Long-Acting Narcotic Analgesics

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Schedule	Indication(s)
buprenorphine (Butrans™)[1]	Purdue	CIII	Management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time
fentanyl transdermal (Duragesic®)[2]	generic, OMJPI	CII	Persistent moderate to severe chronic pain in patients who require continuous opioid analgesia for pain that can not be managed by lesser means (age > two years). For opioid tolerant patients only.
hydromorphone extended release (Exalgo™)[3]	Covidien	CII	Management of moderate to severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time
methadone (Dolophine®)[4]	generic	CII	Relief of moderate to severe pain Detoxification and maintenance treatment of narcotic addiction
morphine sulfate extended release (Avinza™)[5]	Monarch	CII	Moderate to severe pain requiring around-the-clock, continuous opioid analgesia for an extended time
morphine sulfate extended release (Kadian®)[6]	generic, Actavis	CII	
morphine sulfate controlled release (MS Contin®)[7]	generic	CII	
morphine sulfate extended release (Oramorph® SR)[8]	generic	CII	Relief of pain in patients who require opioid analgesia for more than a few days
morphine sulfate extended release and naltrexone (Embeda™)[9]	Monarch	CII	Moderate to severe pain requiring around-the-clock, continuous opioid analgesia for an extended time
oxycodone controlled release (OxyContin®)[10]	generic, Purdue	CII	
oxymorphone extended release (Opana® ER)[11]	Endo	CII	
tapentadol extended release (Nucynta® ER)[12]	Janssen	CII	
tramadol extended release (Ryzolt™)[13]	Purdue	Not scheduled	Moderate to moderately severe chronic pain requiring around-the-clock treatment for an extended time period
tramadol extended release (Ultram® ER)[14]	generic, OMJPI	Not scheduled	
tramadol extended release (ConZip™)[15]	Vertical	Not scheduled	

Overview

Pain of multiple etiologies remains a substantial problem for many patients presenting in the clinical setting.[16] Pain management must be individualized for each of these patients. There are many opioid

analgesic products available, differing in specific opioid, dosage form, and duration of action. In this review, the terms “narcotic” and “opioid” are used interchangeably.

Pain is often under treated, and pain management greatly misunderstood. Seventy-three percent of hospitalized medical patients receiving opiates were found in moderate or severe distress despite their analgesic regimen.[17] Caregivers’ misconceptions regarding opiate doses, duration of analgesic effect, and fear of addiction were partly responsible for this under treatment. Similar problems have been reported in ambulatory patients.[18] 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 increase periods of consistent pain control.

The World Health Organization’s (WHO) guidelines for cancer pain management, long recognized as the foundation of cancer pain relief, recommend a three-stepped approach with consideration for the type of pain and response to therapy.[19] Initial therapy should include non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs). For mild to moderate pain, oral combinations of acetaminophen and NSAIDs with opioids are recommended. For moderate to severe pain, opioid analgesics are the treatment of choice. The American Pain Society does not distinguish amongst the available products in their 2009 clinical guidelines for the use of chronic opioid therapy for the treatment of chronic non-cancer pain.[20] Titration of dose and frequency should be individualized to the patient’s response and experience of adverse effects.

The 2009 Evidence Review performed by the American Pain Society in conjunction with the American Academy of Pain Medicine made no mention of any significant differences in the benefits or harms of extended-release opioids and related products in the treatment of chronic non-cancer pain.[21] There were also no discernable differences in patient populations that made these analgesics more or less likely to meet the needs of certain patient types.

PHARMACOLOGY [22,23,24,25,26,27,28,29,30,31,32,33,34,35,36]

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 (Butrans) differs in that it is a partial agonist/antagonist of opioid receptors.

Naltrexone is a centrally acting mu-receptor antagonist that reverses the analgesic effects of mu-receptor agonists by competing for binding sites with opioids.

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.

PHARMACOKINETICS

Drug	Half-Life (hr)	Tmax (hr)	Excretion
buprenorphine (Butrans)[37]	26	about 48-72	70% metabolized and eliminated in feces and approximately 27% excreted in urine.
fentanyl transdermal (Duragesic)[38]	17	27.5-38.1	75% metabolized and renally eliminated
hydromorphone ER (Exalgo)[39]	8-15	12-16	highly metabolized; 75% eliminated in urine
methadone (Dolophine)[40]	8-59	1-7.5	highly metabolized; eliminated in urine and feces
morphine sulfate ER (Avinza)[41]	2-15	0.5	90% metabolized and renally eliminated
morphine sulfate ER (Kadian)[42]	2-15	8.6-10.3	90% metabolized and renally eliminated
morphine sulfate CR (MS Contin)[43]	2-15	~ 1.5	90% metabolized and renally eliminated
morphine sulfate ER (Oramorph SR)[44]	2-4	3.6-3.8	90% metabolized and renally eliminated
morphine sulfate ER / naltrexone (Embeda)[45]	29	29	90% metabolized and renally eliminated
oxycodone CR (OxyContin)[46]	4.5	1.6-3.2	primarily metabolized and renally eliminated
oxymorphone ER (Opana ER)[47]	9.4-11.3	1-2	highly metabolized; eliminated in urine and feces
tapentadol ER (Nucynta® ER)[48]	5	3-6	97% metabolized and renally eliminated
tramadol ER (Ultram ER)[49]	tramadol 7.9 metabolites 8.8	tramadol 12 metabolites 15	30% excreted as tramadol, 60% excreted as active metabolites in the urine
tramadol ER (Ryzolt)[50]	tramadol 6.5 metabolites 7.5	tramadol 4 metabolites 5	30% excreted as tramadol, 60% excreted as active metabolites in the urine
tramadol ER (ConZip™)[51]	tramadol 10 metabolites 11	tramadol 5.9 metabolites 11	30% excreted as tramadol, 60% excreted as active metabolites in the urine

CONTRAINDICATIONS/WARNINGS[52,53,54,55,56,57,58,59,60,61,62,63,64]

Contraindications

Buprenorphine transdermal (Butrans) is contraindicated in patients with significant respiratory depression, severe bronchial asthma, suspected paralytic ileus, or hypersensitivity to buprenorphine or any product components. Buprenorphine transdermal is also contraindicated in the management of acute pain in patients who require opioid analgesia for a short time, management of post-operative pain, management of mild pain, or management of intermittent pain.

Fentanyl transdermal (Duragesic) is contraindicated in patients with known hypersensitivity to fentanyl or any components of the product; 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. Fentanyl transdermal is also contraindicated in the management of acute pain, mild pain, or intermittent pain (use on an as-needed basis), 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).

Hydromorphone (Exalgo) is contraindicated in patients with known hypersensitivity to hydromorphone or sulfites; patients who have acute or severe bronchial asthma or hypercarbia or situations of significant respiratory depression (in the absence of resuscitative equipment or monitors); patients with known or suspected paralytic ileus; and patients with a narrow or obstructed GI tract.

Methadone (Dolophine) is contraindicated in patients with known hypersensitivity to methadone or any other components; patients who have acute bronchial asthma or hypercarbia; situations of significant respiratory depression (in the absence of resuscitative equipment or monitors); and patients with known or suspected paralytic ileus.

Morphine sulfate extended-release (Avinza, Kadian, MS Contin, Oramorph SR, Embeda) is contraindicated in patients with known hypersensitivity to morphine, morphine salts or any other components of the product; patients who have acute or severe bronchial asthma or hypercarbia; situations of significant respiratory depression (in the absence of resuscitative equipment or monitors); and patients with known or suspected paralytic ileus. Morphine sulfate ER/naltrexone is also contraindicated in patients with hypersensitivity to naltrexone.

Oxycodone CR (OxyContin) is contraindicated in patients with known hypersensitivity to oxycodone or any other components of the product; patients who have acute or severe bronchial asthma or hypercarbia; situations of significant respiratory depression (in the absence of resuscitative equipment or monitors); and patients with known or suspected paralytic ileus.

Oxymorphone ER (Opana ER) is contraindicated in patients with known hypersensitivity to oxymorphone hydrochloride or any other components of the product; patients with a known hypersensitivity to morphine analogs such as codeine; patients who have acute or severe bronchial asthma or hypercarbia; situations of significant respiratory depression (in the absence of resuscitative equipment or monitors); and patients with known or suspected paralytic ileus. Oxymorphone ER is not indicated for pain in the immediate post-operative period (the first 12 to 24 hours following surgery), or if the pain is mild or not expected to persist for an extended period of time. Oxymorphone ER is contraindicated in patients with moderate and severe hepatic impairment.

Tapentadol ER (Nucynta ER) is contraindicated in patients with significant respiratory depression, or severe bronchial asthma or hypercapnia in unmonitored settings or in the absence of resuscitative equipment; patients with known or suspected paralytic ileus; patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events; and in patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product. Tapentadol ER is not intended for use as an as-needed analgesic or for the management of acute or postoperative pain.

Tramadol ER (Ryzolt, Ultram ER, and ConZip) is contraindicated in patients with known hypersensitivity to tramadol hydrochloride or any other components of the product or opioids; patients who have acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs; and situations where opioids may be contraindicated.

Warnings

Serious or life-threatening hypoventilation may occur at any time during the use of long-acting narcotics, especially during the initial 24 to 72 hours following initiation of therapy and following increases in dose. Respiratory depression is the chief hazard of opioid agonists. 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.

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.

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.

buprenorphine transdermal

Boxed warnings for buprenorphine transdermal include assessing patients for clinical risks for opioid abuse or addiction prior to prescribing opioids, not exceeding a dose of one 20 mcg/hr patch due to the risk of QTc prolongation, and avoiding exposing patches to direct heat.

Avoid using buprenorphine transdermal in patients with Long QT Syndrome or a family history of the disease. Buprenorphine transdermal may worsen increased intracranial pressure and obscure its signs. Patients at increased risk of hypotension and those in circulatory shock could experience worsened conditions with buprenorphine treatment.

fentanyl transdermal

Fentanyl transdermal has a black box warning reminding prescribers that Schedule II opioids have the highest potential for abuse and are associated with the risk of fatal overdoses due to respiratory depression. The warning also states that fentanyl transdermal should be used only in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, or who require a total daily dose at least equivalent to fentanyl transdermal 25 mcg/h. Patients who are considered opioid-tolerant are those who have been taking, for a week or longer, 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.

In 2007, the Food and Drug Administration (FDA) issued an update that highlights important information on appropriate prescribing, dose selection, and the safe use of the fentanyl transdermal system (patch).[65] The FDA had previously issued a Public Health Advisory and Information for Healthcare Professionals in July 2005 regarding the appropriate and safe use of the transdermal patch. 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. Patients must avoid exposing the patch to excessive heat as this promotes the release of fentanyl from the patch and increases the absorption of fentanyl through the skin, which can result in fatal overdose. Directions for prescribing and using the

fentanyl patch must be followed exactly to prevent death or other serious side effects from fentanyl overdose.

The patches are for transdermal use on intact skin only. Use of damaged or cut patches should not be used. Fentanyl transdermal should only be used in children over two years of age who are opioid-tolerant.

hydromorphone

Hydromorphone has black box warnings that describe the abuse potential of this product. Hydromorphone is for opioid-tolerant patients only; fatal respiratory depression could occur in patients who are not opioid-tolerant. Accidental consumption of hydromorphone can result in fatal overdose. It is for long-term use and not for as-needed treatment or for the treatment of pain in the immediate post-operative period. The tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed tablets leads to a rapid release and absorption of a potentially fatal dose of hydromorphone.

Hydromorphone should not be used concomitantly with alcohol or other CNS depressants due to the potential for additive effects. Severe hypotension, elevated cerebrospinal fluid pressure, and obstructive symptoms are all possible with hydromorphone therapy.

methadone

The black box warning for methadone 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.

morphine extended-release

The black box warning for morphine sulfate ER products states that tablets and capsules are to be swallowed whole and not chewed, crushed, broken, or dissolved, which may lead to a rapid release and absorption of a potentially fatal dose of morphine. Morphine ER products are not indicated for pain in the immediate post-operative period (the first 12-24 hours following surgery) for patients not previously taking the drug. Morphine ER products are not indicated for pain in the post-operative period if the pain is mild or not expected to persist for an extended period of time.

Morphine sulfate ER (Avinza) should not be taken concomitantly with alcohol, which may cause a rapid release of active ingredient. This may cause an increase in adverse events and may lead to a potentially fatal overdose of morphine. The daily dose of morphine sulfate ER (Avinza) must be limited to a maximum of 1,600 mg per day. Doses greater than 1,600 mg per day of Avinza contain a quantity of fumaric acid that has not been demonstrated to be safe, and which may result in serious renal toxicity.

Morphine sulfate ER 100 mg and 200 mg tablets (MS Contin) and capsules (Kadian) are for opioid-tolerant patients. Their use in opioid-naïve patients may lead to fatal respiratory depression.

Morphine sulfate ER/naltrexone (Embeda) capsules contain pellets of morphine sulfate with a sequestered core of naltrexone. Tampering with the pellets by crushing or chewing pellets causes the rapid release and absorption of both morphine and naltrexone, resulting in a potentially fatal morphine dose, particularly in opioid-naïve individuals. In opioid-tolerant patients, the absorption of naltrexone may increase the risk of precipitating withdrawal. Morphine sulfate ER/naltrexone 100/4

mg capsules are for opioid-tolerant patients. Patients should not consume alcoholic beverages or use prescription or non-prescription medications containing alcohol while on this therapy.

oxycodone CR (OxyContin)

Oxycodone CR has a black box warning that describes the abuse potential of this product. It also states that it is for long-term use and not for as-needed treatment or for the treatment of pain in the immediate post-operative period (the first 12 to 24 hours following surgery). Oxycodone CR also should not be used for the treatment of mild pain or when pain is not expected to persist for an extended period of time. Oxycodone CR is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain). The tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed tablets leads to a rapid release and absorption of a potentially fatal dose of oxycodone. A reformulation of oxycodone CR (OxyContin) was approved in 2010 by the Food and Drug Administration (FDA). The new formulation was designed to decrease the likelihood that this medication will be misused or abused, and result in overdose. The new formulation added in tamper-resistant features aimed at preserving the controlled release of the active ingredient, oxycodone. [66] Any attempt to dissolve the tablets in liquid results in a gummy substance. The oxycodone CR 60 mg and 80 mg tablets (or a single dose greater than 40 mg) are to be used with care 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.

oxymorphone ER (Opana ER)

Oxymorphone ER has an abuse liability similar to that of other opioids, legal or illicit. Oxymorphone ER is to be swallowed whole, not broken, chewed, crushed, or dissolved. Oxymorphone ER is not for as-needed use or indicated for pain in the immediate post-operative period (12 to 24 hours following surgery) for patients not previously taking opioids; there is substantial risk of oversedation and respiratory depression requiring reversal with opioid antagonists. Concomitant use of oxymorphone ER with alcoholic beverages or prescription or nonprescription medications containing alcohol may increase blood levels of oxymorphone and cause a potentially fatal overdose.

tapentadol extended-release (Nucynta ER)

Tapentadol ER tablets are to be swallowed whole and are not to be split, broken, chewed, dissolved, or crushed. Tapentadol ER may cause severe hypotension. Patients at higher risk of hypotension include those with hypovolemia or those taking concurrent products that compromise vasomotor tone (e.g., phenothiazines, general anesthetics). Cases of life-threatening serotonin syndrome have been reported with the concurrent use of tapentadol and serotonergic drugs.

tramadol extended-release (Ryzolt, Ultram ER, ConZip)

Seizures have been reported in patients taking tramadol within the recommended dosage range; use caution in patients taking other neuroleptics such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and monoamine oxidase (MAO) inhibitors. Serotonin syndrome is also possible with concomitant use of these drugs. Tramadol ER should not be prescribed for patients who are suicidal or addiction-prone.

Risk Evaluation and Mitigation Strategy (REMS)[67,68,69,70,71]

Buprenorphine transdermal, hydromorphone ER, oxycodone ER, and tapentadol ER prescriptions are to be dispensed with a medication guide. Elements to assure safe use have also been implemented, such as training for prescribers of these products.

Morphine ER/naltrexone prescriptions are to be dispensed with a medication guide, as well. A communication plan is also in place to support REMS implementation.

DRUG INTERACTIONS[72,73,74,75,76,77,78,79,80,81,82,83,84,85,86]

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.

Agonist/antagonist analgesics (e.g., pentazocine, nalbuphine, butorphanol, or 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 may alter the analgesic effect or may precipitate withdrawal symptoms.

Monoamine oxidase inhibitors (MAOI) may intensify the actions of other opioids.

Drugs that induce cytochrome P450 3A4 enzymes may affect the metabolism of buprenorphine transdermal (Butrans). However, co-administration of ketoconazole with buprenorphine transdermal did not result in changes in the buprenorphine pharmacokinetic profile. Studies have not been performed with 3A4 inducers.

Fentanyl (Duragesic) is mainly metabolized by the CYP450 enzyme pathway, so coadministration of this agent with CYP450 enzyme inducers or inhibitors may adversely affect the metabolism. The concomitant use of transdermal fentanyl with any CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause fatal respiratory depression. Patients receiving fentanyl transdermal and any CYP3A4 inhibitor should be carefully monitored for an extended period of time, and dosage adjustments should be made if necessary.

Oxycodone CR (OxyContin) is metabolized in part by CYP450 2D6 and CYP450 3A4 and, in theory, can be affected by other drugs.

Concomitant administration of CYP2D6 or 3A4 enzyme inhibitors may reduce metabolic clearance of tramadol (Ryzolt, Ultram ER, ConZip), increasing the risk for serious adverse events.

The use of tapentadol ER (Nucynta ER) with anticholinergic products may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Caution is advised when tapentadol ER is co-administered with other drugs that may affect serotonergic neurotransmitter systems such as SSRIs, SNRIs, and triptans.

ADVERSE EFFECTS

Drug	Asthenia	Constipation	Dizziness	Dyspnea	Headache	Nausea	Rash	Somnolence	Vomiting
buprenorphine (Butrans)[87]	1-5	3-14 (1-5)	2-16 (1-8)	3 (1)	5-16 (5-11)	13-23 (8-11)	3-9 (6)	2-14 (2-5)	2-11 (2)
fentanyl transdermal (Duragesic)[88]	>10	>10	3-10	3-10	3-10	>10	> 1	>10	>10
hydromorphone ER (Exalgo)[89]	1-4 (4)	7-15 (4)	2-4 (1)	reported	5-8 (7)	9-12 (7)	reported	1-9 (0)	6 (4)
methadone (Dolophine)[90]	nr	reported	reported	reported	reported	reported	reported	reported	reported
morphine sulfate ER (Avinza)[91]	5-10	>10	nr	5-10	>10	>10	5-10	>10	>10
morphine sulfate ER (Kadian)[92]	< 3	9	6	< 3	< 3	7	< 3	9	< 3
morphine sulfate CR (MS Contin)[93]	reported	reported	reported	nr	reported	reported	reported	reported	reported
morphine sulfate ER (Oramorph SR)[94]	reported	reported	reported	nr	reported	reported	reported	reported	reported
morphine sulfate ER / naltrexone (Embeda)[95]	reported	31.2	4.1	nr	6.9	22.2	< 1	7.3	8
oxycodone CR (OxyContin)[96]	6 (nr)	23 (7)	13 (9)	1-5	7 (7)	23 (11)	1-5	23 (4)	12 (7)
oxymorphone ER (Opana ER)[97]	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)98	2 (1)	17 (7)	17 (7)	1 (1)	15 (13)	21 (7)	1 (1)	12 (4)	8 (3)
tramadol ER (Ryzolt)[99]	1-5	13 (4)	10 (3)	< 1	4 (3)	16 (6)	nr	7 (2)	5 (1)
tramadol ER (Ultram ER)[100]	3.5-6.5	12.2-29.7	15.9-28.2	<5	<1	15.1-26.2	nr	8.2-20.3	5-9.4
tramadol ER (ConZip)[101]	3.5-8.6	9.3-21.3	9.6-13.6	nr	19.0-23.1	16.1-25.1	nr	11.7-16.1	6.5-10.4

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.

SPECIAL POPULATIONS[102,103,104,105,106,107,108,109,110,111,112,113,114,115,116]

Pediatrics

Fentanyl transdermal (Duragesic) is approved for use in patients as young as two years of age who are opioid-tolerant.

Safety and efficacy of buprenorphine (Butrans), hydromorphone ER (Exalgo), methadone (Dolophine), morphine sulfate extended-release (Avinza, Kadian, MS Contin, Oramorph SR), morphine sulfate ER/naltrexone (Embeda), oxycodone controlled-release (OxyContin), oxymorphone extended-release (Opana ER), tramadol extended-release (Ryzolt, Ultram ER, ConZip), and tapentadol ER (Nucynta) have not been established in patients younger than 18 years of age.

Geriatrics

The 2002 American Geriatric Society (AGS) guideline addresses opioids in the geriatric population. Among these agents is tramadol.[117] According to these guidelines, tramadol has opioid activity with apparently low abuse potential and is reportedly about as effective and safe as codeine or hydrocodone. However, tramadol has the additional low risk of inducing seizures.

Pregnancy

Buprenorphine transdermal, fentanyl transdermal, hydromorphone ER, morphine sulfate extended-release products, morphine sulfate ER/naltrexone (Embeda), oxymorphone ER, tramadol ER, and tapentadol ER have a Pregnancy Category C designation.

Methadone also has a Pregnancy Category C designation. Women on high-dose methadone maintenance already nursing should be counseled to wean breast-feeding gradually to prevent neonatal abstinence syndrome.

Oxycodone CR has a Pregnancy Category B designation. 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 CR should be used during pregnancy only if clearly required.

Other Considerations

Administration of oxymorphone ER in elderly patients resulted in plasma levels that were 40 percent higher than those in younger subjects. Bioavailability of oxymorphone ER may also be increased in patients with hepatic or renal insufficiency. Formal studies have not yet been done. Hydromorphone ER should be initiated at lower doses in patients with moderate or severe renal or hepatic impairment.

Tapentadol ER should be used with caution in patients with moderate hepatic impairment. In patients with severe renal impairment, tapentadol ER should be avoided because the safety and effectiveness has not been established.

DOSAGES[118,119,120,121,122,123,124,125,126,127,128,129,130,131,132]

Drug	Starting Dose	Titration	Available Strengths
buprenorphine transdermal (Butrans)	One patch changed every seven days	For opioid-naïve patients: Initiate treatment with buprenorphine transdermal 5 mcg/hour and titrate as needed after 72 hours. For opioid-experienced patients, there is a dosing conversion chart in the prescribing information. Do not exceed a dose of one 20 mcg/hour patch due to the risk of QTc prolongation.	5, 10, 20 mcg/hr patches
fentanyl transdermal (Duragesic)	25 mcg/hr patch changed every three days for opioid-tolerant patients	For patients on other opioids, calculate their total 24-hour analgesic requirement. Convert this amount to an equivalent analgesic oral morphine dose (see Package Insert Tables C and D). Package Insert Table E displays the recommended initial Duragesic dose based on the total daily oral morphine dose. Dosage increase may occur after every three days by adding up the rescue medication dosage. Initial doses should be reduced in elderly or debilitated patients.	12, 25, 50, 75, 100 mcg/hr patches
hydromorphone ER (Exalgo)	8 to 64 mg once daily	Adjust dosage not more often than every three to four days; increases of 25-50 percent of the current daily dose are recommended for each step.	8, 12, 16 mg tablets
methadone (Dolophine)	2.5 mg to 10 mg every eight 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, 10, 40 mg tablets 1, 2, 10 mg/mL oral solutions
morphine sulfate ER (Avinza)	30 mg daily	Titrate 30 mg per day every four days until sufficient pain control is maintained. Swallow capsules whole. Do not crush, chew, or dissolve capsules or contents of capsules. Do not drink alcohol while on Avinza. May sprinkle beads on applesauce. Maximum daily doses should not exceed 1,600 mg. The 60 mg, 90 mg, and 120 mg capsules should only be used in opioid-tolerant patients.	30, 45, 60, 75, 90, 120 mg capsules
morphine sulfate ER (Kadian)	One 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, 20, 30, 50, 60, 80, 100, 200 mg capsules
morphine sulfate CR (MS Contin)	15 mg every 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, 30, 60, 100, 200 mg tablets

Dosages (continued)

Drug	Starting Dose	Titration	Available Strengths
morphine sulfate ER (Oramorph SR)	15 mg every 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.	15, 30, 60, 100 mg tablets
morphine sulfate ER/naltrexone (Embeda)	One capsule every 12 to 24 hours	Titrate to pain control. Initiate therapy at the lowest dose for patients who use Embeda as their first opioid analgesic. For patients who are converting from another oral morphine product, therapy should begin with half of the total established daily morphine dose being given twice daily, or with the full dose being given once a day. Swallow capsules whole or may sprinkle on applesauce. Do not crush, chew, or dissolve capsules or contents of capsules. The 100/4 mg capsules are reserved for opioid-tolerant patients.	20/0.8, 30/1.2, 50/2, 60/2.4, 80/3.2, 100/4 mg capsules
oxycodone CR (OxyContin)	10 mg every 12 hours	Except for the increase from 10 mg to 20 mg every 12 hours, the total daily oxycodone CR dose can be increased by 25 to 50 percent at each increase. Patients should be titrated so that they need no more than two 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 33-50 percent. For patients with creatinine clearance<60 mL/min, dosage may need to be lowered by up to 50 percent. The 60 and 80 mg tablets should only be used in opioid-tolerant patients.	10, 15, 20, 30, 40, 60, 80 mg tablets
oxymorphone ER (Opana ER)	5 mg every 12 hours	Increase by 5 to 10 mg twice a day every three to seven days based on patient pain intensity and adverse effects. Do not 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, 7.5, 10, 15, 20, 30, 40 mg tablets
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) every three days. Do not exceed maximum daily dose of 500 mg (250 mg twice a day.	50, 100, 150, 200, 250 mg tablets
tramadol ER (Ryzolt)	One tablet daily	Initiate at 100 mg daily then titrate at 100 mg increments every two to three days as needed to relief of pain. Do not use in patients with severe renal or hepatic impairment.	100, 200, 300 mg tablets

Dosages (continued)

Drug	Starting Dose	Titration	Available Strengths
tramadol ER (Ultram ER)	One tablet daily	Initiate at 100 mg daily then titrate at 100 mg increments every five days as needed to relief of pain. Do not use in patients with severe renal or hepatic impairment.	100, 200, 300 mg tablets
tramadol ER (ConZip)	100 mg daily	Initiate at 100 mg daily then titrate at 100 mg increments every five 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 max 300 mg/day. Consider lower doses in elderly. The concomitant use of the extended-release capsules with other tramadol products is not recommended.	100, 200, 300 mg capsules

The naltrexone component of morphine sulfate ER/naltrexone (Embeda) is formulated such that if the capsule is swallowed whole or opened and sprinkled over applesauce, the morphine component will be released while the naltrexone will remain sequestered in a film coating that is resistant to digestion.[133] However, if the capsule contents are chewed or crushed, the naltrexone is released, reversing the effects of the morphine, thus reducing the likelihood that the product will be abused by disabling the extended-release mechanism. No studies have established whether this hypothesized reduction of morphine effects following chewing or crushing were clinically significant; the product labeling states that there is no evidence that the naltrexone in Embeda reduces the abuse liability.

Oxymorphone ER (Opana ER) should be given on an empty stomach at least one hour prior to or two hours after eating. Maximum serum concentration was increased by 50 percent when given with food.[134] An *in vivo* study with oxymorphone ER showed that the maximum concentration increased 31 to 70 percent, on average, following concomitant administration with ethanol. Coadministration must be avoided.

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 buprenorphine transdermal patch falls off during the seven days dosing interval, dispose of the transdermal system properly and place a new patch on at a different skin site.

Fentanyl transdermal patch (Duragesic) 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 three days of use, discard and apply a new patch at a different skin site.

Dietary caution should be taken when patients are initially titrated to 160 mg oxycodone CR (OxyContin) tablets.[135]

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 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

buprenorphine (Butrans)

Opioid-naïve patients (n=1,024) with chronic low back pain enrolled in an open-label dose-titration period for up to four weeks.[136] Fifty-three percent of patients were able to titrate to a tolerable and effective dose and entered the randomized, double-blind portion of this study and received continued buprenorphine transdermal or placebo with breakthrough oral medication allowed. Sixty-six percent of buprenorphine transdermal patients completed the 12-week study. The score of average pain over the last 24 hours at the end of the study was statistically significant in favor of buprenorphine transdermal treatment compared to placebo.

In a study of opioid-experienced patients (n=1,160) with low back pain, patients entered a dose-titration period with buprenorphine transdermal following a taper of prior opioids.[137] Fifty-seven percent of patients entered the randomized, double-blind phase and received continued buprenorphine 20 mcg/hour or were switched to an active control or buprenorphine 5 mcg/hour for 12 weeks. Breakthrough medication was allowed. Sixty-seven percent of 20 mcg/hour patients completed the study, compared to 58 percent of the 5 mcg/hour group. The score for average pain over the last 24 hours at week 12 was statistically significantly lower for 20 mcg/hour patients compared to the 5 mcg/hour group. A higher proportion of the 20 mcg/hour patients (49 percent) had at least a 30 percent reduction in pain score from screening to study endpoint when compared to the 5 mcg/hour patients (33 percent).

hydromorphone ER (Exalgo)

A double-blind, placebo-controlled, randomized, 12-week study performed by the manufacturer showed that hydromorphone ER in patients with moderate to severe low back pain.[138] Hydromorphone ER provided superior analgesia compared to placebo, as determined by the average weekly pain intensity NRS scores obtained from patient diaries.

methadone (Dolophine) 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 four hours as needed or morphine 15 mg sustained release every 12 hours and 5 mg every four hours as needed.[139] After four weeks, patients receiving methadone had more opioid-related discontinuations than those receiving morphine (22 versus six percent; p=0.019). The opioid escalation index at days 14 and 28 were similar between the two groups. More than three-fourths of patients in each group reported a 20 percent or more reduction in pain intensity by day eight; at four weeks, the proportion of patients with a 20 percent or more reduction in pain was similar: 0.49 in the methadone group and 0.56 in the morphine group.

morphine sulfate ER (Avinza) versus morphine sulfate ER (MS Contin) versus placebo

In a four-week randomized, placebo-controlled, double-blind trial, 295 osteoarthritis patients who had previously failed to obtain adequate pain relief with NSAIDs and acetaminophen received one of three treatments: morphine sulfate ER (Avinza) 30 mg once daily, morphine sulfate ER (MS Contin) 15 mg twice daily, or placebo twice daily.[140] Both Avinza and MS Contin reduced pain and improved several sleep measures versus placebo. Analgesic efficacy was comparable between both morphine sulfate ER dosage forms. The active treatment groups documented similar occurrences in adverse drug reactions, with nausea and constipation being the most common.

morphine sulfate ER / naltrexone (Embeda)

In a randomized, double-blind, placebo-controlled, 12-week study performed by the manufacturer, patients with osteoarthritis of the hip or knee with moderate to severe pain started open-label treatment with morphine ER/naltrexone and titrated to effect.[141] Once pain was controlled, they were randomized to either active treatment with morphine ER/naltrexone or tapered off treatment using a double-dummy design and placed on placebo. The primary endpoint was measured by the weekly diary Brief Pain Inventory average pain score. Morphine ER/naltrexone was found to more effective than placebo.

oxycodone controlled-release (OxyContin) versus oxycodone immediate release

A multicenter, randomized, double-blind, parallel-group study was performed in 111 patients with cancer pain.[142] Patients were being treated with fixed-combination opioid/nonopioid analgesics at study entry. Patients received 30 mg of oxycodone CR every 12 hours or 15 mg of oxycodone IR four times daily for five 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 CR-treated group and 1.3 for the group given oxycodone IR (p>0.05). The five-day mean pain intensity was 1.4 and 1.1 for the CR and IR groups, respectively (p>0.05). Discontinuation rates were equivalent (33 percent). 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 CR every 12 hours (n=81) or oxycodone IR four times daily (n=83) for five days in a multicenter, double-blind study.[143] Rescue medication was allowed. Pain intensity remained slight during the study, with mean oxycodone doses of 114 mg/day for CR and 127 mg/day for IR. Acceptability of therapy was fair to good with both treatments. Discontinuation rates for lack of acceptable pain control were four

percent with CR and 19 percent with IR. Fewer adverse events were reported with CR than with IR (p=0.006).

oxymorphone ER (Opana ER) and oxycodone CR (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 CR in patients with moderate to severe chronic low back pain requiring opioid therapy.[144] Patients (n=213) were randomized to receive oxymorphone ER (10 to 110 mg) or oxycodone CR (20 to 220 mg) every 12 hours during a seven- 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 CR (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 frequent were constipation and sedation. Oxymorphone ER was equianalgesic to oxycodone CR at half the milligram daily dosage with comparable safety.

tapentadol ER (Nucynta ER)

A randomized, double-blind, placebo- and active-controlled study was conducted to compare the efficacy of tapentadol ER with placebo in patients with chronic low back pain (LBP).[145] Patients with a baseline pain score of less or equal to five on an 11-point numerical rating scale (NRS), ranging from zero to 10 were enrolled and randomized to one of three treatments: tapentadol ER, active-control (an extended-release Schedule II opioid analgesic), or placebo. Patients randomized to tapentadol ER initiated therapy with a dose of 50 mg twice daily for three days. After three days, the dose was increased to 100 mg twice daily. Subsequent titration was allowed over a 3-week titration period to a dose up to 250 mg twice daily, followed by a 12-week maintenance period. There were 981 patients randomized. The number of patients completing the study was 51 percent in the placebo group, 54 percent in the tapentadol ER group and 43 percent in the active-control group. After 15 weeks of treatment, patients taking tapentadol ER had a significantly greater pain reduction compared to placebo.

tramadol ER (Ryzolt) and placebo

Tramadol ER was studied in four 12-week, randomized, double-blind, controlled, manufacturer-performed approval studies in patients with moderate to severe pain due to osteoarthritis.[146] In one double-blind, placebo-controlled, randomized withdrawal design, manufacturer-performed approval study, patients were randomized to tramadol ER 200 or 300 mg daily or placebo for 12 weeks. Approximately 24 percent of patients discontinued treatment during the study, with more patients discontinuing from the tramadol ER arm than the placebo arm due to adverse events (10 versus five percent, respectively) and more patients discontinuing from the placebo arm than the tramadol ER arm due to lack of efficacy (10 versus eight percent). P-values were not available. Patients treated with tramadol ER demonstrated a greater improvement in pain intensity, measured on an 11-point numerical rating scale, at the end of treatment compared to placebo patients.

tramadol ER (Ultram ER) and placebo

A randomized, double-blind, placebo-controlled, parallel-group, 12-week study evaluated 246 patients with radiographically confirmed osteoarthritis of the knee meeting the American College of

Rheumatology diagnostic criteria.[147] Following a wash-out period, patients were randomized to tramadol ER or placebo. Tramadol ER was initiated at 100 mg daily and increased to 200 mg daily by the end of one week of treatment. After the first week, further increases to tramadol ER 300 mg or 400 mg daily were allowed. The mean tramadol ER dose was 276 mg. On the primary outcome variable of average change from baseline in Arthritis Pain Intensity VAS over 12 weeks, tramadol ER was superior to placebo ($p<0.001$). All efficacy outcome measures statistically significantly favored tramadol ER over placebo.

tramadol ER (Ultram ER, ConZip) and placebo

A 12-week randomized, double-blind, placebo-controlled flexible-dosing trial of the extended-release tramadol was conducted in patients with osteoarthritis of the knee.[148,149] Patients were titrated to an average daily dose of approximately 270 mg/day. Forty-nine percent of patients randomized to the active treatment group completed the study, while 52 percent of patients randomized to placebo completed the study. Most of the early discontinuations in the active treatment group were due to adverse events, accounting for 27 percent of the early discontinuations in contrast to 7 percent of the discontinuations from the placebo group. Thirty-seven percent of the placebo-treated patients discontinued the study due to lack of efficacy compared to 15 percent of active-treated patients. The active treatment group demonstrated a statistically significant decrease in the mean Visual Analog Scale (VAS) score, and a statistically significant difference in the responder rate, based on the percent change from baseline in the VAS score, measured at 1, 2, 4, 8, and 12 weeks, between patients receiving the extended-release tramadol product and placebo. P-values were not available.

SUMMARY

Pain of multiple etiologies remains a substantial problem for many patients presenting in the clinical setting. Pain management must be individualized for each patient.

No clinical data exist that distinguish any of these products from the others. However, there are certain characteristics for some that have clinical benefits: Buprenorphine (Butrans) and fentanyl (Duragesic) are available as transdermal dosage forms. Methadone (Dolophine) 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 dosage form (MS Contin, Oramorph SR) for many years. More recently, controlled-release dosage forms (Avinza, Kadian) approved for once daily use have been marketed. Although the ability of these agents to relieve pain is little, if any, better than the twice-daily dosage forms, the once-daily products are preferred by patients. Morphine ER/Naltrexone (Embeda) is a formulation of morphine that theoretically reduces abuse potential, but considering the lack of evidence to suggest that the abuse-limiting mechanism is effective, there appears to be no justification to support its use over any other long-acting morphine product. Tramadol ER products (Ryzolt, Ultram ER, ConZip) are non-scheduled analgesics and provide other once-daily analgesic options. ConZip is the new tramadol-ER capsule formulation.

Tapentadol ER (Nucynta ER) is a centrally acting oral analgesic that binds to mu-opioid receptors and inhibits norepinephrine re-uptake. The tapentadol ER tablet formulation is designed to provide a high degree of mechanical resistance, such as to crushing or chewing.

Like the controlled-release forms of morphine, oxycodone CR (OxyContin) allows for less frequent (12-hour) dosing of an opioid. No data exist to suggest that this agent is any more effective than

controlled-release morphine sulfate. Oxycodone CR has a significant potential for abuse and has been associated with increases in crime, as well as deaths, due to illicit use. However, all opioids and tramadol can be abused and are subject to illicit use. Oxycodone CR has been reformulated to a delivery system that causes a gummy substance to be created when tablets are crushed; the effects of this redesign on illicit use have yet to be seen.

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