 7-day dosing, alternate analgesic therapy should be considered in patients with severe hepatic impairment.

The pharmacokinetics of morphine in patients with severe hepatic impairment have not been adequately studied; however, there are reports of altered pharmacokinetics in this population. Initiation at a lower dose is generally recommended, followed by cautious titration to monitor for adverse effects.

Buccal buprenorphine (Belbuca) has not been evaluated in patients with severe hepatic impairment; dosage adjustments are not required for patients with mild to moderate hepatic impairment.

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Renal Impairment

Avoid use of fentanyl transdermal, tapentadol ER, and tramadol ER in patients with severe renal impairment.

Use oxycodone ER with caution in patients with renal impairment. In renally-impaired patients (estimated creatinine clearance [CrCl] < 60 mL/min), plasma exposure may be 50% higher than in individuals with normal renal function. An alternative analgesic is recommended in those requiring a dose < 9 mg.

Titrate oxymorphone ER slowly in patients with moderate to severe renal impairment.

Although accumulation of morphine metabolites has been found in people with renal failure, adequate studies of the pharmacokinetics of morphine in patients with severe renal impairment have not been performed. Initiation at a lower dose is generally recommended, followed by cautious titration to monitor for adverse effects.

Start hydromorphone ER therapy at 50% of the usual starting dose in patients with moderate renal impairment and 25% of the usual starting dose in patients with severe renal impairment. Closely monitor patients for respiratory and CNS depression during initiation and during dose titration. Hydromorphone ER is only intended for once-daily administration; consider an alternate analgesic that may provide more dosing flexibility in patients with severe renal impairment.

Initiate therapy with 50% of the initial dose of hydrocodone ER in patients with moderate or severe renal impairment or end-stage renal disease and monitor closely for adverse events such as respiratory depression.

No impact of creatinine clearance on steady state buprenorphine concentrations has been found. No differences in pharmacokinetics of buccal buprenorphine (Belbuca) were found between patients on dialysis and those with normal renal function.

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

Drug	Starting Dose	Titration	Available Strengths	Abuse-Deterrent Formulation*
buprenorphine buccal (Belbuca)	75 mcg buccally every 12 to 24 hours, as tolerated	For opioid-naïve patients: 75 mcg buccally every 12 to 24 hours, as tolerated, for ≥ 4 days prior to increasing to 150 mcg every 12 hours; can proceed in 150 mg increments every 12 hours, no more than every 4 days For opioid-experienced patients, there is a dosing conversion chart in the prescribing information; do not initiate until patient has been tapered to an oral morphine sulfate equivalent of 30 mg or less; Maximum dose: 900 mcg every 12 hours due to risk of QTc prolongation	75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg buccal film	No
buprenorphine transdermal (Butrans)	1 patch changed every 7 days	For opioid-naïve patients: Initiate treatment with buprenorphine transdermal 5 mcg/hour and titrate as needed after 72 hours For opioid-experienced patients, refer to the dosing conversion chart in the prescribing information; do not initiate until patient's around-the-clock opioids have been tapered to an oral morphine equivalent of ≤ 30 mg for up to days Do not exceed a dose of one 20 mcg/hour patch due to the risk of QTc prolongation	5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr patches	No
fentanyl transdermal	25 mcg/hr patch changed every 3 days for opioid-tolerant patients	For patients on other opioids converting to fentanyl, calculate their total 24-hour analgesic requirement, then convert this amount to an equivalent analgesic oral morphine dose (see Package Insert for dosing table); however, using the conversion table to convert *from* fentanyl transdermal *to* other opioids will result in an unsafe overestimation of the dose Dosage increase may occur 3 days after the first dose and then every 6 days by adding up the rescue medication dosage Initial doses should be reduced in elderly or debilitated patients More than 1 patch may be used for patients requiring more than 100 mcg/hr	12 mcg/hr, 25 mcg/hr, 37.5 mcg/hr, 50 mcg/hr, 62.5 mcg/hr, 75 mcg/hr, 87.5 mcg/hr, and 100 mcg/hr patches	No
hydrocodone ER (Hysingla ER)	20 mg orally every 24 hours	Adjust the dose in increments of 10 mg to 20 mg every 3 to 5 days, as needed, to achieve adequate analgesia	20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, and 120 mg tablets	Yes (Formulation deters misuse and abuse via chewing, snorting, or injection)

* Has met requirements by the FDA to be approved as an abuse-deterrent formulation.

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Dosages (continued)

Drug	Starting Dose	Titration	Available Strengths	Abuse-Deterrent Formulation*
hydrocodone ER (Zohydro ER)	10 mg every 12 hours	Adjust dosage in increments of 10 mg every 12 hours every 3 to 7 days until adequate pain relief with minimal adverse reactions is achieved; refer to the package insert for conversion factors For opioid-tolerant patients, use the conversion chart to calculate the approximate hydrocodone daily dose and then divide in half for administration every 12 hours; always round down, if necessary, to the appropriate hydrocodone ER strengths available	10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg capsules†	No (Viscous gel develops if crushed and dissolved in liquids or solvents)
hydromorphone ER	8 to 64 mg once daily for opioid-tolerant patients	Adjust dosage not more often than every 3 to 4 days; individually titrate dosing to allow pain control while minimizing adverse reactions	8 mg, 12 mg, 16 mg, and 32 mg tablets	No (Uses Osmotic Extended-Release Oral delivery System or OROS, making it difficult to crush or extract for injection)
methadone (Diskets, Methadose)	2.5 mg to 10 mg every 8 to 12 hours	Adjust dosage according to the severity of pain and patient response; for exceptionally severe pain, or in those tolerant of opioid analgesia, it may be necessary to exceed the usual recommended dosage	5 mg and 10 mg tablets; 40 mg tablets for oral suspension; 1 mg/mL and 2 mg/mL oral solutions (generic only); 10 mg/mL oral concentrate	No
morphine sulfate ER	1 capsule every 12 to 24 hours based on previous opioid requirements	Titrate to pain control; do not exceed upward titration of more than 20 mg every other day Swallow capsules whole; do not crush, chew, or dissolve capsules or contents of capsules; may sprinkle pellets on applesauce The 100 mg, and 200 mg capsules should only be used in opioid-tolerant patients	10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg, 100 mg capsules‡ 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg capsules§	No

* Has met requirements by the FDA to be approved as an abuse-deterrent formulation.

† Reformulated Zohydro ER with abuse-deterrent *properties* is available; originally-marketed formulations are no longer available.

‡ Select strengths are generics for brand-name Kadian (morphine sulfate extended-release), which is no longer marketed. The morphine sulfate ER 130 mg, 150 mg, and 200 mg formulations have been discontinued.

§ Select strengths are generics for brand-name Avinza (morphine sulfate extended-release), which is no longer marketed.

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Dosages (continued)

Drug	Starting Dose	Titration	Available Strengths	Abuse-Deterrent Formulation*
morphine sulfate ER (MS Contin)	15 mg every 8 to 12 hours	In adjusting dosing regimens, attention should be given to daily dose, degree of opioid tolerance, if any, and general condition and mental status of the patient Do not crush, chew, break, or dissolve tablets The 100 mg and 200 mg tablets should only be used in opioid-tolerant patients	15 mg, 30 mg, 60 mg, 100 mg, and 200 mg tablets	No
oxycodone ER (Oxycontin)	10 mg every 12 hours	Except for the increase from 10 mg to 20 mg every 12 hours, the total daily oxycodone ER dose can be increased by 25 to 50% at each increase; patients should be titrated so that they need no more than 2 supplemental analgesia doses per day; a conversion chart is found in the package insert for patients on other opioid therapy For elderly, debilitated, and patients with hepatic impairment, the dosage should be reduced by 33% to 50% For patients with creatinine clearance < 60 mL/min, dosage may need to be lowered by up to 50% Pediatric dosing is similar to adult dosing Single doses > 40 mg or total dose > 80 mg should only be used in opioid-tolerant patients	10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets	Yes (Reformulated to diminish the ease of cutting, breaking, chewing, crushing, or dissolving and to form viscous gel when mixed with aqueous liquid)
oxycodone ER (Xtampza ER)	9 mg orally every 12 hours taken with food (may sprinkle capsule contents onto food or in a cup for administration by mouth, nasogastric tube, or gastronomy tube)	Adjustments in dosing are recommended to occur no earlier than every 1 to 2 days Single doses of ≥ 36 mg and total daily doses of ≥ 72 mg should be reserved for patients who have shown tolerance for comparable opioid potency analgesia Maximum daily dose is 288 mg (320 mg oxycodone HCl per day)	9 mg, 13.5 mg, 18 mg, 27 mg, and 36 mg capsules	Yes (Employs Deterx® technology: a microsphere-in-capsule formulation; in each microsphere, oxycodone is present as a solid solution of a fatty acid salt [oxycodone myristate] in a hydrophobic matrix that also contains waxes)[205]

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Dosages (continued)

Drug	Starting Dose	Titration	Available Strengths	Abuse-Deterrent Formulation*
oxymorphone ER	5 mg every 12 hours	Increase by 5 to 10 mg twice a day every 3 to 7 days based on patient pain intensity and adverse effects Do not attempt to break, crush, chew, or dissolve tablets In patients with creatinine clearance < 50 mL/min, oxymorphone should be started with the lowest dose and titrated slowly while carefully monitoring adverse effects	5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablets	No
tapentadol ER (Nucynta ER)	50 mg every 12 hours	Titrate to pain control within therapeutic range of 100 to 250 mg twice a day; in patients previously taking other opioid therapy, initiate with 50 mg then titrate to effective and tolerable dose within range of 100 to 250 mg twice a day; titrate dose by no more than 50 mg/dose twice a day (100 mg/day) no more than every 3 days Do not exceed maximum daily dose of 500 mg (250 mg twice a day)	50 mg, 100 mg, 150 mg, 200 mg, and 250 mg tablets	No (Resistant to breaking or crushing)
tramadol ER (Conzip)	100 mg daily	Initiate at 100 mg daily then titrate at 100 mg increments every 5 days as needed to relieve pain, up to max 300 mg/day; dose no more frequently than every 24 hours For patients maintained on tramadol immediate-release tablets, calculate the 24-hour tramadol dose, and initiate a total daily dose of the extended-release capsules rounded down to the next lowest 100 mg increment; individualize dose as needed, up to a maximum of 300 mg/day Consider lower doses in elderly; The concomitant use of the extended-release capsules with other tramadol products is not recommended	100 mg, 200 mg, and 300 mg capsules	No
tramadol ER	1 tablet daily	Initiate at 100 mg daily then titrate at 100 mg increments every 5 days as needed to relieve pain, up to a max of 300 mg/day; do not use in patients with severe renal or hepatic impairment	100 mg, 200 mg, and 300 mg tablets (generics with reference product of Ultram ER) 100 mg, 200 mg, and 300 mg tablets (generics with reference product of Ryzolt)	No

* Has met requirements by the FDA to be approved as an abuse-deterrent formulation.

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The following medications are available as abuse-deterrent formulations: hydrocodone ER (Hysingla ER) tablets; oxycodone ER (Oxycontin) tablets; oxycodone ER (authorized generics for OxyContin) tablets; and oxycodone ER capsules (Xtampza ER). Although hydromorphone ER, tapentadol ER (Nucynta ER), and hydrocodone ER (Zohydro ER) have abuse-deterrent properties, they have not been approved by the FDA as abuse-deterrent formulations.

The tapentadol ER tablet formulation is designed to provide a high degree of mechanical resistance to crushing or chewing.

Due to significant pharmacokinetic variability among patients, close observation and slow titration of methadone (Diskets, Methadose) is required. The peak respiratory depressant effect lasts longer than the peak therapeutic effect; extra caution when dosing is recommended.

Patients receiving other oxycodone products may convert on the basis of administering one-half of the current daily dose every 12 hours with oxycodone ER (Xtampza ER). For other opioids, see prescribing information. A 9 mg dose of Xtampza ER is equivalent to a 10 mg dose of other oxycodone HCl products (ratio of 9:10 for other doses as well).

Oxymorphone ER should be given on an empty stomach at least 1 hour prior to or 2 hours after eating. Maximum serum concentration was increased by 50% when given with food. An *in vivo* study with oxymorphone ER showed that the maximum concentration increased 31% to 70%, on average, following concomitant administration with ethanol. Co-administration must be avoided.

Apply buprenorphine buccal film to the inside of the cheek. It will dissolve in approximately 30 minutes. Individual titration should be in increments of no more than 150 mcg every 12 hours and should not occur any sooner than every 4 days. Reduce dose (and titration increments) in half for patients with severe hepatic impairment or mucositis.

Apply buprenorphine transdermal patch (Butrans) to the upper outer arm, upper chest, upper back, or the side of the chest. Rotate application sites, waiting a minimum of 21 days before reapplying to the same skin site. Apply to a hairless or nearly hairless, dry skin site. Do not apply to irritated skin. Do not use soaps, lotions, oils, or alcohol on the skin before the patch is applied. If the buprenorphine transdermal patch falls off during the 7-day dosing interval, dispose of the transdermal system properly and place a new patch on at a different skin site. During the dose titration, 2 patches can be used for a total max dose of 20 mcg.

Fentanyl transdermal patch should be applied to the chest, back, flank, or upper arm on dry, intact, hairless skin. Do not use soaps, lotions, oils, or alcohol on the skin before the patch is applied. If the patch falls off before 3 days of use, discard and apply a new patch at a different skin site. In an effort to minimize the risk of accidental exposure to fentanyl patches, the FDA has required the manufacturer to print the name and strength of the drug on the patch in long-lasting ink, in a color that is clearly visible to patients and caregivers.[206] The prior ink color varies depending on the strength and was not always easy to read. This change was intended to enable patients and caregivers to find patches more easily on patients' bodies and see patches that have fallen off, which children or pets could accidentally touch or ingest.

Opioids should be stored securely, out of sight and reach of children, in a location not accessible to other individuals. Once the medication is expired or no longer being used it should be disposed of properly

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through a drug take-back program, if available or in another appropriate manner as determined by the FDA.[207]

Opioid Morphine Equivalent Conversions[208]

This 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 1 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. See prescribing information for detailed recommendations, when available, for converting among formulations and active ingredients. While previously assigned a 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 hydrochloride§	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).

‡ Extended-release formulations of morphine sulfate are not bioequivalent. A ratio of approximately 3 mg oral to 1 mg parenteral morphine sulfate may be used to estimate exposure, but not for dosing conversions as a more cautious approach is recommended.

§ Strengths of oxycodone ER capsules (Xtampza ER) should be converted to the oxycodone HCl equivalent prior to calculation using a ratio of 9 mg Xtampza ER to 10 mg oxycodone HCl.

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CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-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/funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are no published comparative clinical studies with the following agents: buprenorphine (Belbuca), buprenorphine (Butrans), hydrocodone ER (Hysingla ER, Zohydro ER), hydromorphone ER, oxycodone ER (Xtampza ER), tapentadol ER (Nucynta ER), and tramadol ER (Conzip).[209,210,211,212,213,214,215,216,217,218,219,220, 221,222]

The following agents have demonstrated abuse-deterrence in placebo-controlled and/or active-comparator studies, which is commonly measured by a measure of drug-liking using a visual analog scale (VAS), although other measurements have also been used: Hysingla ER tablets, Oxycontin biconcave tablets, oxycodone ER (authorized generics of OxyContin) tablets, and Xtampza ER capsules.

methadone versus morphine sulfate SR

A total of 103 patients with pain requiring initiation of strong opioids were randomly assigned to treatment with methadone 7.5 mg every 12 hours and 5 mg every 4 hours, as needed, or morphine 15 mg sustained release every 12 hours and 5 mg every 4 hours, as needed.[223] After 4 weeks, patients receiving methadone had more opioid-related discontinuations than those receiving morphine (22 versus 6%; p=0.019). The opioid escalation index at days 14 and 28 were similar between the 2 groups. More than three-fourths of patients in each group reported a 20% or more reduction in pain intensity by day 8; at 4 weeks, the proportion of patients with a 20% or more reduction in pain was similar: 0.49 in the methadone group and 0.56 in the morphine group.

oxycodone controlled-release (Oxycontin) versus oxycodone immediate-release

A multicenter, randomized, double-blind, parallel-group study was performed in 111 patients with cancer pain.[224] Patients were being treated with fixed-combination opioid/nonopioid analgesics at study entry. Patients received oxycodone ER 30 mg every 12 hours or oxycodone IR 15 mg 4 times daily for 5 days. No titration or supplemental analgesic medications were permitted. The mean baseline pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) was 1.5 for the oxycodone ER-treated group and 1.3 for the oxycodone IR group (p>0.05). The 5-day mean pain intensity was 1.4 and 1.1 for the ER and

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IR groups, respectively (p>0.05). Discontinuation rates were equivalent (33%). There was no significant difference between treatment groups in the incidence of adverse events.

Cancer patients who required therapy for moderate to severe pain were randomized to oxycodone ER every 12 hours (n = 81) or oxycodone IR 4 times daily (n = 83) for 5 days in a multicenter, double-blind study.[225] Rescue medication was allowed. Pain intensity remained slight during the study, with mean oxycodone ER doses of 114 mg/day and mean oxycodone IR doses of 127 mg/day. Acceptability of therapy was fair to good with both treatments. Discontinuation rates for lack of acceptable pain control were 4% with oxycodone ER and 19% with oxycodone IR. Fewer adverse events were reported with oxycodone ER than with oxycodone IR (p=0.006).

oxymorphone ER versus oxycodone ER (Oxycontin)

A multicenter, randomized, double-blind, placebo- and active-controlled trial was conducted to compare the analgesic efficacy and safety of oxymorphone ER with placebo and oxycodone ER in patients with moderate to severe chronic low back pain requiring opioid therapy.[226] Patients (n=213) were randomized to receive oxymorphone ER (10 to 110 mg) or oxycodone ER (20 to 220 mg) every 12 hours during a 7- to 14-day dose-titration phase. Patients achieving effective analgesia at a stable opioid dose entered an 18-day double-blind treatment phase and either continued opioid therapy or received placebo. With stable dosing throughout the treatment phase, oxymorphone ER (79.4 mg/day) and oxycodone ER (155 mg/day) were superior to placebo for change from baseline in pain intensity as measured on a visual analog scale (p=0.0001). Adverse events for the active drugs were similar; the most frequently reported were constipation and sedation. Oxymorphone ER was equianalgesic to oxycodone ER at one-half the milligram daily dosage with comparable safety.

tapentadol ER (Nucynta ER) versus oxycodone ER (Oxycontin)

A randomized, double-blind study was conducted to compare the safety and efficacy of tapentadol ER in patients with moderate-to-severe chronic osteoarthritis knee pain.[227] A total of 990 patients with pain requiring initiation of strong opioids were randomly assigned to tapentadol ER, oxycodone ER, or placebo for a double-blind, 3-week titration period and a 12-week maintenance period. After 15 weeks, the primary endpoints were not significantly different for patients receiving tapentadol ER or for oxycodone ER versus placebo at week 12 (p=0.152). Significantly more patients rated their pain to be “much improved” with tapentadol ER at the end of treatment (56% versus 42.5%, respectively). Tapentadol ER was associated with better gastrointestinal tolerability with constipation, nausea, and/or vomiting (p<0.001). However, the study did not demonstrate assay sensitivity or significant pain reduction.

META-ANALYSES

A meta-analysis compared tapentadol ER and oxycodone/naloxone ER (not available) to oxycodone ER (3 trials of tapentadol ER versus oxycodone ER with or without a placebo group; n=3,105).[228] Compared to oxycodone ER, tapentadol ER resulted in a better risk ratio reduction for discontinuation due to adverse effects (RR, 0.526 [95% CI, 0.456 to 0.607]), discontinuation due to nausea and vomiting (RR, 0.526 [95% CI, 0.471 to 0588]), and constipation (RR, 0.609 [95% CI, 0.545 to 0.68]).

A Cochrane review of opioids (immediate and extended release formulations) for chronic low back pain (15 trials; n=5,540), found that tramadol was more effective for pain control than placebo (standardized mean difference [SMD], -0.55 [95% CI, -0.66 to -0.44]; 5 trials; n=1,378).[229] Transdermal buprenorphine

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had a small, but significant impact on pain control (SMD, -2.47 [95% CI, -2.69 to -2.25]; 2 trials; n=653), and stronger opioids (morphine, hydromorphone, oxycodone, oxymorphone, and tapentadol) were also superior to placebo for pain control (SMD, -0.43 [95% CI, -0.52 to -0.33]; 6 trials; n=1,887). Similarly, a Bayesian network meta-analysis of randomized controlled trials evaluating fentanyl, morphine, tapentadol, oxycodone, buprenorphine, oxymorphone, tramadol for chronic low back pain concluded oxymorphone, tapentadol, and fentanyl were the most effective; however, the various formulations and pharmacokinetic profiles should be considered when individualizing therapy.[230]

A systematic review compared transdermal buprenorphine to transdermal fentanyl using 17 clinical trials, including trials for indirect comparison.[231] Transdermal fentanyl was associated with a greater risk of nausea (odds ratio [OR], 4.66 [95% CI, 1.07 to 20.39]) and treatment discontinuations due to adverse effects compared to transdermal buprenorphine (OR, 5.94 [95% CI, 1.78 to 19.87]). No differences were found in efficacy.

SUMMARY

Pain of multiple etiologies remains a substantial problem for many patients presenting in the clinical setting. No clinical data exist that distinguish analgesic efficacy of any of these products from the others. Pain management must be individualized, and patients who do not respond to one opioid may respond to another.

Full opioid agonists do not typically have a ceiling for their analgesic effectiveness, but the dose is limited by their adverse effects. Morphine is the standard drug of comparison. Methadone (Diskets, Methadose) may provide an effective alternative in palliative care of most patients with cancer pain referred for poor pain control and/or adverse effects. It is also useful in the treatment of opioid dependence. Morphine sulfate has been available as a twice-daily sustained-release oral dosage form (MS Contin) for many years; 2 abuse-deterrent formulations that were approved (Arymo ER and Morphabond) are no longer commercially available. A morphine extended-release dosage form (previously available as brand-name, Kadian, currently available as generic) is used once daily. Hydrocodone bitartrate extended-release (Hysingla ER, Zohydro ER) is available without an acetaminophen component. Both Hysingla ER and a new formulation of Zohydro ER contain properties to limit abuse, but only Hysingla ER has met FDA abuse-deterrent formulation requirements. Hysingla ER is dosed once every 24 hours, while Zohydro ER is taken every 12 hours. Hydromorphone ER is available for once-daily dosing.

Tapentadol ER (Nucynta ER) and tramadol ER (Conzip) are centrally-acting oral analgesics that bind to mu-opioid receptors and inhibit norepinephrine re-uptake. The tapentadol ER tablet formulation is designed to provide a high degree of mechanical resistance to crushing or chewing. Tapentadol ER is dosed twice daily, while tramadol ER is dosed once daily.

Like the controlled-release forms of morphine, oxycodone ER (Oxycontin) allows for less frequent (12-hour) dosing of an opioid. Oxycodone ER has a significant potential for abuse and has been associated with increases in crime and deaths due to illicit use. However, all opioids can be abused and are subject to illicit use. Oxycodone ER has been reformulated to include a delivery system that causes a gummy substance when tablets are crushed; the effects of this redesign on illicit use have yet to be seen. A new formulation of oxycodone ER, Xtampza ER capsules, offers another twice-daily treatment option as an abuse-deterrent formulation. These capsules may also be opened and administered in alternative ways for patients unable to swallow them whole.

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Oxymorphone hydrochloride, an opioid agonist, is a metabolite of oxycodone, which is taken twice daily.

The following medications are available as abuse-deterrent formulations: Hysingla ER tablets, Oxycontin tablets, oxycodone ER (authorized generics of Oxycontin) tablets, and Xtampza ER capsules.

Two agents in this review provide analgesia via transdermal routes. Buprenorphine (Butrans), a partial opioid agonist, and fentanyl, a full agonist, are available as transdermal patches. In April 2020, the FDA reported that the manufacturer of Duragesic made a business decision to discontinue the branded fentanyl product. Buprenorphine transdermal patch should be changed every 7 days, while a new fentanyl transdermal patch is recommended every 72 hours.

One agent provides a buccal route for analgesia, buprenorphine buccal (Belbuca), which is dosed twice daily.

REFERENCES

1 Belbuca [package insert]. Raleigh, NC; BioDelivery Sciences; March 2021.
2 Butrans [package insert]. Stamford, CT; Purdue; March 2021.
3 Duragesic [package insert]. Titusville, NJ; Janssen; March 2021.
4 Fentanyl patch [package insert]. Morgantown, WV; Mylan; March 2021.
5 Hysingla ER [package insert]. Stamford, CT, Purdue; March 2021.
6 Zohydro ER [package insert]. Morristown, NJ; Currax; March 2021.
7 Dilaudid [package insert]. Coventry, RI; March 2021.
8 Hydromorphone ER [package insert]. Alpharetta, GA; Trigen; November 2021.
9 Diskets [package insert]. Berkeley Heights, NJ; Hikma; June 2021.
10 Methadose [package insert]. Webster Groves, MO; Mallinckrodt; September 2021.
11 Kadian [package insert]. Madison, NJ; Allergan; March 2021.
12 Morphine sulfate ER [package insert]. Parsippany, NJ; Actavis; March 2021.
13 MS Contin [package insert]. Coventry, RI; Rhodes; March 2021.
14 Oxycontin [package insert]. Stamford, CT; Purdue; October 2021.
15 Xtampza ER [package insert]. Cincinnati, OH; Patheon; March 2021.
16 Opana ER [package insert]. Malvern, PA; Endo; March 2021.
17 Oxymorphone ER [package insert]. Brookhaven, NY; Amneal; April 2021..
18 FDA news release. FDA requests removal of Opana ER for risks related to abuse. June 8, 2017. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm562401.htm. Accessed February 19, 2022.
19 Endo Press Release. July 6, 2017. Endo Provides Update On Opana ER. Available at: http://investor.endo.com/newsroom/news-releases?field_nir_news_date_value%5Bmin%5D=2017#views-exposed-form-widget-news-widget-news-ul. Accessed February 19, 2022.
20 Nucynta ER [package insert]. Stoughton, MA; Collegium; March 2021.
21 Conzip [package insert]. Bridgewater, NJ; Vertical; September 2021.
22 Tramadol HCl ER [package insert]. Baltimore, MD; Lupin; September 2021.
23 Tramadol HCl ER [package insert]. Cranbury, NJ; Sun; June 2021.
24 Barkin RL. Acetaminophen, aspirin, or ibuprofen in combination analgesic products. Am J Ther. 2001; 8(6): 433–442.
25 Zelaya C, Dahlhamer JM, Lucas Jacqueline W, et al. Chronic pain and high-impact chronic pain among U.S. adults, 2019. Available at: https://www.cdc.gov/nchs/products/databriefs/db390.htm. Accessed February 13, 2022.
26 Marks RM, Sacher EJ. Undertreatment of medical inpatient pain with narcotic analgesics. Ann Intern Med. 1973; 78: 173–181.
27 Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm. Rep. 2016; 65(1): 1-49. DOI: 10.15585/mmwr.rr6501e1. Available at: http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm. Accessed February 13, 2022.
28 Lister BJ. Dilemmas in the treatment of chronic pain. Am J Med. 1996; 101(suppl 1A): 2S-5S.
29 Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep. 2016; 65(1): 1-49. DOI: 10.15585/mmwr.rr6501e1. Available at: http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm. Accessed February 13, 2022.
30 CDC Drug Overdose Deaths. March 3, 2021. Available at: https://www.cdc.gov/drugoverdose/data/statedeaths.html. Accessed February 13, 2022.
31 Centers for Disease Control and Prevention. Annual Surveillance Report of Drug-Related Risks and Outcomes — United States, 2019. Surveillance Special Report 1. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. Published November 1, 2019. Available at: https://www.cdc.gov/drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdf. Accessed February 13, 2022.
32 Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep. 2016; 65(1): 1-49. DOI: 10.15585/mmwr.rr6501e1. Available at: http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm. Accessed February 15, 2022.
33 WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. January 1, 2019. Available at: https://www.who.int/publications/i/item/9789241550390. Accessed February 13, 2022.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
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34 Paice JA, Protenov R, Lacchetti C, et al. Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology clinical practice guidelines. J Clin Oncol. 2016; 34(27): 3,325-3,345. DOI: 10.1200/JCO.2016.68.5206. Available at: https://www.nccn.org/guidelines/category_3. Accessed February 13, 2022.
35 Swarm RA, Youngwerth JM, Anghelescu DL, et al. National Comprehensive Cancer Network (NCCN) Adult Cancer Pain V1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf. Accessed February 13, 2022.
36 Goadsby P, Goldenberg JN, Hinson H, et al. Position Statement: Opioids. American Academy of Neurology 2018. Available at: https://www.aan.com/policy-and-guidelines/policy/position-statements/. Accessed February 13, 2022.
37 Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep. 2016; 65(1): 1-49. DOI: 10.15585/mmwr.rr6501e1. Available at: http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm. Accessed February 13, 2022.
38 Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep. 2016; 65(1): 1-49. DOI: 10.15585/mmwr.rr6501e1. Available at: http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm. Accessed February 13, 2022.
39 Proposed 2022 CDC Clinical Practice Guideline for Prescribing Opioids. February 10, 2022. Available at: https://www.federalregister.gov/documents/2022/02/10/2022-02802/proposed-2022-cdc-clinical-practice-guideline-for-prescribing-opioids. Accessed February 14, 2022.
40 Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017; 166(7): 514-530. DOI: 10.7326/M16-2367. Available at: https://www.acponline.org/clinical-information/guidelines. Accessed February 13, 2022.
41 Qaseem A, McLean RM, O'Gurek D, et al. Nonpharmacologic and pharmacologic management of acute pain from non-low back, musculoskeletal injuries in adults: a clinical guideline from the American College of Physicians and American Academy of Family Physicians. Ann Intern Med. 2020; 173(9): 739-748. DOI: 10.7326/M19-3602. Available at: https://www.acpjournals.org/doi/10.7326/M19-3602. Accessed February 13, 2022.
42 Manchikanti L, Kaye AM, Knesevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Physician. 2017; 20(2S): S3-S92. Available at: https://asipp.org/guidelines/. Accessed February 13, 2022.
43 Bruce RD, Merlin J, Lum PJ, et al. 2017 HIVMA of IDSA Clinical practice guideline for the management of chronic pain in patients living with HIV. Clinical Infectious Diseases. 2017; 65(10); e1–e37. Available at: http://www.idsociety.org/PracticeGuidelines/. Accessed February 13, 2022.
44 American Association of Oral and Maxillofacial Surgeons. White Paper. Opioid prescribing: Acute and postoperative pain management. Available at: https://www.aaoms.org/practice-resources/aaoms-advocacy-and-position-statements/white-papers. Accessed February 13, 2022.
45 Institute for Clinical and Economic Review. Abuse-deterrent formulations of opioids: Effectiveness and value. Final Evidence Report. August 8, 2017. Available at: https://icer-review.org/topics/#past-topics. Accessed February 13, 2022.
46 Silber MH, Becker PM, Buchfuhrer MJ, et al. The Appropriate use of opioids in the treatment of refractory restless legs syndrome. Mayo Clinic. 2018; 93(1): 59-67. DOI: 10.1016/j.mayocp.2017.11.007. Available at: https://www.mayoclinicproceedings.org/article/S0025-6196(17)30825-X/fulltext. Accessed February 13, 2022.
47 Naloxone: the opioid reversal drug that saves lives. Available at: https://www.hhs.gov/opioids/sites/default/files/2018-12/naloxone-coprescribing-guidance.pdf. Accessed February 13, 2022.
48 HHS guide for clinicians on the appropriate dosage reduction or discontinuation of long-term opioid analgesics. Available at: https://www.hhs.gov/opioids/treatment/clinicians-guide-opioid-dosage-reduction/. Accessed February 13, 2022.
49 Drug Enforcement Administration. Schedules of controlled substances: Placement of tramadol Into Schedule IV. Effective August 18, 2014. Available at: http://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0702.htm. Accessed February 13, 2022.
50 FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics. September 10, 2013. Available at: https://wayback.archive-it.org/7993/20170111161119/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2013/index.htm?Page=2. Accessed February 13, 2022.
51 FDA Guidance Document. Abuse-deterrent opioids-evaluation and labeling. April 2015. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf. Accessed February 13, 2022.
52 Hysingla ER [package insert]. Stamford, CT; Purdue; March 2021.
53 Oxycontin [package insert]. Stamford, CT; Purdue; October 2021.
54 Xtampza ER [package insert]. Cincinnati, OH; Patheon; March 2021.
55 FDA. General principles for evaluating the abuse deterrence of generic solid oral opioid drug products guidance for industry. November 2017. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf. Accessed February 13, 2022.
56 FDA news release. Califf, FDA top officials call for sweeping review of agency opioids policies. February 5, 2016. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm484765.htm. Accessed February 13, 2022.
57 FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. April 20, 2017. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm. Accessed February 13, 2022.
58 Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse. Available at: https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse. Accessed February 13, 2022.
59 H.R.6 - SUPPORT for Patients and Communities Act. October 24, 2018. Available at: https://www.congress.gov/bill/115th-congress/house-bill/6. Accessed February 13, 2022.
60 DEA announces enhanced tool for registered drug manufacturers and distributors to combat opioid crisis. February 26, 2019. Available at: https://www.dea.gov/press-releases/2019/02/26/dea-announces-enhanced-tool-registered-drug-manufacturers-and. Accessed February 13, 2022.
61 FDA news release: FDA launches public education campaign to encourage safe removal of unused opioid pain medicines from homes. April 25, 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-launches-public-education-campaign-encourage-safe-removal-unused-opioid-pain-medicines-homes. Accessed February 13, 2022.

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004–2022 Magellan Rx Management. All rights reserved.

62 FDA Drug Safety Communication: FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering. April 9, 2019. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes. Accessed February 14, 2022.
63 FDA news release: FDA launches public education campaign to encourage safe removal of unused opioid pain medicines from homes. Available at: https://www.fda.gov/news-events/press-announcements/fda-launches-public-education-campaign-encourage-safe-removal-unused-opioid-pain-medicines-homes. Accessed February 14, 2022.
64 Timeline of selected FDA activities and significant events addressing opioid misuse and abuse. Available at: https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm. Accessed February 14, 2022.
65 FDA Statement. Statement on National Academies of Sciences, Engineering, and Medicine report on framing opioid prescribing guidelines for acute pain. December 19, 2019. Available at: https://www.fda.gov/news-events/press-announcements/statement-national-academies-sciences-engineering-and-medicine-report-framing-opioid-prescribing. Accessed February 14, 2022.
66 DEA. DEA reduces amount of opioid controlled substances to be manufactured in 2017. October 4, 2016. Available at: https://www.dea.gov/press-releases/2016/10/04/dea-reduces-amount-opioid-controlled-substances-be-manufactured-2017. Accessed February 14, 2022.
67 DEA. DEA proposes to reduce the amount of five opioids manufactured in 2020, marijuana quota for research increases by almost a third. September 11, 2019. Available at: https://www.dea.gov/press-releases/2019/09/11/dea-proposes-reduce-amount-five-opioids-manufactured-2020-marijuana-quota. Accessed February 14, 2022.
68 Established aggregate production quotas for Schedule I and II controlled substances and assessment of annual needs for the list I chemicals ephedrine, pseudoephedrine, and phenylpropanolamine for 2020. December 2, 2019. Available at: https://www.deadiversion.usdoj.gov/fed_regs/quotas/2019/fr1202.htm. Accessed February 14, 2022.
69 Established aggregate production quotas for schedule i and ii controlled substances and assessment of annual needs for the list i chemicals ephedrine, pseudoephedrine, and phenylpropanolamine for 2021. November 30, 2020. Available at: https://www.deadiversion.usdoj.gov/fed_regs/quotas/2020/fr1130.htm. Accessed February 14, 2022.
70 Established Aggregate Production Quotas for Schedule I and II Controlled Substances and Assessment of Annual Needs for the List I Chemicals Ephedrine, Pseudoephedrine, and Phenylpropanolamine for 2022. December 2, 2021. Available at: https://www.federalregister.gov/documents/2021/12/02/2021-26227/established-aggregate-production-quotas-for-schedule-i-and-ii-controlled-substances-and-assessment. Accessed February 14, 2022.
71 FDA. Opioid pain relievers or medicines to treat opioid use disorder: MedWatch safety alert – FDA recommends health care professionals discuss naloxone with all patients when prescribing. July 23, 2020. Available at: https://www.fda.gov/safety/medical-product-safety-information/opioid-pain-relievers-or-medicines-treat-opioid-use-disorder-medwatch-safety-alert-fda-recommends. Accessed February 14, 2022.
72 Belbuca [package insert]. Raleigh, NC; BioDelivery Sciences; March 2021.
73 Butrans [package insert]. Stamford, CT; Purdue; March 2021.
74 Fentanyl patch [package insert]. Morgantown, WV; Mylan; March 2021.
75 Hysingla ER [package insert]. Stamford, CT; Purdue; March 2021.
76 Zohydro ER [package insert]. Morristown, NJ; Currax; March 2021.
77 Hydromorphone ER [package insert]. Alpharetta, GA; Trigen; November 2021..
78 Methadose [package insert]. Webster Groves, MO; Mallinckrodt; September 2021.
79 MS Contin [package insert]. Coventry, RI; Rhodes; March 2021.
80 Morphine sulfate ER [package insert]. Parsippany, NJ; Actavis; March 2021..
81 Oxycontin [package insert]. Stamford, CT; Purdue; October 2021.
82 Xtampza ER [package insert]. Cincinnati, OH; Patheon; March 2021.
83 Oxymorphone ER [package insert]. Brookhaven, NY; Amneal; April 2021..
84 Nucynta ER [package insert]. Stoughton, MA; Collegium; March 2021.
85 Conzip [package insert]. Bridgewater, NJ; Vertical; September 2021.
86 Tramadol HCl ER [package insert]. Baltimore, MD; Lupin; September 2021..
87 Tramadol HCl ER [package insert]. Cranbury, NJ; Sun; June 2021..
88 Clinical Pharmacology. Available at: www.clinicalpharmacology.com. Accessed February 19, 2022.
89 Belbuca [package insert]. Raleigh, NC; BioDelivery Sciences; March 2021.
90 Butrans [package insert]. Stamford, CT; Purdue; March 2021.
91 Fentanyl patch [package insert]. Morgantown, WV; Mylan; March 2021.
92 Hysingla ER [package insert]. Stamford, CT; Purdue; March 2021.
93 Zohydro ER [package insert]. Morristown, NJ; Currax; March 2021.
94 Hydromorphone ER [package insert]. Alpharetta, GA; Trigen; November 2021..
95 Methadose [package insert]. Webster Groves, MO; Mallinckrodt; September 2021.
96 MS Contin [package insert]. Coventry, RI; Rhodes; March 2021.
97 Morphine sulfate ER [package insert]. Parsippany, NJ; Actavis; March 2021.
98 Oxycontin [package insert]. Stamford, CT; Purdue; October 2021.
99 Xtampza ER [package insert]. Cincinnati, OH; Patheon; March 2021.
100 Oxymorphone ER [package insert]. Brookhaven, NY; Amneal; April 2021..
101 Nucynta ER [package insert]. Stoughton, MA; Collegium; March 2021.
102 Conzip [package insert]. Bridgewater, NJ; Vertical; September 2021.
103 Tramadol HCl ER [package insert]. Baltimore, MD; Lupin; September 2021..
104 Tramadol HCl ER [package insert]. Cranbury, NJ; Sun; June 2021.
105 Clinical Pharmacology. Available at: www.clinicalpharmacology.com. Accessed February 19, 2022.
106 Belbuca [package insert]. Raleigh, NC; BioDelivery Sciences; March 2021.
107 Butrans [package insert]. Stamford, CT; Purdue; March 2021.

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108 Fentanyl patch [package insert]. Morgantown, WV; Mylan; March 2021.
109 Hysingla ER [package insert]. Stamford, CT; Purdue; March 2021.
110 Zohydro ER [package insert]. Morristown, NJ; Currax; March 2021.
111 Hydromorphone ER [package insert]. Alpharetta, GA; Trigen; November 2021..
112 Methadose [package insert]. Webster Groves, MO; Mallinckrodt; September 2021.
113 MS Contin [package insert]. Coventry, RI; Rhodes; March 2021.
114 Morphine sulfate ER [package insert]. Parsippany, NJ; Actavis; March 2021.
115 Oxycontin [package insert]. Stamford, CT; Purdue; October 2021.
116 Xtampza ER [package insert]. Cincinnati, OH; Patheon; March 2021.
117 Oxymorphone ER [package insert]. Brookhaven, NY; Amneal; April 2021..
118 Nucynta ER [package insert]. Stoughton, MA; Collegium; March 2021.
119 Conzip [package insert]. Bridgewater, NJ; Vertical; September 2021.
120 Tramadol HCl ER [package insert]. Baltimore, MD; Lupin; September 2021..
121 Tramadol HCl ER [package insert]. Cranbury, NJ; Sun; June 2021..
122 Clinical Pharmacology. Available at: www.clinicalpharmacology.com. Accessed February 19, 2022.
123 FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. April 20, 2017. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm. Accessed February 19, 2022.
124 FDA Drug Safety Communication. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. August 31, 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm518473.htm. Accessed February 19, 2022.
125 FDA Drug Safety Communication. FDA warns about several safety issues with opioid pain medicines; requires label changes. March 22, 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm489676.htm. Accessed February 19, 2022.
126 FDA Drug Safety Communication. FDA warns about several safety issues with opioid pain medicines; requires label changes. March 22, 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm489676.htm. Accessed February 19, 2022.
127 Fentanyl Transdermal System (marketed as Duragesic and generics). December 21, 2007. Available at: https://wayback.archive-it.org/7993/20170112170250/http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152289.htm. Accessed February 19, 2022.
128 FDA News Release. FDA approves new formulation for OxyContin. April 5, 2010. Available at: https://wayback.archive-it.org/7993/20170112130258/http:/www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm207480.htm. Accessed February 19, 2022.
129 Abusing pain drug Opana can cause blood disorder: FDA . Available at: https://www.reuters.com/article/us-opana-warning/abusing-pain-drug-opana-can-cause-blood-disorder-fda-idUSBRE89A13W20121011. Accessed February 19, 2022.
130 FDA news release. FDA requests removal of Opana ER for risks related to abuse. June 8, 2017. Available at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm562401.htm. Accessed February 19, 2022.
131 Endo Press Release. Endo Provides Update on Opana ER. July 6, 2017. Available at: http://investor.endo.com/news-releases/news-release-details/endo-provides-update-opanar-er. Accessed February 19, 2022.
132 FDA Drug Safety Communication. FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. April 20, 2017. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm. Accessed February 19, 2022.
133 REMS@FDA. Available at: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed February 19, 2022.
134 Belbuca [package insert]. Raleigh, NC; BioDelivery Sciences; March 2021.
135 Butrans [package insert]. Stamford, CT; Purdue; March 2021.
136 Fentanyl patch [package insert]. Morgantown, WV; Mylan; March 2021.
137 Hysingla ER [package insert]. Stamford, CT; Purdue; March 2021.
138 Zohydro ER [package insert]. Morristown, NJ; Currax; March 2021.
139 Hydromorphone ER [package insert]. Alpharetta, GA; Trigen; November 2021.
140 Methadose [package insert]. Webster Groves, MO; Mallinckrodt; September 2021.
141 MS Contin [package insert]. Coventry, RI; Rhodes; March 2021.
142 Morphine sulfate ER [package insert]. Parsippany, NJ; Actavis; March 2021.
143 Oxycontin [package insert]. Stamford, CT; Purdue; October 2021.
144 Xtampza ER [package insert]. Cincinnati, OH; Patheon; March 2021.
145 Oxymorphone ER [package insert]. Brookhaven, NY; Amneal; April 2021.
146 Nucynta ER [package insert]. Stoughton, MA; Collegium; March 2021.
147 Conzip [package insert]. Bridgewater, NJ; Vertical; September 2021.
148 Tramadol HCl ER [package insert]. Baltimore, MD; Lupin; September 2021.
149 Tramadol HCl ER [package insert]. Cranbury, NJ; Sun; June 2021.
150 Clinical Pharmacology. Available at: www.clinicalpharmacology.com. Accessed February 19, 2022.
151 FDA Drug Safety Communication: FDA warns about several safety issues with opioid pain medicines; requires label changes. March 22, 2016. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm489676.htm. Accessed February 19, 2022.
152 Belbuca [package insert]. Raleigh, NC; BioDelivery Sciences; March 2021.
153 Butrans [package insert]. Stamford, CT; Purdue; March 2021.
154 Fentanyl patch [package insert]. Morgantown, WV; Mylan; March 2021.
155 Hysingla ER [package insert]. Stamford, CT; Purdue; March 2021.
156 Zohydro ER [package insert]. Morristown, NJ; Currax; March 2021.
157 Hydromorphone ER [package insert]. Alpharetta, GA; Trigen; November 2021..

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158 Methadose [package insert]. Webster Groves, MO; Mallinckrodt; September 2021.
159 MS Contin [package insert]. Coventry, RI; Rhodes; March 2021.
160 Morphine sulfate ER [package insert]. Parsippany, NJ; Actavis; March 2021.
161 Oxycontin [package insert]. Stamford, CT; Purdue; October 2021.
162 Xtampza ER [package insert]. Cincinnati, OH; Patheon; March 2021.
163 Oxymorphone ER [package insert]. Brookhaven, NY; Amneal; April 2021.
164 Nucynta ER [package insert]. Stoughton, MA; Collegium; March 2021.
165 Conzip [package insert]. Bridgewater, NJ; Vertical; September 2021.
166 Tramadol HCl ER [package insert]. Baltimore, MD; Lupin; September 2021.
167 Tramadol HCl ER [package insert]. Cranbury, NJ; Sun; June 2021.
168 Clinical Pharmacology. Available at: www.clinicalpharmacology.com. Accessed February 19, 2022.
169 FDA Drug Safety Communication. FDA warns about several safety issues with opioid pain medicines; requires label changes. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm489676.htm. Accessed February 19, 2022.
170 Belbuca [package insert]. Raleigh, NC; BioDelivery Sciences; March 2021.
171 Butrans [package insert]. Stamford, CT; Purdue; March 2021.
172 Fentanyl patch [package insert]. Morgantown, WV; Mylan; March 2021.
173 Hysingla ER [package insert]. Stamford, CT; Purdue; March 2021.
174 Zohydro ER [package insert]. Morristown, NJ; Currax; March 2021.
175 Hydromorphone ER [package insert]. Alpharetta, GA; Trigen; November 2021.
176 Methadose [package insert]. Webster Groves, MO; Mallinckrodt; September 2021.
177 MS Contin [package insert]. Coventry, RI; Rhodes; March 2021.
178 Morphine sulfate ER [package insert]. Parsippany, NJ; Actavis; March 2021.
179 Oxycontin [package insert]. Stamford, CT; Purdue; October 2021.
180 Xtampza ER [package insert]. Cincinnati, OH; Patheon; March 2021.
181 Oxymorphone ER [package insert]. Brookhaven, NY; Amneal; April 2021.
182 Nucynta ER [package insert]. Stoughton, MA; Collegium; March 2021.
183 Conzip [package insert]. Bridgewater, NJ; Vertical; September 2021.
184 Tramadol HCl ER [package insert]. Baltimore, MD; Lupin; September 2021.
185 Tramadol HCl ER [package insert]. Cranbury, NJ; Sun; June 2021.
186 Clinical Pharmacology. Available at: www.clinicalpharmacology.com. Accessed February 19, 2022.
187 FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm. Accessed February 19, 2022.
188 Belbuca [package insert]. Raleigh, NC; BioDelivery Sciences; March 2021.
189 Butrans [package insert]. Stamford, CT; Purdue; March 2021.
190 Fentanyl patch [package insert]. Morgantown, WV; Mylan; March 2021.
191 Hysingla ER [package insert]. Stamford, CT; Purdue; March 2021.
192 Zohydro ER [package insert]. Morristown, NJ; Currax; March 2021.
193 Hydromorphone ER [package insert]. Alpharetta, GA; Trigen; November 2021.
194 Methadose [package insert]. Webster Groves, MO; Mallinckrodt; September 2021.
195 MS Contin [package insert]. Coventry, RI; Rhodes; March 2021.
196 Morphine sulfate ER [package insert]. Parsippany, NJ; Actavis; March 2021.
197 Oxycontin [package insert]. Stamford, CT; Purdue; October 2021.
198 Xtampza ER [package insert]. Cincinnati, OH; Patheon; March 2021.
199 Oxymorphone ER [package insert]. Brookhaven, NY; Amneal; April 2021.
200 Nucynta ER [package insert]. Stoughton, MA; Collegium; March 2021.
201 Conzip [package insert]. Bridgewater, NJ; Vertical; September 2021.
202 Tramadol HCl ER [package insert]. Baltimore, MD; Lupin; September 2021.
203 Tramadol HCl ER [package insert]. Cranbury, NJ; Sun; June 2021.
204 Clinical Pharmacology. Available at: www.clinicalpharmacology.com. Accessed February 19, 2022.
205 Available at: https://www.collegiumpharma.com/about/company-overview/. Accessed February 19, 2022.
206 FDA Drug Safety Communication: FDA requiring color changes to Duragesic (fentanyl) pain patches to aid safety—emphasizing that accidental exposure to used patches can cause death. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm368902.htm. Accessed February 19, 2022.
207 FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering. FDA Drug Safety Communication. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes. Accessed February 19, 2022.
208 Centers for Disease Control and Prevention. Data Resources. Available at: https://www.cdc.gov/opioids/data-resources/index.html. Accessed February 19, 2022.
209 Belbuca [package insert]. Raleigh, NC; BioDelivery Sciences; March 2021.
210 Zohydro ER [package insert]. Morristown, NJ; Currax; March 2021.
211 Hysingla ER [package insert]. Stamford, CT; Purdue; March 2021.
212 Methadose [package insert]. Webster Groves, MO; Mallinckrodt; September 2021.
213 Nucynta ER [package insert]. Stoughton, MA; Collegium; March 2021.
214 Buynak R, Shapiro DY, Okamoto A. et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. Expert Opin Pharmacother. 2010; 11(11): 1,787–1,804.

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215 Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin. 2011; 27(1): 151–162.
216 Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. Clin Drug Investig. 2010; 30(8): 489–505.
217 Babul N, Noveck R, Chipman H, et al. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. J Pain Symptom Manage. 2004; 28(1): 59–71.
218 Tramadol HCl ER [package insert]. Baltimore, MD; Lupin; September 2021.
219 Conzip [package insert]. Bridgewater, NJ; Vertical; September 2021.
220 Butrans [package insert]. Stamford, CT; Purdue; March 2021.
221 Xtampza ER [package insert]. Cincinnati, OH; Patheon; March 2021.
222 Webster LR, Smith MD, Lawler J, Lindhardt K, Dayno JM. Human abuse potential of an abuse-deterrent (AD), extended-release (ER) morphine product candidate (morphine-ADER injection-molded tablets) vs extended-release morphine administered intranasally in nondependent recreational opioid users. Pain Medicine: The Official Journal of the American Academy of Pain Medicine. 2017; 18(9): 1,695-1,705. DOI:10.1093/pm/pnw219.
223 Methadose [package insert]. Webster Groves, MO; Mallinckrodt; September 2021.
224 Parris WC, Johnson BW Jr., Croghan MK, et al. The use of controlled-release oxycodone for the treatment of chronic cancer pain: a randomized, double-blind study. J Pain Symptom Manage. 1998; 16(4): 205–211.
225 Kaplan R, Parris WC, Citron ML, et al. Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. J Clin Oncol. 1998; 16(10): 3,230–3,237.
226 Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. J Pain. 2005; 6(1): 21–28.
227 Serrie A, Lange B, Steup A. Tapentadol prolonged-release for moderate-to-severe chronic osteoarthritis knee pain: a double-blind, randomized, placebo- and oxycodone controlled release-controlled study. Curr Med Res Opin. 2017; 33(8): 1,423-1,432. DOI: 10.1080/03007995.2017.1335189.
228 Coluzzi F, Ruggeri M. Clinical and economic evaluation of tapentadol extended release and oxycodone/naloxone extended release in comparison with controlled release oxycodone in musculoskeletal pain. Curr Med Res Opin. 2014; 30(6): 1,139–1,151. DOI: 1185/03007995.2014.894501.
229 Chaparro LE, Furlan AD, Deshpande A, et al. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database Syst Rev. 2103; 8: CD004959. DOI: 10.1002/14651858.CD004959.pub4.
230 Migliorini F, Maffulli N, Baroncini A, et al. Opioids for chronic low back pain management: a Bayesian network meta-analysis. Expert Rev Clin Pharmacol. 2021 May;14(5):635-641. DOI: 10.1080/17512433.2021.1903316.
231 Wolff RF, Aune D, Truyers C, et al. Systematic review of efficacy and safety of buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. Curr Med Res Opin. 2012; 28(5): 833-845. DOI: 10.1185/03007995.2012.678938.

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