Drug Class Review

Long-Acting Opioid Analgesics

28:08.08 Opiate Agonists

Transdermal

Buprenorphine transdermal system (Butrans®)

Fentanyl transdermal system (Duragesic®)

Oral

Buprenorphine oral buccal film (Belbuca®)

Hydrocodone ER (Zohydro ER®, Hysingla ER®)

Hydromorphone hydrochloride extended-release tablets (Exalgo®)

Methadone tablets (Dolophine®)

Morphine sulfate controlled-release tablets (MS Contin®, MorphaBond®)

Morphine sulfate extended-release capsules (Kadian®)

Oxycodone hydrochloride controlled-release tablets (OxyContin®)

Oxymorphone hydrochloride extended-release (Opana ER®)

Tapentadol extended-release oral tablets (Nucynta ER®)

Tramadol hydrochloride extended-release capsule (Conzip, others)

Tramadol hydrochloride extended-release tablet (biphasic) (Ultram ER, others)

Combination Products

Morphine sulfate and naltrexone extended-release capsules (Embeda®)

Oxycodone ER/acetaminophen (Xartemis XR®)

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Executive Summary

Introduction: The opioid analgesic agents have been used for centuries and are the most commonly used pharmacologic agents for the treatment of moderate to severe pain. Opioid analgesics stimulate opiate receptors and produce pain relief without producing loss of consciousness.

Long-acting opioids are often used in the management of chronic pain, which affects 1/3 of the US population, including 17.5 million elderly. Up to 32% of people with chronic pain are unable to work. The cost of chronic pain is estimated between $560-600 billion yearly split evenly between healthcare costs and lost productivity.

Long-acting opioids are indicated in the treatment of pain severe enough to require daily, around the clock treatment when an alternative is inadequate. Public health problems associated with opioid analgesic use in the United States include increases in non-medical use of these agents, emergency department visits and poisonings. Recommendations for the use of long-acting opioids include careful patient selection and consideration of the efficacy and safety of each long-acting opioid. Close monitoring is recommended in older and younger patients, those with renal or hepatic dysfunction, those using concomitant interacting medications and those with a history of drug abuse, addiction or misuse. Methadone is identified as an agent of particular safety concern and prescribing by experienced clinicians may increase the safe use of this agent.

The World Health Organization recommendations include an analgesic ladder addressing pain relief strategies at three levels. Non-opioid pain relievers are used at the lowest level, weak opioid agents (codeine) are used for moderate pain and strong opioid agents (morphine, hydromorphone, oxymorphone, methadone and fentanyl) are recommended for the highest level of pain. Patients may be switched from one opioid to another using equipotent dosing. This report reviews the safety and efficacy of the long-acting opioid agents in the treatment of pain disorders. Seventeen opioid agents were included in the review

Clinical Efficacy: Clinical experience with the long-acting agents in treating patients with pain is extensive. Nine systematic reviews published from 2002 to 2014 evaluating the comparative efficacy of the agents found insufficient evidence to differentiate among long-acting opioid analgesics with regard to pain relief, reduction in pain intensity, improvement in sleep parameters, quality of life, global assessments and risk of abuse, addiction or misuse.

Adverse Drug Reactions: The most common adverse effects associated with the opioid analgesics include nausea, vomiting, sedation, pruritus and constipation. Serious adverse effects frequently reported with opioid use include respiratory depression, urinary retention, hypotension and delirium. There is insufficient evidence to identifying significant adverse event differences among the agents although limited evidence suggests transdermal fentanyl is associated with a lower incidence of gastrointestinal side effects and sedation. Low-strength evidence suggests the harms associated with long-acting opioids are dose-related. Methadone is identified as an agent of particular safety concern and prescribing by experienced clinicians may increase the safe use of this agent. Clinical trials demonstrate no differences in rates of serious adverse events when oral morphine and morphine-like agents are dosed with

equianalgesic dosing schemes. Long-acting opioid analgesics are potent schedule II controlled opioid agonists that have the high potential for abuse and risk of producing respiratory depression.

Summary: Overall, the opioid analgesic agents are effective treatment options for pain disorders. When compared at equianalgesic doses, the opioid agents demonstrate similar rates of safety and efficacy. Pain management must be individualized for each patient and include careful evaluation of patient history, age, comorbidities, type of pain, underlying diseases and concurrent medications.

Introduction

Currently, ten long-acting opioids are approved in 17 different formulations by the FDA: buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, tapentadol and tramadol.

Product Comparison

Extended-release tramadol containing products (Conzip, Ultram ER, and generics) are DEA Schedule IV. Other long-acting opioids agents are Schedule II. The tramadol products are the only opioid agents, which may be prescribed with refills. Extended-release tramadol is indicated for round-the-clock treatment of moderate to severe pain.[1,2] Only tramadol ER and oxycodone/acetaminophen (Xartemis XR) are approved for administration on an as needed (PRN) basis.[1-3] No other agents are recommended for PRN use. OxyContin is the only oral agent with a pediatric indication, approved for use in patients $\geq$ 11 years of age.[4] Transdermal fentanyl may be used in opioid-tolerant children $\geq$ 2 years of age.[5] Transdermal fentanyl and extended-release hydromorphone (Exalgo) are not indicated in opioid-naïve patients while other agents may be used to initiate strong-opioid therapy.[5,6] Tapentadol ER (Nucynta ER) has an indication for the treatment of neuropathic pain and methadone has an indication for the use in detoxification from or maintenance treatment of heroin and other morphine-like drugs.[7,8] Methadone concentrate and dispersible tablets are only indicated for detoxification treatment or maintenance treatment of opioid addiction.[9,10] In March 2014, the FDA implemented class-wide changes to the labeling of opioids to define appropriate utilization and prevent problems with their use.[11] Post-marketing study requirements were introduced for all long-acting, extended-release opioids to further assess the risks of misuse, abuse, overdose and death.[12] Table 1 presents a comparison of these agents. Table 2 provides information concerning initiation, titration and dosage ranges of the products.

Dosage and Administration

The selection of an opioid for pain relief should include consideration of the severity of pain, chronicity, type of pain, status of the patient as opioid-naïve or experienced, age, renal and hepatic function, other diagnosis, concomitant medications, dosage formulation, abuse/misuse potential and a careful consideration of risk of harm vs. benefit.[34-36] Studies are unavailable to validate long-term use in noncancer pain.[21]

Once daily dosing is recommended for Exalgo ER (hydromorphone).[6] Once or twice daily dosing is common with Kadian and Embeda (morphine /naltrexone).[13,14] Twice daily dosing is recommended with OxyContin, Opana ER, Nucynta ER, Xartemis XR.[3,4,7,15] In the treatment of pain, methadone and MS Contin are administered two or three times daily.[8,16] A maximal daily dose of Xartemis XR is 4 tablets daily (30 mg/1300 mg) due to the acetaminophen content; a 4000 mg daily acetaminophen maximum is recommended to prevent hepatotoxicity.[3] Methadone has varied pharmacokinetics and pharmacodynamics requiring more caution in dose initiation and titration.[8]

Table 1. Comparison of Long-Acting Opioid Analgesic [1-8,13-23]

	Available Doses	Labeled Uses	Generic Available
Transdermal Products			
Buprenorphine Transdermal System (Butrans®)	Transdermal System: 5 mcg/hour, 7.5mcg/hour, 10 mcg/hour, 15 mcg/hour, 20 mcg/hour	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.	NO
Fentanyl transdermal system (Duragesic®)	Transdermal System: 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, 100 mcg/hr	Management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Patients considered opioid-tolerant are those who are taking, for one week or longer, at least (oral doses) 60 mg morphine daily, 30 mg oxycodone daily, 8 mg hydromorphone daily, or equianalgesic dose of another opioid.	YES
Oral Products			
Buprenorphine Oral buccal film (Belbuca®)	Oral Film: 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.	NO
Hydrocodone ER (Zohydro ER®, Hysingla ER®)	Zohydro ER Oral Capsules, Extended Release: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg Hysingla ER Oral Tablets, Extended Release: 20 mg, 30 mg, 40 mg 60 mg, 80 mg, 100 mg, 120 mg	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	NO
Hydromorphone extended-release tablets (Exalgo®, others) Mallinckrodt	Oral Tablets, Extended Release: 8 mg, 12 mg , 16 mg, 32 mg *Exalgo® contains sulfites	Management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Patients considered opioid-tolerant are those who are taking daily oral doses for one week or longer of: 60 mg morphine, 25 mcg fentanyl TDS/hr, 30 mg oxycodone, 25 mg oxymorphone, 8 mg hydromorphone or equianalgesic dose of another opioid	YES (some strengths)
Methadone (Dolophine®, Diskets Disperible, Methadone HCl Intensol, Methadose)	Injection Solution: 10 mg/1 mL Oral Solution: 5 mg/5 mL, 10 mg/5 mL, 10 mg/1 mL Oral Tablet: 5 mg, 10 mg, 40 mg Oral Tablet for Suspension: 40 mg Diskets Dispersible, Oral Tablet: 40 mg Methadone HCl Intensol: Oral Solution: 10 mg/mL Methadose: Oral Tablet: 5 mg, 10 mg, 40 mg	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Detoxification treatment of opioid addiction (heroin or other morphine-like drugs). Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.	YES (some dosage forms)

	Available Doses	Labeled Uses	Generic Available
Morphine controlled-release tablets (MS Contin®, MorphaBond®, others)	Oral Tablets, Extended Release: 15 mg 30 mg, 60 mg, 100 mg MS Contin® additionally available as 200 mg tablet	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.	Yes (MS Contin) No (MorphaBond®)
Morphine extended-release capsules (Kadian®, others)	Oral Capsules, Extended Release (containing pellets): 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg, 100 mg, 200 mg	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.	YES (some strengths)
Oxycodone controlled-release tablets (OxyContin®)	Oral Tablets, Extended Release: 10 mg, 15 mg, 20 mg, 30 mg , 40 mg, 60 mg, 80 mg	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in: adults, and opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.	NO (non-therapeutically equivalent products are available)
Oxymorphone extended-release (Opana ER®, others)	Oral Tablets, Extended Release: 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	YES
Tapentadol extended-release oral tablets (Nucynta ER®)	Oral Tablets, Extended Release: 50 mg, 100 mg, 150 mg, 200 mg, 250 mg	Management of (1) pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (2) neuropathic pain associated with diabetic peripheral neuropathy in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	NO
Tramadol extended-release tablet (Ultram ER®)	Oral Tablets, Extended Release: 100 mg, 200 mg, 300 mg	Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.	YES
Tramadol extended-release capsule (Conzip®)	Oral Capsules, Extended Release: 100 mg, 150 mg, 200 mg, 300 mg	Management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.	NO
Combination Agents			
Morphine and naltrexone extended-release capsules (Embeda®)*	Oral Capsule, Extended Release: 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2mg, 100 mg/4 mg	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	NO
Oxycodone ER/acetaminophen (Xartemis XR)	Oral Tablet, Extended Release: Oxycodone 7.5 mg/Acetaminophen 325 mg	Management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.	NO

Key: IM=intramuscular, IV=intravenous, hr=hour

Table 2: Dosage Initiation, Titration and Dosage Range [1-8,13-23]

Drug	Initial Dose	Titration Schedule	Dose Range
Transdermal Products			
Buprenorphine transdermal system (Butrans®)	Opioid naïve patients: 5 mcg/hour patch x 7 days Conversion from other opioids: Dosing based on daily MEU >80mg daily MSE: Consider alternative analgesic; Butrans may not provide adequate analgesic relief	Titration of Butrans should proceed in increments of 5, 7.5, or 10 mcg/hour, not to exceed more than 2 patches at once. The minimum titration interval for Butrans is 3 days.	Doses should not exceed one 20 mcg/hour system due to increased risk of QTc prolongation. Doses of 7.5, 10, 15, and 20 mcg/hour are intended for opioid-experienced patients only.
Fentanyl transdermal system (Duragesic®, others)	Opioid naïve patients: DO NOT USE Conversion from other opioids: Dosing may be based on daily MSE Multiple patches may be used for patients requiring >100 mcg/hour doses	Titration for Duragesic should proceed in increments based on the daily dose of supplementary opioids, with the ratio of 45 mg/day of MSE to a 12 mcg/hour increase in Duragesic dose. Dose increases should occur at a minimum of 3 days after initial application. Further dose increases should occur at a minimum of 6-day intervals.	Duragesic is intended only for use in opioid-tolerant patients (defined as patients taking at least 60 mg of morphine daily/equianalgesic dose for ≥1 week). Few adults may require 48 hour dosing intervals only if adequate pain control is not achieved with a 72 hour interval.
Oral Products			
Buprenorphine oral buccal film (Belbuca®)	Opioid naïve patients: 75 mcg film Q12H or Q24H as tolerated Conversion from other opioids: Dosing based on daily morphine sulfate equivalents (MSE) >160 mg daily oral MSE: Consider alternative analgesic; Belbuca may not provide adequate analgesic relief	Titration of Belbuca should proceed in increments no greater than 150 mcg Q12H at a minimum of every 4 days.	For opioid naïve patients, only doses up to 450 mcg Q12H have been evaluated in clinical trials. Total daily doses should not exceed 1800 mcg due to increased risk of QTc prolongation.
Hydrocodone bitartrate extended-release capsule (Zohydro ER®)	Opioid naïve patients: 10 mg Q12H Conversion from other opioids: Convert current regimen to daily hydrocodone equivalents, then initiate Zohydro ER dose at 50% of hydrocodone equivalent Q12H. Zohydro ER may be initiated 18 hours after removal of fentanyl patches.	Titration of Zohydro ER should proceed in increments of 10 mg Q12H every 3-7 days	Single doses of Zohydro ER >40 mg, Zohydro ER 50 mg capsules, or daily doses >80 mg are intended to be used in opioid-tolerant patients only.

Drug	Initial Dose	Titration Schedule	Dose Range
Hydrocodone bitartrate extended-release tablet (Hysingla ER®)	Opioid naïve patients: 20 mg Q24H Conversion from other opioids: Convert current regimen to daily hydrocodone equivalents, then initiate Hysingla ER dose at 75% of hydrocodone equivalent. Hysingla ER may be initiated 18 hours after removal of fentanyl patches.	Titration of Hysingla ER should proceed in increments of 10 mg-20 mg every 3-5 days	Doses of Hysingla ER >80 mg/day are intended to be used in opioid-tolerant patients only. Hysingla ER is designed to be taken no more frequently than every 24 hours.
Hydromorphone hydrochloride extended-release tablets (Exalgo®, others)	Opioid naïve patients: DO NOT USE Conversion from other opioids: Convert oral opioid to appropriate dose based on conversion factor, then administer 50% of calculated daily dose of Exalgo every 24 hours initially. Exalgo bay be initiated 18 hours after removal of fentanyl patches.	Titration of Exalgo should proceed in increments of 25%-50% of current daily dose every 3-4 days. Exalgo should not be administered more frequently than 24 hours	Exalgo is intended only for use in opioid-tolerant patients (defined as patients taking at least 60 mg of morphine daily/equianalgesic dose for ≥1 week).
Methadone tablets (Dolophine®)	Opioid naïve patients: 2.5 mg Q8-12H Conversion from other opioids: Calculate daily MSE, multiply by appropriate conversion factor for daily Dolophine dose, and then divide dose BID or TID (rounding down if necessary). For conversion of parenteral methadone to Dolophine, use a conversion ratio of 1:2.	Dolophine dose adjustments should occur every 3-5 days, and up to 12 days in some patients.	Due to high inter-patient variability in the pharmacokinetics of Dolophine, close therapeutic monitoring of initiation and titration are warranted under supervision of an experienced practitioner.
Morphine sulfate extended-release tablets (MS Contin®, others)	Opioid naïve patients: 15 mg Q8-12H Conversion from other oral morphine: Administer 33% to 50% of patient's daily dose of morphine as MS Contin divided BID or TID respectively Conversion from other opioids: Established conversion ratios from other opioids to MS Contin have not been adequately defined from clinical trials. Initiate with MS Contin 15 mg Q8-12H.	MS Contin dose adjustments should occur every 1-2 days based on patient response at a frequency of twice or three times daily.	Doses of MS Contin >15 mg Q12H in opioid naïve patients may lead to fatal respiratory depression.

Drug	Initial Dose	Titration Schedule	Dose Range
Morphine sulfate extended-release tablets (MorphaBond®)	Opioid naïve patients: 15 mg Q12H Conversion from other oral morphine: Administer 50% of patient's daily dose of morphine as MorphaBond divided BID Conversion from other opioids: Established conversion ratios from other opioids to MS Contin have not been adequately defined from clinical trials. Start with MorphaBond 15 mg Q12H.	MorphaBond dose adjustments should occur every 1-2 days based on patient response.	Doses of MorphaBond >15 mg Q12H in opioid naïve patients may lead to fatal respiratory depression.
Morphine sulfate extended-release capsules (Kadian®, others)	Opioid naïve patients: Kadian has not been evaluated for pain management as an initial opioid analgesic. Conversion from other oral morphine: Administer 50% to 100% of patient's daily dose of morphine as MS Contin divided BID or QD respectively Conversion from other opioids: Established conversion ratios from other opioids to Kadian have not been adequately defined from clinical trials. Initiate therapy with 50% daily MSE as starting dose.	Titrate doses accordingly to provide adequate analgesia while minimizing adverse events at a frequency of once or twice daily. Dosage adjustments should occur every 1-2 days based on patient response.	Kadian doses of 100-200 mg are intended for use in opioid-tolerant patients only.
Oxycodone hydrochloride controlled-release tablets (OxyContin®)	Opioid naïve patients: 10 mg Q12H Conversion from other oral oxycodone: Administer 50% of patient's daily dose of oxycodone as OxyContin divided BID. Conversion from other opioids: Established conversion ratios from other opioids to OxyContin are not adequately defined from clinical trials. Start with OxyContin 10 mg Q12H. OxyContin may be initiated 18 hours after removal of fentanyl patches, using OxyContin 10 mg Q12H for each 25 mcg/hour fentanyl patch.	Titration of OxyContin should proceed in increments of 25%-50% of current daily dose every 1-2 days.	OxyContin doses of >10 mg Q12H, 40 mg, 60 mg, and ≥80 mg are intended for use in opioid-tolerant patients only.

Drug	Initial Dose	Titration Schedule	Dose Range
Oxymorphone hydrochloride extended-release (Opana ER®)	Opioid naïve patients: 5 mg Q12H on an empty stomach Conversion from other opioids: Utilize appropriate conversion factors to obtain Opana ER dosing.	Titration of Opana ER should proceed in increments of 5-10 mg Q12H every 3-7 days.	Doses of Opana ER >5 mg Q12H in opioid naïve patients may lead to fatal respiratory depression.
Tapentadol extended-release tablets (Nucynta ER®)	Opioid naïve patients: 50 mg Q12H Conversion from other opioids: Utilize appropriate conversion factors to obtain Nucynta ER dosing.	Titration of Nucynta ER should proceed in increments of 50 mg Q12H every 2-3 days.	Doses of Nucynta ER >50 mg Q12H in opioid naïve patients may lead to fatal respiratory depression. Do not exceed >500 mg Nucynta ER in 24 hours
Tramadol hydrochloride extended-release capsule (Conzip®)	Opioid naïve patients: 100 mg Q24H Conversion from immediate release tramadol: Administer total daily dose of tramadol as once daily Conzip, rounded down in a 100 mg increment	Titration of Conzip should proceed in increments of 100 mg Q24H every 5 days.	Do not exceed >300 mg Conzip in 24 hours. Due to limitations in dosing, conversion from immediate-release tramadol to Conzip may not be appropriate for some patients. Conzip should not be used with other tramadol products.
Tramadol hydrochloride extended-release tablet (Ultram ER®, others)	Opioid naïve patients: 100 mg Q24H Conversion from immediate release tramadol: Administer the total daily dose of tramadol as once daily Ultram ER, rounded down in a 100 mg increment.	Titration of Ultram ER should proceed in increments of 100 mg Q24H every 5 days.	Do not exceed >300 mg Ultram ER in 24 hours. Due to limitations in dosing, conversion from immediate-release tramadol to Ultram ER may not be appropriate for some patients. Ultram ER should not be used with other tramadol products.
Combination Products			
Morphine sulfate/naltrexone hydrochloride (Embeda®)	Opioid naïve patients: 20 mg/0.8 mg Q24H Conversion from other oral morphine: Administer 50% to 100% of patient's daily dose of morphine as Embeda divided BID or QD respectively Conversion from other opioids: Established conversion ratios from other opioids to Embeda are not adequately defined from clinical trials. Start with Embeda 30 mg/1.2 mg Q24H.	Adjust Embeda doses every 1 to 2 days according to patient response.	Embeda doses >20 mg/0.8 mg Q24H are intended for use in opioid-tolerant patients only.
Oxycodone hydrochloride/ acetaminophen (Xartemis XR®)	Opioid naïve patients: 2 tablets (2 x 7.5 mg/325 mg) Q12H	Titrate Xartemis XR according to patient response to analgesia.	Do not exceed >4000 mg acetaminophen in 24 hours.

Abbreviations: MEU – morphine equivalent units; Q12H - every 12 hours; Q24h - every 24 hours; BID – twice a day; TID – three times a day

Withdrawal/Discontinuation of Long-acting Opioid Agents

Discontinuation or withdrawal of most of the agents is recommended via a gradual taper every 2-4 days (OxyContin, Opana ER, Nucynta ER, MS Contin, Kadian, Embeda, Belbuca, Ultram ER, and Conzip). Recommendations for other agents are presented in Table 3.

Table 3. Recommendations for Discontinuation/Withdrawal[1-8,13-23]

<table>
<tr><th></th><th>Recommendation</th></tr>
<tr><td colspan="2">Transdermal Products</td></tr>
<tr><td>Buprenorphine
(Butrans®)</td><td>• Titrate with lower doses every 7 days
• Consider the use of an immediate release opioid to minimize withdrawal symptoms</td></tr>
<tr><td>Fentanyl (Duragesic®)</td><td>• Decrease dose by 50% every 6 days.
• It is unknown at what dose the medication may be discontinued without withdrawal symptoms
• Serum concentrations fall by ~ 50%, 17 hours after removal of a patch</td></tr>
<tr><td colspan="2">Oral Products</td></tr>
<tr><td>Hydrocodone ER
(Hysingla ER®)</td><td>• Decrease dose < 50% every 2 to 4 days
• Discontinue after a dose of 20 mg for 2 to 4 days</td></tr>
<tr><td>Hydrocodone ER capsule
(Zohydro ER®)</td><td>• Gradual taper every 2-4 days
<table>
<tr><td>20 to 30 mg Q12</td><td>10 mg Q12 on days 1 & 2; then stop</td></tr>
<tr><td>40 to 70 mg Q12</td><td>40 mg Q12 on days 1 & 2
20 mg Q12 on days 3 & 4
10 mg Q12 on days 5 & 6; then stop</td></tr>
<tr><td>80 to 100 mg Q12</td><td>80 mg Q12 on days 1 & 2
60 mg Q12 on days 3 & 4
40 mg Q12 on days 5 & 6
20 mg Q12 on days 7 & 8
10 mg Q12 on days 9 & 10; then stop</td></tr>
<tr><td>> 100 mg Q12</td><td>(no recommendation)</td></tr>
</table></td></tr>
<tr><td>Hydromorphone ER
(Exalgo®)</td><td>• Taper by 25% to 50% every 2 to 3 days
• Discontinue at a daily dose of 8 mg</td></tr>
<tr><td>Methadone
(Dolophine®)</td><td>• Decrease dose by < 10% every 10 to 14 days.
• A high risk of relapse to illicit drug use may occur with discontinuation in patients at risk</td></tr>
<tr><td colspan="2">Combination Products</td></tr>
<tr><td>Oxycodone/acetaminophen
(Xartemis XR®)</td><td>• Decrease dose by ~ 50% every 2 to 4 days</td></tr>
</table>

Abbreviations: Q12 - every 12 hours

Disease Overview

The long-acting opioid analgesics are indicated for the treatment of pain severe enough to require daily, around-the-clock, long-term analgesia for which other agents are inadequate. This recent labeling change (March 2014) was aimed at assisting prescribers in making the best decisions concerning the use of these agents and to prevent problems with their use.[1] Inappropriate prescribing of these agents has been documented. An increase in the use of an opioid for non-medical use in Americans 12 years of age and older has increased from 30 million in 2002 to 35 million in 2010.[2] Emergency department visits associated with nonmedical use of opioid analgesics topped 343,000 in 2009.[3] In 2008, 41% of all drug poisonings (N-36,500) involved opioid analgesics.[4]

The most commonly quoted definition for pain comes from the International Association for the Study of Pain who define pain as, "an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage."[5] Chronic or persistent pain is among the most common complaints in primary care and is poorly and variably defined.[6] Common to most definitions of chronic pain are a duration of pain greater than 3 to 6 months (or beyond normal healing time), a lack of biological value, a lack of responsiveness to specific treatments resulting in an adverse effect on function or well-being.[5,7,8] Once pain is present for 3 months, spontaneous resolution is uncommon. Most patients will continue to experience pain and secondary problems affecting sleep, depression, mood, debilitation, deconditioning and disability arise.[9] Up to 32% of patients with persistent pain report an inability to work.[10] Persistent pain is associated with a point prevalence of 1/3 of the US population.[11] Chronic pain affects 17.5 million U.S. elderly yearly.[12] An Institute of Medicine report recently estimated the cost of chronic pain in the U.S. at $560 to $600 billion split equally between healthcare costs and lost productivity.[13]

Pain is defined as an unpleasant sensation often expressed as both a physical process and an emotional reaction.[24-27] Pain is indicative of physical harm or a disease process and promotes the physiological healing process. Pain is divided into two main categories: acute and chronic. Acute, or nociceptive, pain is a rapid warning relay within the central nervous system (CNS) to the motor neurons as a result of detected physical harm. Nociceptors are found below the skin, tendons, joints and body organs and detect cutaneous, somatic and visceral pain.[25-27] In general, opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are very effective in the treatment of acute pain. Chronic pain is typically not a symptom of a disease process but is a disease process itself.[20,21,48,50] Chronic pain can be defined as inflammatory nociceptive or neuropathic. Inflammatory nociceptive pain is associated with tissue damage while neuropathic pain is produced by damage to the neurons in the peripheral and central nervous systems resulting in sensitization of these systems. The treatment of chronic pain is more challenging, as the cause is not always clear, and often requires several types and combinations of treatments. These treatments may include opioids, NSAIDs, antidepressants, topical agents, cognitive behavioral therapies and/or surgery.[24,48-50]

Clinical Practice Guideline Recommendations for Long-Acting Opioids

The American Pain Society, American Academy of Pain Medicine and the American Geriatrics Society endorse the use of opioids for noncancer pain syndromes.[28,29] Their expanded approval of opioid use for noncancer indications is a result of additional formulations, clinical

experience, changing risk/benefit ratios for alternatives (e.g. COX-2 inhibitors and acetaminophen) and the documentation of efficacy for neuropathic pain.[30]

The World Health Organization (WHO) recommendations include an analgesic ladder addressing pain relief strategies at three levels.[31] Non-opioid pain relievers are used at the lowest level, weak opioid agents (codeine, tramadol) are used for moderate pain and strong opioid agents (morphine, hydromorphone, oxymorphone, methadone and fentanyl) are recommended for the highest level of pain. They recommend patients be switched from one opioid to another (opioid rotation) or the dose adjusted until a satisfactory response is achieved.[32] The American Pain Society does not recommend one long-acting opioid over another for use in the treatment of chronic, non-cancer pain.[32,33] No differences in efficacy or harms between short- or long-acting opioids for treating chronic, noncancer pain were noted by the joint American Pain Society and American Academy of Pain Medicine groups in 2009.[34]

There are many guidelines relating to the appropriate use of opioid therapy. Table 4 presents published guidelines that give specific recommendations concerning the use of long-acting opioids. Many guidelines recommend extensive evaluation, screening for opioid use, informed consent, treatment contracts and implementation of monitoring plans to identify misuse or abuse. Current guidelines recommend opioid selection is based on efficacy, tolerability and patient related variables (e.g. elderly, neuropathic pain, convenience, renal function, constipation).[55,56,57,35] Drug-interactions are considered particularly important when using methadone (with regard to QTc prolongation) and tramadol (with regard to seizures and serotonin syndrome).[55-57] Long-acting agents are not considered appropriate for opioid naïve patients or in the treatment of acute or noncancer pain. Guidelines suggest an upper dosage limit for morphine (or morphine-equivalent doses of other opioids) ranging from 90 mg daily to 200 mg daily.[24] Methadone is most safely used when prescribed by an experienced practitioner aware of the pharmacokinetic/pharmacodynamics issues relating to its use.[24,17,54,55,57,58] Methadone should not be used for acute pain, in opioid-naïve patients or for breakthrough pain.[51,52,55] Most guidelines recommend monitoring EKGs when using methadone.[24,17,54,58,57,55] Most guidelines recommend use of the same long- and short-acting opioid to manage breakthrough.[17,61,54] Long-acting opioids compared with short-acting opioids in the setting of chronic pain are generally considered more convenient, may benefit sleep patterns and may limit abuse or addiction. However, long- and short-acting agents are considered equally efficacious in the management of pain and these purported advantages are not supported by clear evidence.[53,55]

A notably different view is posed by the American Academy of Neurology.[36] They consider the risk to benefit of opioid use for chronic pain to weigh heavily toward harms. Mortality, overdose morbidity, serious adverse events, dependence/addiction, life-long disability and loss of family and community are identified harms.[18] The American Academy of Neurology identified from observational and epidemiological evidence that harms may also include hypogonadism, infertility, erectile dysfunction, immunosuppression, falls and fractures in the elderly, neonatal abstinence syndrome, arrhythmias secondary to QT prolongation with methadone, sleep-disordered breathing, hyperalgesia, overdoses (mortality and morbidity), emergency department visits and unintentional poisoning.[21,18] Current evidence does not clearly demonstrate the ability of opioids to provide long-term pain relief (> 1 year) or improved physical function. Most studies are of less than 16 weeks duration. A recent report reviewing of the clinical efficacy of the opioid

analgesics (2008) postulates the inability to maintain long-term analgesia may reflect the development of hyperalgesia over time.[37]

Table 4: Clinical Practice Guideline Recommendations for Long-Acting Opioids

Opioid Prescribing: a systematic review and critical appraisal of guidelines for chronic pain[38]

• Systematic review of 13 guidelines meeting criteria published between 2007 & 2013
• MOST guidelines agree (expert consensus or observational data)
  o Morphine
  ▪ Avoid morphine equivalent doses > 90-200 mg/day
  o Methadone
  ▪ Prescribed by experienced practitioners familiar with the variable pharmacokinetics and pharmacodynamics
  ▪ Awareness of QTc prolongation and bioaccumulation risks. Some suggest baseline and ongoing EKG determinations

Acute Pain assessment and opioid prescribing protocol. Health care protocol[39]
• Never use long-acting, extended-release opioids for acute pain
Methadone Safety: A clinical practice guideline from the American Pain Society and College of Drug dependence in collaboration with the Heart Rhythm Society[40]

• Never use methadone for breakthrough pain.
• Obtain an EKG *prior* to initiation of methadone therapy in patients with risk factors for QT prolongation, prior EKG with QTc > 450 ms, history suggestive of prior ventricular arrhythmia. EKG within 3 months with QT > 450 ms is sufficient).
  • Consider a baseline EKG in patients not at risk
  • EKG findings of QTc interval ≥ 450 to <500 consider alternate opioids, identify and correct reversible causes of QTc prolongation if methadone is to be used.
  • For opioid-addicted patients with known risk factors for QTc interval prolongation buprenorphine (agonist/antagonist) as a treatment option.
  • Follow-up EKGs
  • In patients with QTc > 450 ms, syncope or risk factors for QTc prolongation, obtain follow-up EKG 2-4 weeks.
  • At a dose of 30-40 mg for those started with low doses and at a dose of 100 mg/day for all.
  • Anytime there are new risk factors or signs or symptoms of arrhythmia.
  • Any follow-up EKG with a QTc > stop immediately reduce methadone and consider an alternative opioid.
• Methadone should be initiated at low doses, titrated slowly with monitoring for sedation. Patients are considered opioid naïve if they have not received opioids in the prior 1-2 weeks.
  • Opioid addiction – initiate with 30-40 mg daily. Titrate by no more than 10mg/day every 3 to 4 days. Hold for sedation
  • Chronic pain – receiving < 40-60 mg morphine equivalents daily, start with 2.5 mg TID and increase by no more than 5 mg/day every 5-7 days. The starting dose for children is 100 ug/kg (max 5mg/dose) every 6-8 hours. Hold for sedation
  • Chronic pain – receiving > 60 mg morphine equivalents daily, start with < 75-90% of the calculated equianalgesic dose; not more than 30-40 mgs daily, titrating by 10 mg every 5-7 days. Hold for sedation.
  • Face to face or phone assessment for AEs after 3-5 days and 3-5 days following every dosage increase.
  • Monitor for common opioid adverse effects/toxicities

Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain[34]
• Insufficient evidence to recommend short-acting vs long-acting opioids • Insufficient evidence to recommend as needed vs round-the-clock dosing of opioids • Methadone should be initiated and titrated slowly by clinicians experienced with its pharmacokinetics and pharmacodynamics
VA/DOD Clinical Practice Guideline for the management of chronic multi-symptom illness[41]
• Recommend against long-term use of opioids
American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible prescribing in chronic non-cancer pain: part 2 – guidance[42]
• There is no difference in efficacy or adverse effects with short- or long-acting opioids • Methadone is recommended for use after failure of other opioid therapy and by experienced clinicians

Guidelines for prescribing opioids to treat pain in injured workers Washington state[43]
• Use beyond the acute phase only is clinically meaningful improvement in function occurs. • Do not use methadone for breakthrough pain • Do not use long-acting opioids for acute pain, in opioid naïve patient or for post-operative pain (unless the patient received the drug prior) • Use caution with tramadol in patients at risk of seizures or taking drugs which can cause seizures • Use caution with methadone for pain due to non-linear pharmacokinetics, unpredictable clearance and potential for drug-drug interactions. Use extreme caution when using this drug for pain.
Palliative care for the patient with incurable cancer or advanced disease. Part 2: pain and symptom management[44]

• Once a stable, short-acting opioid regimen is achieved, long-acting agents are preferred for better compliance and sleep.
• Opioid selection preferences based on patient-related variables
  • Constipation – transdermal fentanyl or methadone
  • Renal failure – transdermal fentanyl or methadone (avoid morphine)
  • Compliance/convenience – time release formulations of morphine, hydromorphone or oxycodone
  • Neuropathic pain – oxycodone or methadone

Assessment and management of chronic pain[45]

• Pain specific notations
  • Neuropathic pain after initial therapies fail – methadone, tapentadol and tramadol are preferred
• Drug specific notations
  • Morphine – may be toxic in renal insufficiency
  • Methadone – reserve use for experienced clinician
  • Monitor QTc interval at baseline, in 30 days and annually (more often if the dose > 100 mg/day)
  • Tramadol – caution for serotonin syndrome
  • Oxycodone – caution with concomitant CYP3A4 inhibitors which may increase oxycodone concentrations, cause respiratory depression and potentially death

Pain management in the long-term care setting[58]
• Opioids may be used for neuropathic pain • Fentanyl patches must be used in non-opioid naïve patients already receiving opioid therapy and tolerating an equianalgesic dose of at least 25 mcg/hr fentanyl. Avoid heat and monitor closely in the presence of fever. • Avoid or use with caution in debilitated patients, Pharmacokinetic differences may result from poor fat stores, muscle wasting and altered clearance. • Doses of transdermal buprenorphine should not exceed 20 mcg/hr due to the risk of QTc interval prolongation. Avoid external heat and monitor for respiratory depression. • Methadone metabolism and elimination half-life may be prolonged and variable, multiple drug interactions are possible and severe adverse events and death may occur with moderate doses. QTc interval prolongation may occur especially in patients with cardiac disease or take QTc interval-prolonging medications. An experienced practitioner is recommended
Guideline for the evidence-informed primary care management of low back pain[46]
• Long-acting opioids establish steady-state blood/tissue levels which may reduce the experience of pain from medication withdrawal from short-acting opioids
Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults (NICE CG140)[47]
• Starting treatment options include sustained-release morphine • First-line treatment for patients with advanced/progressive disease on strong opioids is sustained-release morphine. • Transdermal patch formulations are not first-line maintenance therapy. If oral therapy is not possible and under a specialist advise, consider transdermal therapy
VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain[35]

• Choice of agent should be individualized considering drug interactions, adverse events, formulation/dosing, patient preference, ease of administration, risk for use/misuse
• Continuous chronic pain treatment is recommended with a long-acting agent such as controlled-release morphine or methadone.
  • Risk with conversion to/from methadone as conversion ratios vary with dose
• Fentanyl: Recognize the risks of fentanyl patches
  • Opioid-tolerant patients only

• Variable absorption which is increased with heat or exercise
Opioids and the Management of Chronic Severe Pain in the Elderly: Consensus Statement of an International Expert Panel with Focus on the Six Clinically Most Often Used[48]

• Cancer Pain: No well-designed studies in the elderly are available
  • Transdermal fentanyl and buprenorphine appear effective with low toxicity and good tolerability
• Non-cancer pain: No well-designed studies in the elderly are available
  • Drug choice should be based on safety and tolerability
• Neuropathic pain
  • Earlier addition of an opioid to therapy may be beneficial
  • Buprenorphine demonstrates a particular benefit
  • Higher doses of opioids are often required
  • Buprenorphine has a respiratory depression ceiling and may be the preferred agent in the elderly

Adult Cancer Pain in Oncology[49]
• Use extended release or long-acting agents for chronic persistent pain to provide background analgesia. • Prefer the same opioid in a short-acting formulation for breakthrough pain • Use transmucosal fentanyl only in opioid-tolerant patients • Consultation with a specialist is recommended for the use of methadone
Managing chronic non-terminal pain in adults including prescribing controlled substances[50]
• For continuous treatment scheduled, long-acting opioids (morphine ER, methadone, buprenorphine) are preferred. OxyContin has a higher misuse, diversion risk. • Chronic opioids are not indicated for central pain syndrome

Abbreviations: EKG – electrocardiogram

Pharmacology

The opioid analgesics are a class of agents which stimulate opioid receptors and produce pain relief without producing loss of consciousness.[24,51] These agents may be naturally occurring, semisynthetic, or synthetic and can produce equianalgesic effects, which allows for conversion between agents and routes of administration. The opioid analgesics are divided into categories based on receptor subtype and potency.[20,21] These agents can also be divided into groups based on onset and duration of action: long-acting, short-acting, and rapid-onset.

Opioid analgesics bind to receptors within and without the central nervous system (CNS).[24,51] Opioid analgesia is mediated by mu, delta, and kappa opioid receptors. Activation of the mu-opioid receptor is most associated with both the analgesic and euphoric effects associated with opioid use. Mu receptors are located within the CNS, gastrointestinal (GI) tract and peripherally in association with sensory nerves and mast cells.[24,51] Activation of opioid receptors is variable and results in differing responses between patients. Renal and hepatic function, age and genetic factors also affect an individual's response to opioids.[52,53]

Opioids are classified as full agonists, partial agonists or mixed agonist-antagonists.[54,20,21] Full mu-opioid receptor agonists produce analgesia without a ceiling effect.[20,21] These agents do not reverse or antagonize the effects of other full agonists given simultaneously. Codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, methadone, morphine, oxycodone, oxymorphone, tapentadol and tramadol are classified as full agonists with hydrocodone, tramadol and tapentadol often considered weak, full opioid-agonists.[54] Although buprenorphine has been classified as a partial-agonist this label is currently being challenged.[55,56] In vitro assays in animal models classified buprenorphine as a partial agonist, implying less analgesia is produced. Buprenorphine displays full agonist or partial agonist effects at different signal transduction pathways.[55] Clinically, a dose-response ceiling is not observed with buprenorphine. Experts

evaluating the evidence for buprenorphine consider it a full agonist in clinical practice.[56] Morphine, the oldest opioid, originally extracted from poppy straw or opium remains the opioid agent against which all analgesics are compared.[24,51]

Tramadol has a dual mechanism of analgesic action. Low affinity binding of the parent compound and higher binding of the O-demethylated metabolite to mu-opioid receptors produces analgesia, while also inhibiting the reuptake of norepinephrine and serotonin in the central nervous system.[17,57] Methadone acts as an agonist at mu- and delta-opioid receptors, an antagonist at N-methyl-D-aspartate (NMDA) receptors and blocks pre-synaptic serotonin uptake.[17,57] Tapentadol acts as an agonist at mu-opioid receptors inhibiting norepinephrine uptake.[17,57,58] Naltrexone is an opioid receptor antagonist with highest activity at the mu-opioid receptor. It is virtually devoid of agonist activity and competitively binds to receptors to inhibit opioid effects.[17,57]

Pharmacokinetics[1-8,13-23]

The pharmacokinetics of the long-acting opioids is presented in Table 5. Most long-acting opioids agents have active metabolites. Renal elimination of the unchanged drug and active- and inactive-metabolites is the most common mechanism of elimination. The elimination half-lives of agents vary from 4.5 to 59 hours. Changes to the medication regimen should be undertaken only when a steady state (3-5 half-lives) has been achieved with special attention to renal and hepatic function as well as the geriatric population where drug exposures may be greater resulting in a greater risk of adverse events.

Table 5: Pharmacokinetics[1-8,13-23]

Agents	Bioavailability	Half-life	Active Metabolite	Renal Excretion
Transdermal Products				
Buprenorphine Transdermal system Butrans®	~15%	~26 hours	Norbuprenorphine	27%
Fentanyl Transdermal Duragesic®	92%	20-27 hours	None	75% as metabolites; 7-10% as unchanged drug
Oral Products				
Buprenorphine oral buccal film Belbuca®	46-65%	~27.6 hours	Norbuprenorphine	27%
Hydrocodone ER capsules Zohydro ER®	~19-45%	8 hours	Norhydrocodone, Hydromorphone	Renal (unspecified)
Hydrocodone ER tablets Hysingla®	~36%	~7-9 hours	Norhydrocodone, Hydromorphone	Renal (unspecified)
Hydromorphone ER® Exalgo®	24%	~11 hours	Hydromorphone-3-glucuronide	75%; 7% unchanged
Methadone Dolophine®	36% to 100%	8-59 hours	None reported	Unspecified
Morphine controlled release MS Contin®	<40%	~15 hours	Morphine-6-glucuronide, morphine-3-glucoronide (neurotoxic)	90%; 2-12% as unchanged drug
Morphine extended release capsule Kadian®	<40%	11 to 13 hours	Morphine-6-glucuronide, morphine-3-glucoronide (neurotoxic)	Renal (unspecified); 10% unchanged
Morphine extended-release tablet MorphaBond®	<40%	1.5 to 4.5 hours	Morphine-6-glucuronide, morphine-3-glucoronide (neurotoxic)	Renal (unspecified); 2-12% unchanged)
Oxycodone CR OxyContin®	60-87%	4.5 hours	Noroxycodone, Noroxymorphone	Renal (unspecified); 19% unchanged; 50% conjugated oxycodone; <14% conjugated oxymorphone
Oxymorphone ER Opana ER®	10%	9.4 to 11.3	6-OH-oxymorphone	90%; ≤ 1% unchanged drug; <1% 6-OH-oxymorphone
Tapentadol ER Nucynta ER®	32%	5 hr	None	70%; 3% unchanged drug
Tramadol ER capsule Conzip®	85-90%	6-8 hour	O-desmethyl tramadol	60%; 30% unchanged drug
Tramadol ER tablet Ultram ER®	85-95%	7.9-8.8 hours	O-desmethyl tramadol	60%; 30% unchanged drug
Combination Products				
Morphine/naltrexone Embeda®	<40%	29 hours	Morphine-6-glucuronide, morphine-3-glucoronide (neurotoxic)	90; %10% unchanged
Oxycodone ER/acetaminophen Xartemis XR®	60-87%	~5.8 hours	Noroxycodone, Oxymorphone	Renal (unspecified); 19% unchanged; ≤50% conjugated oxycodone; ≤14% conjugated oxymorphone

Special Populations
Recommendations for use in special populations are presented in Table 6.

Pediatrics – Only transdermal fentanyl and oral OxyContin are approved for use in children. Fentanyl transdermal system may be used in opioid-tolerant patients as young as 2 years old and OxyContin is approved for use in opioid-tolerant children 11 years and older.[4,5]

Geriatrics – No consensus guidelines or systematic reviews address the efficacy or safety of long-acting opioids in the elderly. Accumulation of metabolites and greater systemic exposure in older patients may be minimized with the use of hydromorphone or buprenorphine.[6,20,48] An advantage of buprenorphine is its documented ceiling on respiratory depression.[48,59] Clinical evidence in older adults found lower rates of nausea and vomiting with tapentadol ER compared with OxyContin while equianalgesic activity was maintained.[98] Although tramadol is a less potent opioid with additional mechanism(s) of action, constipation, nausea and dizziness occurred in the elderly population a similar incidence to other opioids (>20% each).

Pregnancy/Lactation – No agent has sufficient evidence to support use in pregnancy or lactation. Opioids do cross to breast milk, often in low concentrations and the risk of harm to the infant vs the need for the use of a strong opioid for analgesia should be assessed cautiously.

Renal dysfunction - Reductions in the elimination of unchanged drug or active metabolites may result in increased concentrations and accumulation of renally eliminated drugs. Accumulation of the active morphine metabolite, morphine-3-glucoronide, may result in neurotoxicity. Methadone and fentanyl are preferred opioids in this setting (including dialysis) although they are not typically considered first-line agents. Morphine and hydromorphone are considered first line with dose adjustment and careful monitoring in patients with mild to moderate dysfunction.[60]

Hepatic dysfunction – Major transformation of opioids occurs in the liver. Reductions in hepatic function result in higher levels of parent drug with repeat administration. Fentanyl metabolism is affected more by liver blood flow than hepatic function and may be preferred in this setting. Reductions in CYP metabolism and glucuronidation result in higher systemic exposures of morphine, oxymorphone, hydromorphone and oxycodone. Methadone is considered unsafe for use with severe hepatic dysfunction and may accumulate in mild to moderate dysfunction.[60]

Table 6: Special Populations

	Renal Dysfunction	Hepatic Dysfunction	Pregnancy	Lactation (excreted in breast milk)	Pediatric	Geriatric
Transdermal Products						
Buprenorphine Transdermal system Butrans®	Studies document no accumulation	Not well studied; in mild to moderate impairment pharmacokinetics appear unchanged	C	Yes Use not advised	Not established	Use with caution
Fentanyl transdermal system Duragesic®	Use with caution	Use with caution	C	Yes Do not use	Approved in opioid-tolerant children ≥ 2 years of age (receiving ≥ 60 mg MEU/day) Age ≤ 5 years serum plasma concentrations were twice that in adults	Use with caution
Oral Products						
Buprenorphine Oral buccal film Belbuca®	Studies document no accumulation	Moderate: No change Severe: Reduce the starting dose and the titration dose by 50%	C	Yes Monitor infant for sedation and respiratory depression	Not established	Pharmacokinetics did not differ between younger and older adults, however, adverse events were more common in clinical studies in older patients
Hydrocodone ER Hysingla® Zohydro ER®	Initiate therapy with lower doses and monitor	Initiate therapy with lower doses and monitor; especially in the presence of renal dysfunction	C	Yes Consider risk/benefit of discontinuing medication or nursing	Not established	Initiate therapy with lower doses and use with caution
Hydromorphone ER Exalgo®	Moderate (40-60 mL/min): Initiate therapy with 50% normal dose Severe (< 30 mL/min) Initiate with 25% normal dose. Alternate therapy may offer more flexibility. Monitor closely for respiratory/CNS depression	Moderate: Initiate therapy with 25% of the normal dose. Monitor for respiratory/CNS depression. Severe: Not studied, not recommended	C	Yes Do not use	Not established	May be more sensitive to effects; monitor closely during initiation and titration
Methadone (Dolophine®, Diskets Disperible, Methadone HCl Intensol, Methadose)	Use caution: Lower initial doses, longer dosing intervals and titrate more slowly	Use caution: lower initial doses, longer dosing intervals and titrate more slowly	C	Yes Monitor infant for sedation	Not established	Use with caution

Morphine Long-acting products MorphaBond®, Kadian®, MS Contin® (*No differences reported for Embeda with naltrexone*)	Pharmacokinetics affected; no dosing recommendation provided; use caution	Pharmacokinetics affected; no dosing recommendation provided; use caution	C	Yes Consider risk/benefit	Not established	Use with caution
Oxycodone controlled-release tablets OxyContin®	Initiate the dose with 33-50% of the normal dose and titrate	Initiate the dose with 33-50% of the normal dose and titrate	C	Yes Use not advised	Indicated for opioid-tolerant* patients 11 years and older *receiving opioids for at least 5 days, with the most recent 2 day doses of 20 mg/day of oxycodone-equivalents	Initiate the dose with 33-50% normal dose and titrate
Oxymorphone extended-release Opana ER®	Initiate therapy with lower doses and monitor	Opioid naïve + mild impairment: Initiate therapy with 5mg dose and monitor closely Opioid tolerant: initiate therapy at 50% equivalent dose Moderate/Severe impairment: Contraindicated	C	Unknown	Not established	Initiate therapy with a 5 mg dose. Patients on prior opioid therapy: initiate therapy with 50% of the usual dose and titrate slowly.
Tapentadol extended-release oral tablets Nucynta ER®	Severe impairment (CrCl < 30 mL/min): Not recommended	Moderate impairment: Reduced dosing recommended Severe Impairment: Not recommended	C	Yes Consider risk/benefit of discontinuing medication or nursing	Not established	Due to the effects of age on renal and hepatic function initiate therapy at the lower range of normal dosing
Tramadol extended-release Ultram®	Moderate impairment (CrCl 30-50 mL/min): M1 metabolite concentrations increase 20-40% Severe impairment (CrCl < 30 mL/min): Do not use	Metabolism of tramadol and the M-1 metabolite are decreased with advanced cirrhosis. Due to limited dosing flexibility, tramadol is not recommended in hepatic dysfunction No specific recommendation?	C	Not recommended	Not established Not recommended	Use with great caution in those > 75 years of age
Combination Products						
Oxycodone ER/acetaminophen Xartemis XR®	Initiate therapy with one tablet and titrate	Initiate therapy with one tablet and titrate	C	Yes Consider risk/benefit of discontinuing medication or nursing	Not established	Use with caution

Abbreviations: Pregancy category C – Animal studies demonstrate fetal risk but there are no adequate or well-controlled studies in humans. Potential benefit should be weighed against potential risks in pregnant women.

Methods

A literature search was conducted to identify articles evaluating long-acting opioid agents, searching the MEDLINE database (1950 – 2016), EMBASE database (1966-2016), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English, are included.

Systematic Evidence

A systematic review published by the Agency for Healthcare Research and Quality asked and answered a number of questions concerning long-acting opioids.[61] A number of their findings tangentially apply to this review and are included in Appendix 1. The finding directly related to a consideration of the safety and efficacy of the long-acting opioid agents follows. The review included 39 studies including large cohort studies in which patients received long-term, long-acting opioid therapy for chronic cancer or noncancer pain.[61]

Efficacy Questions

Do any long-acting opioids have advantages over other agents with respect to efficacy endpoints relating to pain, physical function or quality of life?

No differences in well performed studies have documented the superiority of one long-acting opioid agent over another for pain relief, pain intensity, quality of life, supplemental analgesic use, work loss or quality of life. [61] The utility of the available data is limited because treatment arms were titrated to pain control yielding non-equivalent opioid dosages. Three randomized head to head trials compared long-acting opioids and found no differences in outcomes relating to pain or function. Transdermal fentanyl and sustained-release morphine performed similarly in 680 patients with chronic low back pain over 13 months with regard to pain relief, pain intensity, quality of life, supplemental analgesic use, work loss and quality of life.[62] A large, fair-quality trial comparing sustained-release tapentadol vs sustained-release oxycodone in 1,117 patients with chronic low back or osteoarthritis found no difference in pain intensity over 1 year.[58] A small study of 46 patients with chronic, noncancer pain found no difference in pain intensity, pain relief, quality of life or function over 1 year when treated with transdermal buprenorphine or transdermal fentanyl.[63]

A retrospective cohort study using national pharmacy data from the Veteran's Affairs system analyzed over 100,000 patients receiving either long-acting morphine (N=79,938) or methadone (N=28,554).[64] Methadone patients treated for opioid dependence or palliative care we excluded from the analysis. Methadone patients were younger and healthier with more psychiatric diagnosis while the morphine patients were older with more comorbidities. A propensity-stratified analysis was implemented to control for these variables. Use of methadone was associated with a lower mortality risk from accidental ingestion than long-acting morphine. (Adjusted HR 0.56, 95% CI 0.51 to 0.62). The study is limited by statistically significant baseline characteristic differences and residual confounding by indication.[64] This study suggests that methadone may be used safely to treat pain in some populations while in others the risks associated with the variable pharmacokinetics, pharmacodynamics and effects on QTc interval prolongation may be more problematic.

Efficacy Question – Are transdermal opioids superior to long-acting, oral opioids?

A systematic review identified four trials (n=425) evaluating transdermal fentanyl or buprenorphine with long-acting morphine in moderate to severe cancer pain.[65] A significantly lower incidence of constipation was noted with the transdermal preparations compared with oral, long-acting morphine (OR=0.38; p<0.001). Patients' also preferred the transdermal patch to oral tablets (OR = 0.43; p = 0.014). Overall, gastrointestinal, neurological, CNS adverse events and withdrawal rates were similar between treatments.[65]

A number of other systematic reviews were identified often with overlapping studies. Conclusions, briefly, from these reviews are found below.

A systematic review by Noble et al, (17 trials, N=3079) of patients treated with opioids for noncancer pain for ≥6 months report oral opioids were successful in reducing pain 63.4% (standardized mean difference 1.99; 95% CI 1.17 to 2.80) while there was insufficient data concerning transdermal therapy. Discontinuation rates were approximately twice a high with oral vs. transdermal therapy both for discontinuation due to adverse events (32.5% [95% CI, 26.1% to 39.6%] vs 17.5% [95% CI, 6.5% to 39.0%], respectively) and insufficient response (11.9% [95% CI, 7.8% to 17.7%] vs 5.8% [95% CI, 4.2% to 7.3%], respectively). Signs of opioid addiction and abuse were low at 0.05% and 7.3%, respectively.[66]

A systematic review by Clark et al, (8 trials, N=1220) of patients with pain, requiring a strong opioid reported no differences in pain scores with transdermal fentanyl or sustained release morphine. Fentanyl was associated with significantly fewer adverse events, serious adverse events, nausea and somnolence (p<0.001 for all).[67]

A systematic review by Pedersen et al, (6 trials, N=1066) of patients receiving opioids for low-back pain and/or osteoarthritis found no differences between IR and ER formulations of oxycodone/acetaminophen, Dihydrocodeine, tramadol or tapentadol with respect to pain intensity, use of rescue analgesia, global assessments of efficacy, sleep quality or disturbances or functional capacity scores. Although adverse events were not a primary outcome measure in any study, nausea was more common with short-acting opioids while depression and confusion were more common with long-acting opioids.[68]

A systematic review by Caraceni et al, (16 trials and 1 meta-analysis, N=2487) reported long-acting morphine and methadone and fentanyl transdermal provided equivalent pain relief. Constipation was less common with fentanyl transdermal and methadone was found more sedation than long-acting morphine.[69]

A systematic review by Wiffen et al, (54 trials, N=3749) found equivalent pain relief between long-acting morphine and oxycodone ER/CR, fentanyl transdermal, hydromorphone ER, methadone, morphine immediate release, MS Contin, Avinza and Kadian. Methadone was associated with more adverse events than long-acting morphine which produced more sedation and constipation than transdermal fentanyl.[70]

A Cochrane review of 48 trials and meta-analysis (N=3293) of patients receiving hydromorphone and strong opioids for acute or chronic pain reported no differences in efficacy between hydromorphone extended-release and either oxycodone or morphine extended release (p

value not presented). Pain relief was superior with immediate release vs. extended-release hydromorphone. Withdrawal symptoms occurred more commonly with extended-release morphine than extended-release hydromorphone. Fentanyl transdermal provided anxiety relief greater than hydromorphone extended-release.[71]

A systematic review by Tassinari et al, (4 trials, N=425) of patients with moderate to severe cancer pain comparing transdermal opioids to slow-release oral morphine reported patients prefer transdermal therapy. Rates of withdrawal symptoms or a change to another opioid were similar between groups. Incidence of any adverse event, neurological, nausea or gastrointestinal were similar between groups. Transdermal opioids were associated with a reduced odds ratio for constipation compared with oral opioids (OR=0.38, p<0.001).[65]

Overall, systematic evidence suggests the opioids to produce similar pain relief. Transdermal products appear to have some preference over oral agents and an advantage with respect to fewer gastrointestinal adverse events and lower withdrawal rates.

Comparative Trials

Butrans Transdermal System® (Buprenorphine)

Approval of the transdermal (TD) buprenorphine system was based on four unpublished, 12-week, double-blind trials performed in opioid-naïve and opioid-experienced patients with chronic, severe, low back pain or osteoarthritis. [20,72] The primary endpoint was pain scores. Two trials (N=1,160 and N=1,024) demonstrated the efficacy of buprenorphine TD in patients with chronic, low back pain. The average pain score over 24-hours at 12 weeks favored buprenorphine TD 20 mcg/hr and oxycodone immediate-release compared to buprenorphine TD 5 mcg/hr (p<0.001 for both). In the second trial both buprenorphine TD 10 and 20 mcg/hr were superior to placebo (95% CI, -1.02 to -0.14; p=0.01). Two trials failed to demonstrate a benefit with buprenorphine. In one trial of 134 patients with low back pain treated with either oxycodone/acetaminophen or placebo or buprenorphine, treatment revealed no difference in pain scores between either treatment or placebo at 12 weeks (FDA analysis). The second trial in patients with osteoarthritis (N=418) failed to find a statistically significant difference in average pain score over 24 hours at the completion of therapy between oxycodone immediate release, buprenorphine TD 20 mcg/hr or buprenorphine 5 mcg/hr.

Exalgo® (Oxymorphone)

Oxymorphone ER 20 or 40 mg was compared to oxycodone ER 20 mg or placebo every 12 hours for 4 weeks in 491 patients with osteoarthritis. No differences between treatment groups were found for pain intensity by visual analog scale and at week 3 pain, physical function, stiffness or composite index for either dose of the oxymorphone or oxycodone. Sleep quality was superior to placebo at 3 weeks with oxymorphone ER 20 mg and at 4 weeks for both oxymorphone ER 40 mg and oxycodone CR 20 mg (all values p<0.05).[73]

In 213 patients with chronic, moderate to severe low back pain, oxymorphone ER was compared with oxycodone CR or placebo every 12 hours. Patients achieving pain control with an opioid (mean daily dose oxymorphone ER 79.4 mg or oxycodone CR 155 mg) were randomized to continue therapy or receive a placebo. Oxymorphone ER and oxycodone CR each demonstrated a statistically significant improvement in least square mean pain intensity scores compared with

placebo (P<0.001 for both). Sleep quality was less affected with oxymorphone ER than placebo but the difference was not significant. Constipation and sedation were the most common adverse events noted with both opioids.[74]

OxyContin® (oxycodone)
A trial of 167 patients with moderate to severe osteoarthritis pain uncontrolled with a NSAID compared oxycodone CR to oxycodone IR/acetaminophen for 30 days. Patients were titrated to response with oxycodone IR over 30 days. The titrated, open-label, mean daily dose of oxycodone IR was 40 mg. Stabilized patients were randomized to receive 10 mg oxycodone IR/acetaminophen QID or oxycodone CR 20 mg Q12. During double-blind treatment (n=107), improvements in pain intensity and quality of sleep were comparable between oxycodone treatment groups and significant for both treatments compared with placebo ($p \leq 0.05$). Oxycodone CR was associated with less dry mouth (p=0.03) and nausea (p=0.03) than oxycodone IR/acetaminophen. The global quality of sleep was maintained with both treatments when compared with baseline and each was superior to placebo at 30 days ($p \leq 0.05$).[75]

Duragesic Transdermal System® (fentanyl)
Terminal cancer patients (n=47) with pain were titrated to a stabilized, effective dose of immediate-release morphine and then switched to an equivalent dose of controlled-release morphine of transdermal fentanyl for a 14-day treatment period. Treatment of breakthrough pain with immediate-release morphine was allowed. Significant (p<0.05) improvements from baseline were noted for pain intensity, pain frequency, mood, insomnia and quality of sleep for both the titration period and treatment period. Only activity status did not improve significantly. Drowsiness was the most common adverse event, reported in 6 controlled-release morphine-treated and 5 transdermal fentanyl-treated patients. No differences in adverse events were noted between treatment groups.[76]

Transdermal fentanyl was compared with sustained release morphine in an open-label study in 202 cancer patients requiring strong opioid analgesia in the United Kingdom. Patients received 15 days each, transdermal fentanyl or sustained-release morphine. No differences in pain control were reported between treatment groups by either the Memorial Pain Assessment Care or European Organization for Research and Treatment of Cancer (EORTC) pain scores. Constipation and daytime drowsiness were significantly less common with fentanyl (p<0.001 and p=0.015 respectively). Morphine was superior to fentanyl with respect to sleep disturbances (p=0.004) and sleep duration (p=0.008). The treatments did not differ in WHO performance status or EORTC global quality of life scores. A greater percentage of patients preferred treatment with transdermal fentanyl to sustained-release morphine (p=0.037).[77]

A cross-sectional study compared quality of life, patient satisfaction and side effects in 504 predominantly stage IV/D cancer patients with pain. Eligible patients were outpatients receiving at least two weeks of therapy with sustained-release morphine or transdermal fentanyl. Fentanyl patients were older (P<0.001) and had lower functioning and well-being scores (p=0.001). Validated scales were used for all assessments. Patients reported increased satisfaction with transdermal fentanyl (p=0.035), a lower frequency of side effects (P<0.002) and lower impact of side effects (p<0.001). There were no differences between treatment groups for measures of pain intensity and sleep adequacy.

Nucynta ER® (tapentadol)
The long-term efficacy and tolerability of tapentadol ER vs. oxycodone CR was assessed by pooling data from 3 studies in patients ≥ 75 years of age (n=210). Patients had either moderate to severe osteoarthritis of the knee or chronic low back pain and were titrated to a stable dose of tapentadol ER. Assessments were made over a 12-week maintenance period. Treatment included placebo, tapentadol ER (100-250 mg BID) or oxycodone CR (20-50 mg BID). Active treatment groups performed similarly in reducing pain intensity at week 15 compared with baseline. Treatment-emergent adverse events and the composite measure for nausea/vomiting were lower with Tapentadol ER compared to oxycodone CR ($p \leq 0.0206$ for both).[78]

Conversion to tapentadol ER or morphine SR from other strong opioids was assessed using a conversion ratio of tapentadol ER:oxycodone:morphine:fentanyl = 10:2:3:0.03 in 100 Japanese patients with moderate to severe, well-controlled, chronic cancer pain. Pain control was maintained after conversion in 85% of tapentadol ER treated and 98% of morphine SR treated patients after 1 week. Treatment emergent gastrointestinal adverse effects were more common with morphine SR than tapentadol ER (54% vs 38% overall; 20% vs 12% for constipation and 26% vs 6% for vomiting).[79]

Tapentadol ER was compared to oxycodone CR over 1 year in 1,117 patients with chronic knee or hip osteoarthritis or low back pain. Pain intensity scores were similar at baseline and endpoint with no difference found between the two treatment groups. Treatment emergent adverse events (nausea, vomiting, constipation) occurred sooner with oxycodone CR than tapentadol ER ($p<0.001$). Treatment emergent gastrointestinal adverse events leading to discontinuation of therapy were more common with oxycodone CR than tapentadol ER (21.5% vs 8.6%).[58]

Tapentadol ER was compared to oxycodone CR and placebo in the management of moderate to severe chronic low back over 12 weeks, following a 3 week titration period. Patients (n=981) were randomized 1:1:1 to tapentadol ER 100-250 mg BID, oxycodone CR 20-50 mg BID or placebo. Both tapentadol ER and oxycodone CR reduced average pain intensity at week 12 and throughout the maintenance period compared with placebo ($p<0.001$ for both). Treatment emergent gastrointestinal adverse events were less common with tapentadol ER compared to oxycodone CR (placebo, 26.3%; tapentadol ER, 43.7%; oxycodone CR, 61.9%). Tapentadol ER was associated with lower odds of experiencing constipation and the composite of nausea/vomiting compared to oxycodone CR ($p<0.001$ for both).[80]

Tapentadol ER was compared to oxycodone CR or placebo in patients with chronic, severe, osteoarthritis pain. A total of 1030 patients were randomized to tapentadol ER 100-250 mg daily, oxycodone CR 20-50 mg BID or placebo and titrated for 3 weeks to pain relief. Tapentadol ER and oxycodone CR significantly reduced pain intensity at baseline and during the maintenance period while only tapentadol ER demonstrated significant reduction in pain intensity at week 12. An improvement in pain intensity of ≥ 50% was achieved in 32% of tapentadol ER patients and 17.3% of oxycodone CR patients (no p value provided). Treatment emergent adverse events and gastrointestinal-related adverse events were least common with tapentadol ER. [81]

Embeda® (morphine/naltrexone)

Patients with osteoarthritis pain (N=113) were randomized to receive Embeda (morphine sulfate and naltrexone hydrochloride) extended-release capsules or morphine ER (Kadian) twice a day. Various measures of efficacy (pain scores, Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index; Patient Global Assessment of Medication) did not differ between Embeda and Kadian demonstrating equivalent efficacy in the treatment of osteoarthritis pain.[82]

The long-term safety of Embeda was documented in a 12-month trial in patients (N=465) with chronic, moderate to severe pain. One hundred and sixty patients completed the study. Patient pain diaries demonstrated a reduction in pain with Embeda. Adverse events were reported in 81.3% of patients, most commonly constipation (31.8%) or nausea (25.2%). Discontinuations (30%) occurred most commonly in the first month as a result of adverse events (23.7%). Serious adverse events were reported in 7.1% of patients. Once case of gastrointestinal inflammation and colitis was consider possibly study-drug related. Less than 5% of patients had Clinical Opiate Withdrawal Scale (COWS) scores consistent with mild withdrawal symptoms.[83]

Dolophine® (methadone)
Methadone was compared to transdermal fentanyl and oral morphine ER in 108 cancer patients with moderate pain unresponsive to current opioid therapy over 4 weeks. Oral morphine was used during titration for breakthrough pain. Opioid switching was required in 14 patients (5-morphine ER, 5-transdermal fentanyl, 4-methadone). Pain relief was similar in each of the three treatment groups. The opioid escalation index was lower with methadone ($p<0.0001$) but more up and down dosage adjustments were required. Adverse events were similar between treatment groups.[84]

MS Contin® (morphine)
Morphine ER (Avinza, *no longer marketed*) daily was compared to morphine CR (MS Contin) twice daily in 295 patients with chronic, severe osteoarthritis pain unresponsive to NSAIDs/acetaminophen in a 4-week, randomized, double-blind trial.[85] Patients received Avinza 30 mg daily either in the morning or evening, MS Contin 15 mg twice daily or placebo twice daily. Reductions in pain from baseline were noted with active treatments only. The percent change from baseline pain using the WOMAC (Western Ontario and McMaster Universities Pain Index) score for placebo, Avinza-morning, Avinza-evening and MS Contin were (Least squares mean ± SE, -4.35 ± 4.3, 17.2 ± 4.2, -20.1 ± 4.2 and -18.4 ± 4.2, respectively). Reductions in arthritis pain intensity and physical function favored active treatment vs. placebo but did not achieve statistical significance. The overall quality of sleep was superior with each treatment group compared with placebo. The Avinza-morning and Avinza-evening regimens were not different and both superior to MS Contin.[85] Avinza-morning additionally demonstrated improvement in reducing the need for sleep medications, increasing the hours of sleep and reducing trouble falling asleep compared with placebo. Avinza-evening significantly improved the duration of sleep and MS Contin significantly improved trouble falling asleep vs. placebo.[85] The most common adverse events (constipation 49%, nausea 21%, somnolence 16% and dizziness 10%) occurred similarly between active treatment groups.[85]

An open-label, randomized trial of 220 patients naïve to sustained-release opioids with chronic, moderate to severe low back pain evaluated morphine ER (Avinza) daily compared to

oxycodone CR (OxyContin) twice daily for 8 weeks (ACTION trial).[86] Morphine ER and oxycodone CR both improved sleep and provided pain relief compared to baseline ($p<0.05$). Morphine ER was superior to oxycodone CR in improving pain control ($p=0.002$) and minimizing the need for breakthrough pain medications ($p<0.0001$). Pain control was achieved with fewer morphine-equivalent units (MEU) of morphine ER than oxycodone CR (69.9 MEU/day vs 91.0 MEU/day; $p=0.0125$). Sleep quality was superior with morphine ER than oxycodone CR ($p=0.0026$). Adverse events were similar between treatment groups.

A 4-month, open-label extension of the ACTION trial (N=174) evaluated the stability of pain control, effective dose and effects on quality of sleep between morphine ER and oxycodone CR. Patients in the morphine ER treatment group continued to report lower pain scores, better quality of sleep and comparable use of ibuprofen at lower daily MEUs (morphine ER 86 mg vs oxycodone CR 119 mg) compared to patients in the oxycodone ER treatment group. No changes or differences in adverse events were noted from the 8-week trial and the incidence and type was similar between groups.

Placebo Trials

Belbuca® (buprenorphine)

Belbuca clinical trials are unpublished. Some information is available on the Clinicaltrials.gov website.[87] A trial of 749 patients with chronic low back pain and no risk for arrhythmia were titrated to pain relief with Belbuca buccal film applied every 12 hours. Efficacy with tolerability was achieved in 61% of patients who continued treatment over 12-weeks. Mean pain scores at 12-weeks statistically favored Belbuca vs placebo. Reductions in pain score from baseline of 30% and 50% were achieved in 62% and 41% vs 33% of placebo treated patients.

A second, 12-week study was performed in opioid-experienced patients (n=810) with chronic low back pain and low risk of arrhythmia. Patients were receiving 30-160 morphine equivalent units daily prior to study entry. The titration phase found 63% of patients able to tolerate adverse effects with adequate analgesia. Discontinuation due to lack of efficacy was 2% in the Belbuca arm and 25% in the placebo treatment arm. Belbuca reductions in pain scores from baseline were statistically significant compared to placebo. A reduction in pain score of 30% or 50% (from baseline) was achieved in 64% vs 39% and 31% vs 17% of Belbuca-treated and placebo-treated patients, respectively.[19]

Zohydro ER® (hydrocodone)

Approval of Zohydro ER was based upon an unpublished trial whose results are posted on ClinicalTrials.gov.[88] The trial evaluated Zohydro ER in opioid-experienced patients with moderate to severe chronic low back pain. Patients (N=510) currently receiving chronic opioid therapy were converted to an equianalgesic dose of Zohydro ER and titrated to pain relief, if required, for a period of up to 6 weeks and to a maximum dose of 100 mg every 12 hours. Once stabilized, treatment with Zohydro ER or placebo (with a blinded taper) continued for 12 weeks. Significantly more placebo patients did not complete the study than Zohydro ER patients (82% vs 39%, respectively). Zohydro ER afforded superior pain relief at 12 weeks compared with placebo and a greater percentage of patients achieved at least 30% improvement in pain scores (67.5% vs 31.1%, respectively).

Efficacy was further demonstrated in a placebo controlled, 12-week trial (N=302) evaluating pain at the end of therapy to baseline in opioid-experienced patients with chronic, severe, low back pain.

Zohydro ER therapy resulted in more responders (68% vs 31%; p<0.001) with improved Subject Global Assessment of Medication scores compared with baseline (0.8 ± 1.3 vs 0.0 ±1.4, p<0.0001).[89]

Hysingla ER® (hydrocodone)
Approval of Hysingla ER was based upon a randomized, controlled, 12-week trial in opioid-naïve and experienced patients (n=905) with severe chronic low back pain unresponsive to their current therapy. Patients (n=588; 65%) were converted and titrated to an effective (and tolerated) Hysingla ER dose (20-120 mg daily) over 45 days. Stabilized patients then received either Hysingla ER or a placebo taper over 12 weeks. The completion rate was 77% for Hysingla ER and 72% on placebo. Discontinuations due to lack of efficacy occurred in 5% of Hysingla ER patients and 15% of placebo patients. Discontinuations due to adverse events occurred in 6% of Hysingla and 3% of placebo patients. Reductions in the weekly average pain scores at 12 weeks were statistically significant for Hysingla.

Exalgo® (hydromorphone)
A placebo-controlled trial of Exalgo in low back pain demonstrated superiority to placebo in reducing pain intensity and pain scores (p<0.001 for both). A comparative trial using a formulation available only in Europe demonstrated hydromorphone ER provided similar pain relief to oxycodone ER in patients with osteoarthritis pain.[90]

Xartemis XR® (oxycodone/acetaminophen)
The utility of Xartemis XR for acute pain following unilateral first metatarsal bunionectomy surgery was evaluated postoperatively over 48 hours. Patients (n=329 enrolled, 266 completed study) received two oxycodone ER/acetaminophen tablets (7.5/325 mg) every 12 hours or placebo. Pain intensity index scores at 48 hours were 114.9 (standard error 7.64) for oxycodone ER/acetaminophen and 66.9 (standard error 7.6) for placebo (p<0.0001). 85% Xartemis XR patients and 98% placebo patients took at least one dose of rescue medication. The onset of pain relief with Xartemis XR occurred within one hour (median). Adverse events were more common in the treatment arm (53.61% vs 21.47%) with the most commonly reported AEs nausea (30.72% vs 5.52%), vomiting (9.04% vs 0.0%), dizziness (13.25% vs 1.23%), headache (9.64% vs 4.91%) and somnolence (3.61% vs 0.61%).[91] An open label extension of up to 14 days (n=146 patients) reported adverse events in 43.8% of patients, most commonly gastrointestinal in nature (nausea 17.8%, vomiting 7.5% and constipation 6.2%).[92]

Ultram ER® (tramadol)
Currently, no trials compare tramadol ER with strong opioids. Tramadol ER was compared with placebo in acute pain following total knee-replacement, chronic low back pain, chronic nonmalignant pain, osteoarthritis in geriatric patients and chronic pain.[93-100] Overall, tramadol ER demonstrated superiority to placebo in the various populations with respect to efficacy outcomes, sleep outcomes and requirement for rescue medications. Adverse events (e.g. nausea, vomiting, constipation, headache, dizziness, insomnia and diarrhea) were more commonly reported at a dose of tramadol 400 mg than 100, 200 or 300 mg. The incidence of adverse events in 317 geriatric patients was constipation (27.5%), nausea (23.4%), dizziness (22.7%) and headache (15.6%).[96]

Conzip® (tramadol)

Conzip demonstrated clinical efficacy compared to placebo in 2 trials of osteoarthritis of the knee according to the package insert (clinical trials are unpublished). Discontinuation rates due to adverse events were higher in the Conzip ER group than placebo groups (27% vs 7%). The package insert states, "Four randomized, placebo-controlled clinical trials of ConZip were conducted, none of which demonstrated efficacy but which differed in design from the preceding clinical studies described. Two trials were 12-week randomized placebo-controlled trials of ConZip 100 mg/day, 200 mg/day, and 300 mg/day versus placebo in patients with moderate to moderately severe osteoarthritis pain of the hip and knee. The other two 12-week trials were similar in design, but only studied ConZip ER 300 mg/day. In this fixed-dose design, subjects were required to titrate to a fixed dose, even if their pain responded to a lower titration dose."[2]

Safety
The systematic review by AHRQ answered the following two safety questions.[61]

Safety Question – What is the long-term tolerability of long-acting opioid agents?[61]
A systematic review and meta-analysis in patients with chronic, noncancer pain found withdrawal from oral therapy due to an adverse event was 22.9% [95% CI, 15.3% to 32.8%] and from transdermal therapy 12.1% [95% CI, 4.9% to 27.0%%].[66,101] The most common reason for oral therapy discontinuation related to gastrointestinal events (e.g. constipation, nausea and dyspepsia). Less commonly reported were headache, fatigue, lethargy, somnolence and urinary complications. Withdrawal due an insufficient response with oral therapy was 10.3% [95% CI, 7.6% to 13.9%] and from transdermal therapy 5.8% [95% CI, 4.2% to 7.9%]. Long-term treatment ($\geq$ 6 months) with oral opioids was associated with a reduction in pain scores of 63.4% (standardized mean difference [SMD] 1.99, 95% CI, 1.17 to 2.80). Evidence was insufficient to assess long-term pain control with transdermal therapy. In studies which reported outcomes relating to signs of opioid addiction with oral agents, a low incidence of 0.27% was found in chronic, noncancer patients.[61]

Safety Question - Do long-acting opioids carry a lower risk of addiction, abuse, or overdose in the treatment of chronic non-malignant pain?[61]
It has been theorized that short-acting opioids are more likely to produce addiction. The short-acting agents release drug more quickly and achieve higher Cmax levels which may produce greater euphoria. In recreational drug users, single doses of short-acting opioids had higher "drug liking" compared to the same dosage of a long-acting opioid.[102,103] The shorter half-lives may result in breakthrough pain at the end of the dosing interval and withdrawal symptoms.[104] Published studies often differed in defining outcomes, methodology, were often less than 1 year in duration and published before the American Psychiatric Association published DSM-V diagnostic criteria for opioid-use disorder further standardized terminology making interpretation of results difficult.[105]

A recent phase 1, open label, randomized, 7-period crossover trial compared subjective effects of biphasic immediate/extended release hydrocodone/acetaminophen with an immediate release hydrocodone/acetaminophen product and placebo. Medications were administered intact or crushed. The biphasic tablets produced delayed and lower peaks than the immediate release product. For intact tablets, drug liking was higher for the immediate release product (Emax median difference, -8.5 (95% CI, -12 to -6.0; $p<0.001$). Crushing the tablets delayed the effects

in the biphasic tablet. The authors concluded that the biphasic (immediate and extended release) product had lower abuse potential than the immediate release product.[102]

A retrospective review of 5,684 Oregon Medicaid recipients evaluated abuse and adverse outcomes associated with the use of long-acting opioid agents over 4 years.[106] Patients received at least one new 28-day prescription for either methadone, sustained release morphine, sustained release oxycodone or transdermal fentanyl. Emergency department encounters or hospitalizations for adverse events were more common with sustained-release morphine than oxycodone (HR 0.45, 95% CI 0.26 to 0.77) as was death (HR 0.71, 95% CI 0.54 to 0.95). Patients with noncancer pain were more likely to have an Emergency Department encounter if they were receiving transdermal fentanyl compared to sustained-release morphine (HR 1.27, 95% CI 1.02 to 1.59). Patients receiving methadone vs. sustained-release morphine were more likely to have a non-significant increase in overdose symptoms (HR 1.57, 95% CI 1.03 to 2.40) with no difference in the incidence of death between groups. Evidence from the primary care setting suggest the rate of opioid abuse at 0.6% to 8.0%, opioid dependence at 3.1% to 26% and aberrant drug related behaviors at 5.7% to 37.1%. Conclusions drawn by the systematic review include the following: evidence concerning the safety and efficacy of the agents in the treatment of long-term pain remains weak or insufficient and the risk of harms is real with a growing number of concerns (e.g. hypogonadism, accident, overdose, fracture, myocardial infarction, addiction, abuse and misuse). The data did not define specific differences between agents with regard to efficacy and generally support clinical policy efforts to minimize harms which appear to be dose-dependent.[61,107]

Black Box Warnings

Tramadol products currently bear no Black Box warnings.[1,2] Life-threatening respiratory depression, risk from accidental exposures and risk for neonatal opioid withdrawal syndrome warnings are included for all non-tramadol long-acting opioid agents. The transdermal products carry warnings for abuse, while the other agents have additional risk identified for addiction and misuse. Additional methadone warnings include the risk for QT prolongation and the reminder that its use for opioid addiction carries additional prescribing requirements.[8] Fentanyl patches or the area around the application site must not be exposed to external heat; increased fentanyl release may result in toxicity.[5] Alcohol significantly increases the CNS depressant effects of Kadian, Embeda, Opana ER and Nucynta. Due to the acetaminophen component of Xartemis XR it carries a Black Box warning for hepatotoxicity.[3] Drugs or non-drug agents that act as inducers or inhibitors of cytochrome P450 3A4 isoenzymes may significantly affect the serum concentrations of Duragesic, Zohydro ER, Hysingla ER and OxyContin resulting in withdrawal symptoms or drug toxicity. A comparison of the Black Box Warnings for the Long-Acting Opioid agents is presented in Table 7.

Table 7: Comparison of Black Box Warnings for Long-Acting Opioid Agents[2-6,8,13-16,19,20,22,108]

	Belbuca	Butrans	Duragesic	Zohydro ER	Hysingla ER	Exalgo	Dolophine	MS Contin	Kadian	MorphaBond	Embeda	OxyContin	Xartemis XR	Opana ER	Nucynta ER	Conzip	Ultram ER
Abuse Potential		X	X													ENoneN	NONE
Addiction, Abuse and Misuse	X			X	X	X	X	X	X	X	X	X	X	X	X		
Life-threatening respiratory depression	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Accidental Exposures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Neonatal Opioid Withdrawal Syndrome	X	X	X	X	X	X	X	X	X	X		X	X	X	X		
Cytochrome P450 3A4 Interaction			X	X	X							X					
Exposure to heat			X														
Interaction with Alcohol				X					X		X			X	X		
Life-threatening QT Prolongation							X										
Conditions for Distribution and use of Methadone Products for the Treatment of Opioid Addiction							X										
Hepatotoxicity													X				

Adverse events associated with the use of the long-acting opioid analgesics are presented in Table 8. All opioids have anticholinergic and direct effects on neurons within the CNS and commonly produce sedation and drowsiness to which most patients develop tolerance.[124] The effects are less pronounced with long-acting agents compared to. short-acting agents.[109] Cognitive and motor impairment effects are more common when initiating therapy or titrating doses than with chronic use.[110] When properly initiated and titrated, respiratory depression is uncommon. Buprenorphine has a lower propensity to cause respiratory depression than other opioids.[56,111] Constipation occurs in up to 50% of opioid-treated patients to which tolerance does not develop. The use of stimulant laxatives, stool softeners and perhaps peripheral mu-opioid receptor antagonists may be required. Some evidence suggests fentanyl and methadone are associated with less constipation than other agents.[44,69,70]

Hyperalgesia differs from opioid tolerance as patients appear to require higher doses of narcotics for pain relief yet increasing the dose of the narcotic is often associated with greater pain sensitivity.[112,113] This effect is most commonly associated with opioids of the phenanthrene class.[112,113] Agents with less potential for hyperalgesia, include fentanyl, buprenorphine, methadone and tramadol.[112,113] Hypogonadism appears to occur equally in men and women and is related to the effects of opioids in the hypothalamus.[114] The stress of pain negatively affects immunity and opioid-induced immunological changes add to the immunosuppression. Tramadol increases natural killer cell activity. Morphine, methadone and fentanyl are reported to have the strongest immunosuppressant effects while buprenorphine, hydromorphone and oxycodone demonstrate less effect. [48] Buprenorphine is reported to produce small changes to the QTc

interval at a higher (40 mcg/hr) but not lower (10 mcg/hr) dosage.[20] Hysingla ER®, Opana ER® and OxyContin® carry a caution concerning difficulty swallowing the product, potential for gagging, choking and gastrointestinal obstruction. A risk of hepatotoxicity is listed with buprenorphine although studies suggest increased liver enzymes are likely due to other factors.[115]

All long-acting opioids have the potential to cause addiction. Each agent carries a black box warning to this effect. However, a systematic review of chronic pain found 24 studies (N=2507) yielding a low calculated abuse/addiction rate of 3.27%. Patients with no prior abuse risk or history had an abuse/addiction rate of 0.19%. Seventeen studies (N=2466) evaluated the risk of aberrant drug-related behaviors and found a rate of 11.5% overall and 0.59% for those patients not at risk of aberrant drug-related behaviors. The subset of patients not at risk and in those not at risk the rate was 0.59%. In general, the risk of abuse/addiction or aberrant drug-use with chronic opioid therapy was uncommon in the chronic pain population.[116]

Table 8: Adverse Events[2-6,8,13-16,19,20,22,108, 17,117]

Adverse Event	Buprenorphine	Buprenorphine TDS	Fentanyl	Hydrocodone	Hydromorphone	Methadone	Morphine	Morphine/Naltrexone	Oxycodone	Oxycodone/APAP	Oxycodone/Naloxone	Oxymorphone	Tapentadol	Tramadol
Cardiovascular														
Cardiac Arrhythmias	+	+	+			R			+					
Cardiac Failure			++			++								
Chest Pain	++		++		++		++							++
Tachycardia/Palpitation		++	++		++	R	++					+		
Flushing						++	++	++				++		+++
Hypertension	++	++	++	++			++					++		++
Hypotension/Shock	++	++	++			+++	+++	+	++	++		+	++	++
QTc prolongation	+					R								
Central Nervous System														
Agitation/Anxiety	+++	+++	++	++	++	++	++	++	+			+	++	++
CNS Depression (e.g. drowsiness, sedation, somnolence)	+++	+++	+++	++	+++	+++	+++	+++	+++	++	++	+	+++	+++
Cognitive Dysfunction/Impairment		++	+++			+++	+++	+	++			++	++	++
Coma							++							
Coordination Impairment (e.g. dizziness)	+++	+++	+++	++	+++	+++	+++	++	+++	+++	++	+++	+++	+++
Dependence	+++		++		++	++	++				++		++	++
Depression	+++	+++	++	++	++		++	++	+		++	++	++	++
Dysphoria/Euphoria		+	++		+	++	++	+	++	++		+		++
Fatigue	++		+++	++				++		++		+++	++	
Hallucination/Delirium		+	++			++	++		+		+	+		
Headache	+++	++	+++	++	+++	++	+++	++	+++	++	++	+++	+++	+++
Pain	+++	+++	++	++			++		++					++
Seizure						++	++		+					
Sensory Processing Disorders	++		++				++		++				++	++
Sleep Disorders/Disturbances	+++	+++	++	++	++	++	++	++	++	++		++	++	+++
Speech Disturbance			+				++		+					

Thermoregulation Abnormalities	++	+++	++	++	++		++	++	++				++	++
Dermatologic														
Application Site Irritation	++	+++	++											
Pruritis/Rash/Urticaria	+++	+++	+++	+++	+++	+	+++	++	++	+	++	+	++	+
Sweating Disorders	+++	+++	++	++	++	+++	++	++	+		++	++	++	++
Endocrine/Metabolic														
Dehydration			+++	++								++		
Electrolyte Imbalance			++	++		++	++		++					
Enzyme Abnormalities				++							++			
Fluid Retention						++	++							
Hyperglycemia			++								++			++
Hyperlipidemia				++							++			
Hyperuricemia											++			
Hypoalbuminemia			++											
Sex Hormone Abnormalities		+	++	++		++	++	++	+	++			++	++
Weight Gain						++								
Weight Loss			++				++		++			++		++
Gastrointestinal														
Abdominal Distress	+++	+++	++	+++	++	++	+++	++	++	++	++	++	++	+++
Constipation	+++	+++	+++	++	+++	++	+++	+++	+++	++	++	+++	+++	+++
Decreased Gastrointestinal Motility			++				++		+					
Diarrhea	++	+++	++	++	++		++		++	++	++	++	++	++
Eating Disorders	++		++	++	++	++	++	++	+		++	++	++	++
Eructation/Flatulence		++	++				++	++				++		++
Gastroesophageal Reflux		+	++	++			++		++					
Nausea	+++	+++	+++	++	+++	++	+++	+++	+++	+++	++	+++	+++	+++
Ileus					++				+			+		
Vomiting	++	++	+++	++	+++	++	+++	++	+++	++	++	+++	+++	+++
Xerostomia	++		++	++	++	++	+++	++	++	++	++	++	++	+++
Genitourinary														
Dysuria			++		++		++	+	+	++				
Renal Failure			++				++							
Sexual Disorder/Dysfunction		+	++		++	++	++		+				++	++
Urinary Frequency/Hesitancy		++	++			++	+++		+					++
Urinary Tract Infection	++		++	++							++			++
Vaginal Disorders			++											++
Hematologic														
Erythrocyte Abnormalities			++				+++		++	++	++			
Leukocyte Abnormalities			++				++		++	++				
Lymph Abnormalities		++	++											
Thrombocyte Abnormalities			++			++	++		++	++				
Hepatic														
Ascites			++											
Jaundice			++											
Liver Enzyme Abnormalities			++				++	+	++	++				
Miscellaneous														
Accidental injury		+												++
Application Site Irritation	+++	+++	++											
Hypersensitivity			++				+++							
Polydipsia							++							
Pyrexia	++		++		++		+++		+++			+++		++
Tinnitus				++										
Viral Infection	++		++	++			++				++			++
Wound Healing Impairment			++						++					
Arthralgia/weakness/spasm/myalgia	++	++	++	+++	++		++	++	++					++
Dyskinesia							++							
Dystonia	++		++	++	++		++	++	++		++		++	++
Gait Abnormalities			++				++							
Injury/Swelling	++			++										++

Myasthenia	+++		+++		+++	++	+++		++		++	++	++	+++
Osteoarthritis	++		++	++	++		++	++			++			++
Visual Disturbances	++	++	++			++	++		+			++	++	++
Respiratory														
Cough	++	++	++	++					+	++				++
Nasal/Sinus Discomfort			+	++			++							++
Oropharyngeal Pain	++	++	++	++					++					
Respiratory Congestion						++	++							++
Respiratory Depression	+		++		++	++	+++		++	++		+		
Respiratory Distress	++		+++	++			++		++			++	++	++
Respiratory Tract Irritation	+++	++	++	++			++				++			++
Rhinitis		+++												

R Reported at undefined frequency
\+ ≤1% frequency
++ 1-10% frequency
+++ >10% frequency

Methadone Safety

Methadone poisonings and deaths from overdose have increased in both number and rate, prompting questions concerning its safety.[118,119] This finding parallels an increase in methadone use for analgesia and a report by Krantz et al (2002) identifying the association of torsade de pointes with high doses of methadone.[120,121] Opioid-related deaths are reported with methadone use 3 times more frequently than any other opioid.[122] Methadone is currently the 2nd most commonly reported drug associated with the development of arrhythmia according to the FDA's Adverse Event Reports System.[123] Methadone prolongs the QTc interval, is associated with a number of drug-drug interactions and is a common drug of abuse.[120] The pharmacokinetic profile of methadone between patients is highly variable. An interdisciplinary group representing the American Pain Society (APS), The College on Problems of Drug Dependence (CPDD) and The Heart Rhythm Society (HRS) evaluated methadone safety.[120] According to the evaluation, methadone may be used safely in the treatment of pain with careful patient selection, education and monitoring of adverse events during therapy (including QTc interval measurement in at least at-risk patients), follow-up EKGs, urine drug testing and a keen eye to drug-drug interactions.[120]

One prospective study followed patients converting to methadone therapy with EKG measurements at baseline, 2 weeks, 3 months and 9 months. Patients 40-66 years old with mostly low back pain, stable electrolytes and often taking additional medications were included. The mean dose of morphine was 134 mg/24 hours. Mean QTc measurements at baseline, 2 weeks, 3 months and 9 months (0.42±0.03, 0.44±0.02, 0.43±0.04, 0.43±0.04 respectively) did not differ significantly. The mean QTc interval change from baseline at 2 weeks was 0.02 (95% CI, 0.007 to 0.032; p=0.01).[124]

Methadone metabolism is significantly affected by drugs that are substrates (as inducers or inhibitors) of CYP 3A4 and CYP2B6. The American Pain Society recommends that caution should be used when any drug (prescription, OTC or illicit) which affects the absorption, distribution, metabolism or excretion of methadone is used concomitantly.[120] Methadone may cause respiratory depression and the use of other respiratory depressants should be minimized during therapy.[8]

If the use of methadone is required in the treatment of chronic pain, prescribing by a clinically experienced provider is recommended. A thorough risk-benefit analysis should be conducted with the patient before the initiation of therapy followed by careful monitoring for adverse effects, EKG changes, drug interactions and abuse/misuse.[120,122,125-127]

Long-Acting Opioids With Abuse-Deterrent Properties[128-130]

As of July 9th, 2012, the Food and Drug Administration (FDA) required all extended-release and long-acting formulations of opioids to include a Risk Evaluation and Mitigation Strategy (REMS) due to significant safety issues associated with these drugs.[131] REMS programs include provider education (proper dosing, monitoring, recognizing signs of abuse/addiction). Additionally, the FDA encourages abuse-deterrent technologies and has released guidelines describing various strategies to make opioid formulations abuse-deterrent.[132] The mechanisms of abuse deterrence for the long-acting opioid formulations are found in Table 9.

Table 9: Abuse Deterrent Mechanisms[14 131,6,132,22,23,15,133,134,4,135,136]

Hydrocodone Extended-Release capsules Zohydro ER®	Zohydro capsules incorporate a chemical barrier for abuse deterrent. Zohydro capsules contain 3 different types of visually indistinguishable beads: immediate-release hydrocodone beads, extended-release hydrocodone beads, and inactive polyethylene oxide beads. When crushed and exposed to liquids, the polyethylene oxide beads form a viscous gel that is difficult to draw or inject through a hypodermic needle.
Hydrocodone Extended-Release tablets Hysingla ER®	Hysingla ER tablets incorporate physical/chemical barriers and aversion technology for abuse deterrent. The tablets have been shown to resist crushing and dissolution, and maintain some extended-release properties after manipulation. Additionally, exposure to an aqueous environment causes the tablet to form a viscous gel that is difficult to draw up or inject through a hypodermic needle. Finally, parenteral abuse of Hysingla ER may cause local tissue necrosis and endocarditis due to tablet excipients.
Hydromorphone HCl tablets Exalgo®	Exalgo tablets incorporate physical barriers and aversion technology as abuse deterrents. The tablet is enclosed in a semipermeable shell that has been shown to resist crushing or extraction for injection. Additionally, the tablet excipients, especially polyethylene oxide, can cause inflammation and necrosis of cardiac cells if abused intravenously
Morphine Extended-Release tablets MorphaBond®	The formulation incorporates physical and chemical barriers to abuse. It is resistant to cutting, crushing or breaking and forms a viscous gel in aqueous environment difficult to draw into a hypodermic needle.
Morphine sulfate/ naltrexone HCl capsules Embeda®	Embeda capsules incorporate an agonist/antagonist mechanism for abuse deterrent. The antagonist, naltrexone, is embedded in the core of each pellet and remains intact through the gastrointestinal (GI) tract if taken appropriately. Dissolving, crushing, or chewing the tablet causes the release of the naltrexone core and subsequent antagonist activity along with potential withdrawal symptoms.
Oxycodone Extended-Release tablets OxyContin®	OxyContin tablets were reformulated in 2010 to incorporate physical and chemical barriers for abuse deterrent. The tablets contain a matrix that is difficult to crush or break, and will form a viscous gel when exposed to an aqueous environment.
Oxymorphone Extended-Release tablets Opana ER®	Opana ER tablets incorporate physical and chemical barriers for abuse deterrent. The tablets contain a matrix that is difficult to crush or break, and will form a viscous gel when exposed to an aqueous environment
Tapentadol Extended-Release tablets Nucynta ER®	Nucynta ER tablets incorporate physical and chemical barriers for abuse deterrent. The tablets contain a matrix that is difficult to crush, and will form a viscous gel when exposed to an aqueous environment.

Clinical studies demonstrate significantly lower scores for "drug high", "drug liking" and not "well-liked", with the abuse deterrent formulations Embeda®, Hysingla ER®, MorphaBond®, Xartemis XR®, Nucynta ER® and OxyContin® compared with non-deterrent formulations of the same opioid.[14,137,22,23,134,138-140] Although a post-market analysis of Opana ER® demonstrated a significant majority of patients were unwilling to inject or snort tampered tablets, the FDA declared that the Opana ER® formulation was insufficient in deterring abuse based on study data.[141,133] The impact of abuse deterrent formulations of Exalgo® and Zohydro ER® on abuse potential has not been adequately established.

A post-marketing evaluation reported tapentadol ER and hydromorphone ER are less likely to be abused compared to other long-acting opioids. The NAVIPPRO ASI-MV® surveillance system retrospectively identified 113,914 individuals from 624 facilities in 38 states from January 2011 to September 2012 whom were assessed for substance abuse treatment. When adjusted for covariates and prescription volume tapentadol ER demonstrated the lowest relative risk for abuse. The relative risk for hydromorphone was 1.92 and not statistically different from tapentadol. Statistically significant increases in relative risk for abuse were found with fentanyl ER, tramadol ER, morphine ER, buprenorphine combination, oxycodone ER buprenorphine single entity and oxymorphone ER (RR 1.92, 1.96, 2.31, 3.10, 7.57, 12.54, 15.80, 17.03, respectively).[139]

Drug Interactions[2-6,8,13-16,19,20,22,108,17,117]

Central nervous system depression may occur with any long-acting opioid when combined with other medications having these effects, including other narcotic analgesics, sedative-hypnotics, tranquilizers, tricyclic antidepressants, muscle relaxants, phenothiazines, general anesthetics or other agents with CNS depressant activity (e.g. alcohol). Severe respiratory depression, sedation, hypotension, coma and death have occurred. The addition of a partial-agonist or antagonist to an opioid analgesic may result in a loss of analgesia and/or the development of withdrawal symptoms. No opioid should be initiated within 14 days of stopping a monoamine oxidase inhibitor (MAOI) as the effects of the opioid may be significantly augmented. Cytochrome P450 isoenzymes affect the metabolism of a number of opioids. CYP450 3A4 inhibitors may increase and inducers may decrease serum levels of buprenorphine, fentanyl, oxycodone, hydrocodone and tramadol. P450 2D6 isoenzyme inducers/inhibitors may affect serum levels of oxycodone and tramadol. The use of concomitant anticholinergic drugs with tapentadol may result in urinary retention, severe constipation and paralytic ileus. The use of tramadol or tapentadol with other medications having serotonergic activity (e.g. selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, triptans or cyclobenzaprine) may result in the development of serotonin syndrome. The use of methadone with arrythmogenic agents or drugs which may prolong the QTc interval may result in ventricular arrhythmias including Torsade's de Pointes. Drug interactions are presented in Table 10.

Table 10: Drug Interactions

Medication	Interaction Description
Abacavir + methadone	Possible reduction in concentration of methadone
Amiodarone + fentanyl + methadone	Bradycardia, sinus arrest, hypotension, QT prolongation (methadone)
Amitriptyline + morphine	May increase morphine plasma concentration, increased sedation
Anticholinergics + buprenorphine, fentanyl, hydrocodone, hydromorphone,	May increase risk of urinary retention, constipation and potentially paralytic ileus

methadone, morphine, morphine/naltrexone, oxycodone, oxycodone/acetaminophen, oxymorphone, tapentadol	
Antiretrovirals + methadone	Reduced methadone plasma concentrations
Atomoxetine + methadone	Increased risk of ventricular arrhythmias
Beta-blockers + fentanyl	Severe hypotension
Calcium channel blockers + fentanyl	Severe hypotension
Chlorpromazine + morphine	Enhanced sedative/hypnotic effects
Cimetidine + morphine, morphine/naltrexone, oxymorphone	Potentiates opioid induced respiratory depression
CNS depressants (sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, tranquilizers, alcohol) + all long-acting opioids	Additive/potentiating effects
CYP3A4 Inducers + buprenorphine, fentanyl, hydrocodone, methadone, oxycodone, oxycodone/acetaminophen, tramadol	Increased clearance of the opioid may result in diminished efficacy and potential for withdrawal reactions in opioid-tolerant patients
CYP3A4 Inhibitors + buprenorphine, fentanyl, hydrocodone, methadone, oxycodone, oxycodone/acetaminophen, tramadol	Opioid effects and adverse effects may be augmented
Diazepam + morphine	Enhanced sedative effects
Ethanol + hydromorphone, morphine, tapentadol, oxymorphone	May result in rapid release, additive/potentiating effects, potentially fatal
Diuretics + morphine, morphine/naltrexone, oxymorphone	Reduced diuretic effects via ADH release. Acute urinary retention vis bladder spasm (especially with prostate enlargement).
Fluvoxamine + methadone	Possible increase in methadone plasma concentrations
Haloperidol + morphine	Enhanced sedative and hypotensive effects
Imidazole antifungals + fentanyl	Possible enhanced/prolonged fentanyl effects
Macrolide antibiotics + fentanyl	Possible enhanced/prolonged fentanyl effects
MAO Inhibitors + opioids	Severe/unpredictable potentiation of opioid
Metoclopramide + morphine	Antagonizes the GI effects of metoclopramide
Naloxone/Naltrexone + fentanyl, hydromorphone, methadone + morphine + oxycodone	Reduced analgesic effect and potential to precipitate withdrawal symptoms
Neuromuscular blocking agents + buprenorphine, morphine, morphine/naltrexone, oxycodone, oxycodone/acetaminophen, oxymorphone, tapentadol	Enhanced effects of skeletal muscle relaxants with significant respiratory depression possible
Nitrous oxide + Fentanyl	Possible cardiovascular depression
Opioid antagonist/partial agonist + Fentanyl, hydromorphone, morphine + oxycodone	May precipitate withdrawal symptoms
P-glycoprotein inhibitors (quinidine)+ morphine, morphine/naltrexone, tramadol	The absorption and exposure of morphine may increase two-fold. Tramadol serum concentrations increase
Phenobarbital + Methadone	Possible reduction in methadone plasma concentrations
Protease inhibitors + Fentanyl	Possible enhanced/prolonged fentanyl effects
QT-interval prolonging agents + Methadone	May increase QT interval
Rifampicin + Methadone	Metabolism of methadone is accelerated
Serotonergic medications + oxycodone, tapentadol, tramadol	Increased risk of serotonin syndrome
Skeletal muscle relaxants + opioids	Enhanced neuromuscular blocking activity of skeletal muscle relaxant, increased respiratory depression
Voriconazole + Methadone	Methadone plasma concentration is increased

Summary

The World Health Organization analgesic ladder addresses pain relief strategies at three levels. Non-opioid pain relievers are used at the lowest level, weak opioid agents (codeine) are used

for moderate pain and strong opioid agents (morphine, hydromorphone, oxymorphone, methadone and fentanyl) are recommended for the highest level of pain. Patients may be switched from one opioid to another using equipotent dosing.

Nine systematic reviews from 2002 to 2014 defining the comparative efficacy of the long-acting opioid analgesic agents found insufficient evidence to differentiate among the agents with regard to pain relief, reduction in pain intensity, improvement in sleep parameters, quality of life, global assessments or risk of abuse, addiction or misuse. The most common adverse effects associated with the opioid analgesics include nausea, vomiting, sedation, pruritus and constipation. Serious adverse effects frequently reported with opioid use include: respiratory depression, urinary retention, hypotension and delirium. There is insufficient evidence to identifying significant adverse event differences among the agents although limited evidence suggests transdermal fentanyl is associated with a lower incidence of gastrointestinal side effects and sedation. Low-strength evidence suggests the harms associated with long-acting opioids are dose-related. Clinical trials demonstrate no differences in rates of serious adverse events when oral morphine and morphine-like agents are dosed with equianalgesic dosing schemes. Long-acting opioid analgesics are potent schedule II controlled opioid agonists that have the high potential for abuse and risk of producing respiratory depression.

The selection of a long-acting opioid depends upon the etiology and type of pain, patient-related variables, age, prior exposure to opioid therapy, prior aberrant drug use and the various adverse potentialities of each agent. In differentiating the agents the following nuanced information may be helpful. Eight of the agents are available with abuse-deterrent technologies. Evidence is insufficient to prove abuse-deterrent technology's ability to impact more than nasal or injection abuse, however, they have the potential to be helpful and this should be considered. Methadone has the most potential for serious adverse events but is the only agent approved for use in addiction, detoxification and opioid maintenance. Tramadol (Ultram ER® and Conzip®) and perhaps buprenorphine (Belbuca® and Butrans®) are less potent agents. The use of tramadol or tapentadol with other serotonergic drugs may cause serotonin syndrome. Transdermal products may afford less constipation, sedation and gastrointestinal adverse effects. Buprenorphine has a respiratory depression ceiling. Tapentadol is the only agent approved for use in diabetic neuropathy. OxyContin® and fentanyl have indications in children. Xartemis XR may be used in severe, acute pain and both Xartemis XR® and extended-release tramadol products lack a restriction for PRN use. Tramadol products are Schedule IV allowing for the prescribing of refills. Dual, and tri-mechanisms of action suggest theoretic advantages of tramadol, methadone and tapentadol in certain patient populations. Safety in renal dysfunction is most established with methadone and fentanyl.

Overall, the opioid analgesic agents are effective treatment options for pain disorders. When compared at equianalgesic doses, the opioid agents demonstrate similar rates of safety and efficacy. Pain management must be individualized for each patient and include careful evaluation of patient history, age, comorbidities, type of pain, underlying diseases and concurrent medications.

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Appendix 1: Additional Findings of the AHRQ Report: The Effectiveness and Risks of Long-Term Opioid Treatment for Chronic Pain.[61]

Efficacy Question – Does data support the efficacy of long-acting opioids for longer than 1 year with respect to outcomes such as pain, functional status or quality of life?
Currently there is insufficient evidence to answer this question. The duration of most studies is less than one year (often 4 months or less). Studies have not addressed long-term usage outcome for type of pain, patient demographic or comorbidities.[61]

Efficacy Question – Are short- or long-acting opioids more advantageous for initiating and titrating to stable pain control?
Limited evidence suggests no difference in achieving pain control using either short- or long-acting opioids. Two trials compared controlled-release vs. immediate release oxycodone.[142] One trial titrated 48 patients with cancer pain for up to 21 days while the other titrated 57 patients with low back pain over 10 days. No difference was found between oxycodone formulations in achieving stable pain control, time until pain control or degree of pain control. A third trial compared the combination of morphine controlled-release and oxycodone immediate release to regularly scheduled immediate release oxycodone. The controlled-release morphine and oxycodone immediate release therapy provided better relief of pain intensity, but the average opioid doses and maximum opioid doses differed in each arm making this study difficult to interpret.[143]

Efficacy Question – Are long-acting opioids more efficacious than short-acting opioids for maintaining analgesia?

Long-acting opioid preparations are presumed to offer a number of advantages over short-acting agents. More stable plasma concentrations are predicted to reduce breakthrough pain and allow for improved sleep quality. [144,145] Long-acting agents are associated with lower Cmax concentrations than short-acting agents and may reduce adverse effects and increase tolerability. Finally, the reduced pill-burden is seen as an advantage.[144] Sleep is adversely affected by pain, which further disrupts sleeps. Hyperalgesia has been associated with sleep deprivation and reversed with good sleep patterns. Sleep is adversely affected in 65% of patients with chronic pain. Pain is inversely related to a number of measures relating to restful, restorative sleep. Relief of pain is associated with better night time pain control, less need for night time doses, less clock-watching, less pain related sleep disturbances and improved convenience.[145]

A systematic review comparing long-acting vs. short-acting opioids for the treatment of pain found most trials of short duration ($\leq$30-days or 16 weeks) and inadequate to address the long-term efficacy of long- vs. short-acting opioids for chronic pain. Six randomized trials and one randomized, double-blind, double-dummy trials were identified. Each study compared long- and short-acting versions of the same opioid. No difference was found for pain, pain relief or the stability of pain intensity between the long- and short-acting formulations. In two trials that did report a difference, equivalent opioid doses were not administered limiting the applicability of the results. None of 4 trials assessing sleep outcomes found a difference. Overall, insufficient evidence exists to determine whether long-acting opioids are more efficacious than short-acting opioids for maintaining analgesia. [146]

Efficacy Question – Is there any benefit to a monotherapy, long-acting opioid regimen for treating chronic pain compared with the use of a regimen using both a long-acting and a short-acting opioid? Are there differences in the response of pain to the therapy differences?
There is insufficient evidence to answer this question.[61]

Efficacy Question – Is there an advantage to managing chronic pain with scheduled, continuous opioid therapy compared with intermittent, as-needed dosing?

There is insufficient evidence to answer this question.[61]

Efficacy Question – Is there data supporting the benefit of long-acting opioid rotation vs. the continued maintenance of an established long-acting opioid regimen in patients with chronic pain?
There is insufficient evidence to answer this question.[61]

Safety Question – Are long-acting opioids vs. short-acting opioids associated with adverse outcomes relating to infection, motor vehicle accident, gastrointestinal harms, falls or fractures, endocrine harms, cardiovascular events, cognitive or psychological harms?

Insufficient evidence to determine if long-term use of opioids or long- vs. short-acting opioids are associated with adverse outcomes relating to motor vehicle accidents, fall risk, infection or gastrointestinal, cognitive or psychological harms.[61]

Although some data suggests long-term use of opioids may be associated with myocardial infarction or revascularization, fractures, overdose, abuse and addiction evidence is insufficient to determine whether long- or short-acting opioids carry different risks of harm.[61,107,147-149]

An increased use of medications for erectile dysfunction or testosterone replacement was found in a cross sectional study of 11,327 men receiving chronic opioids (> 10 fills of at least 90 day supply) vs. non-opioids (adjusted OR 1.5, 95% CI 1.1 to 1.9) when adjusted for confounding variables. Long-acting opioids were used by 42% of men. No difference was noted between men receiving long-acting or short-acting opioids.[150]

Appendix 2: Clinical Trials Evaluating the Efficacy of the Long-Acting Opioids (all trials for particular opioids are not presented under each heading, but may be found elsewhere in the table when used in a comparator arm)

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Systematic Reviews Meta-analysis					
AHRQ Evidence Report #218[61] Systematic reivew of 39 studies (>1,000,000 patients; including large cohort studies)		Patients receiving long-term opioid therapy (≥ 1 year) for chronic cancer and noncancer pain		Primary Care Settings • Opioid abuse → 0.6-8.0% • Opioid dependence → 3.1-26% • Aberrant drug related behaviors → 5.7-37.1% Mortality risk • Methadone < Morphine LA • HR0.56, 95% CI 0.51 to 0.62 Comparative effectiveness of long-acting vs short-acting agents with respect to pain, quality of life, function, risk of overdose, addiction, abuse, misuse • Insufficient evidence Comparative effectiveness of different long-acting opioids with respect to pain, quality of life, function, risk of overdose, addiction, abuse misuse • Insufficient to low evidence	Strength of evidence supporting harms of use vs nonuse of long-term opioids for chronic pain* • Abuse/addiction o low to insufficient evidence • Overdose o low (adjusted HR 5.2, 95% CI 2.1 to 12); for serious overdose (adjusted HR 8.4, 95% CI 2.5 to 28) • Fracture o low (cohort study - adjusted HR 1.28, 95% CI 0.99 to 1.64); (case-control study – adjusted OR 1.27, 95% CI 1.21 to 1.,33) • Myocardial infarction o low (adjusted OR 12.8, 95% CI 1.19 to 1.37; incidence rate ratio 2.66, 95% CI 2.30 to 3.08) • Sexual dysfunction/testosterone replacement o low (adjusted OR, 1.5, 95% CI 1.1 to 1.9) • GI harms, motor vehicle accidents, psychological/cognitive harms • Insufficient evidence * Low-strength evidence suggests harms are dose-related (with the exception of motor-vehicle accidents)
Chou et al, 2003[146] Systematic Review of 16 randomized trials, 8 observational studies	2617	Patients treated for chronic noncancer pain	Short-acting vs long-acting opioids	Insufficient evidence to find one class more effective or associate with better safety and tolerability	Insufficient evidence to find one class or any specific agent superior

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Noble et al, 2008[66] Systematic review and meta-analysis of 17 studies	3079	Patients treated with opioids for noncancer pain for ≥ 6 months	Oral opioids Transdermal opioids Intrathecal opioids	Pain scores • Oral opioids: ↓ 63.4%; Standardized mean difference [SMD] 1.99 (95% CI, 1.17 to 2.80) • Transdermal products lack sufficient evidence on pain relief in this setting.	Discontinuation rates due to AEs • Oral 32.5% [95% CI, 26.1% to 39.6%] • Transdermal 17.5% [95% CI,6.5% - 39.0%] Discontinuation rates due to insufficient response • Oral 11.9% [95% CI, 7.8% to 17l.7%] • Transdermal 5.8% [95% CI,4.2% to 7.3%] Signs of opioid addiction 0.05% (1/2042) Signs of abuse 0.43% (3/685)
Clark et al, 2004[67] Systematic review of 8 trials	1220	Cancer and chronic, non-cancer pain requiring a strong opioid	Fentanyl TD (titrated) Morphine SR (titrated)	Improvement in pain scores from baseline • No differences found (pooled or by cancer/non-cancer pain) Changes in pain "right now" at day 28 • Fentanyl TD > Morphine SR (p=0.017)	Any AE • Fentanyl TD < Morphine SR (p<0.001) Serious AEs • Fentanyl TD < Morphine SR (p=0.006) Nausea • Fentanyl TD < Morphine SR (p<0.001) Somnolence • Fentanyl TD < Morphine SR (P<0.001)
Pedersen et al, 2014[68] Systematic Review of 6 randomized trials	1066	Patients treated with opioids for low-back pain, osteoarthritis or both	Treatment > 7 days. Equi-analgesic daily doses Oxycodone/paracetamol IR vs. oxycodone ER Dihydrocodeine IR vs ER Tramadol IR vs ER Tapentadol IR vs ER	Analgesic efficacy: pain intensity, reports of poor to complete pain relief • No differences found Consumption of rescue analgesia • No differences found Global assessment of efficacy • No difference found Sleep quality or disturbances • No difference found Functional capacity score • No difference found	Adverse event rates - not a primary outcome in any trial Nausea • Short-acting > Long-acting Depression/confusion • Long-acting > short-acting
Caraceni et al, 2011[69] Meta-analysis of 16 randomized and 1 meta-analysis	2487	Chronic cancer pain	Morphine long- or short-acting Opioids	Pain Relief • Morphine Long-acting = Methadone • Morphine Long-acting = Fentanyl TD	Constipation • Morphine Long-acting > Fentanyl TD Withdrawal due to sedation • Morphine Long-acting < Methadone

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Wiffen et al, 2007[70] Systematic Review of 54 randomized trials 3-days to 6-weeks	3749	Patients with cancer pain requiring strong opioid therapy	Morphine long-acting or short-acting Opioids or non-opioid analgesics	Pain relief • Morphine LA = Oxycodone ER/CR • Morphine LA = Fentanyl TD (fentanyl TD required more rescue medication) • Morphine LA = Hydromorphone ER • Morphine LA = Methadone • Morphine LA = Morphine IR • Morphine LA = Other long-acting morphine (MS Contin, Avinza, Kadian)	Sedation Morphine LA > Fentanyl TD Constipation Morphine LA > Fentanyl TD AEs Morphine LA < Methadone
Quigley et al, 2002[71] Cochrane review of 48 randomized trials and meta-analysis	3293	Patients receiving strong opioids for acute or chronic pain, including postoperative and cancer pain	Hydromorphone (long- or short-acting) Strong Opioid (long- or short-acting) Placebo	Overall, no differences between hydromorphone and other strong opioids • Hydromorphone ER = Morphine ER • Hydromorphone ER = Oxycodone ER Improvements in pain/anxiety • Fentanyl TD > Hydromorphone ER Chronic or acute pain relief • Hydromorphone IR = Hydromorphone ER	AEs • Hydromorphone < Meperidine Withdrawal symptoms • Hydromorphone ER < Morphine ER
Tassinari et al, 2008[65] Systematic review of 4 trials	425	Moderate to severe cancer pain	Transdermal opioids vs slow release oral morphine	Patient's preference • Transdermal > Oral (OR=0.43, p=0.014) Trial withdrawal • Transdermal = Oral Changes in opioid therapy • Transdermal = Oral	Adverse Events (all) • Transdermal = Oral Constipation • Transdermal < Oral • OR=0.38, p<0.001) Gastrointestinal AEs • Transdermal = Oral Nausea • Transdermal = Oral Neurological AEs • Transdermal = Oral
Buprenorphine TD					
Leng et al, 2015[151] RCT 8 week	280	Moderate to severe musculoskeletal pain inadequately controlled with NSAIDS	Buprenorphine TD (5-20 mcg/h) every 7 days Tramadol ER (100-400 mg/day) Three week titration, 5 week treatment phase	Pain scores on visual analog scale Buprenorphine TD = Tramadol ER (least squares mean difference from baseline between groups 0.45 (95% CI -0.02 to 0.91 demonstrating non-inferiority)	Buprenorphine TD = Tramadol ER

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Karlsson et al, 2009[152] RCT 12-week	134	Osteoarthritis of the hip/knee with suboptimal analgesia using paracetamol 4000 mg/day	Buprenorphine TD 5, 10, 15, 20 mcg/hour every 7 days Tramadol ER 75 to 200 mg BID Supplemental acetaminophen up to 2000 mg/day allowed	Box scale-11 pain score (mean weekly change from baseline) • Buprenorphine TD = Tramadol ER (non-inferiority, difference between groups -0.17 (95% CI, -0.89 to 0.54) Use of supplemental analgesic • Buprenorphine TD = Tramadol ER (206.4 vs 203.7 tablets over 12 weeks) Sleep quality, sleep disturbances • Buprenorphine TD = Tramadol ER Patient rated global assessment of pain relief • Buprenorphine TD > Tramadol ER (p=0.039) Investigator rated global assessment of pain relief • Buprenorphine TD > Tramadol ER (p=0.020) Patient preference Buprenorphine TD weekly > Tramadol ER (70.3%, 95% CI, 62-78)	AEs • Buprenorphine TD = Tramadol ER (88.4% vs 78.5%) Withdrawal due to AEs • Buprenorphine TD - 14.5% • Tramadol ER – 29.2% Most commonly reported AEs • Buprenorphine TD o nausea 30.4%, constipation 18.8%, dizziness 15.9% • Tramadol ER o nausea 24.6%, fatigue 18.5%, pain 12.3%
Embeda Trials					
Katz N et al, 2010[82] RCT 42 days	113	Chronic osteoarthritis pain of the hip of knee	Embeda vs Kadian Period 1: open-label titration of Kadian to optimal dose (max 160 mg BID) Period 2: Treatment phase Embeda or Kadian at optimized morphine dose Period 3: Kadian at predetermined dose for 7 days Period 4: Alternate treatment Embeda or Kadian	In-clinic pain intensity scores • Embeda = Kadian WOMAC total and subscale mean score reduction • Embeda > Kadian (not statistically significant) Summed brief pain inventory (BPI) mean scores • Embeda = Kadian Pharmacokinetic bioequivalence • Embeda = Kadian (95% CI of the ratio of the AUCs was 82% to 107%) Pharmacokinetics, AUC, mean morphine Cmax, morphine time-concentration curves and bioavailability • Embeda = Kadian	Serious Adverse Events • Chest pain unrelated to Embeda Discontinuations due to an AE • 27 during open-label Kadian titration • 1 during blinded Kadian treatment • 1 during blinded Embeda treatment
Fentanyl TD					

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Hartung et al, 2007[106] Retrospective cohort Fair quality	5,684	Medicaid patients receiving at least one ≥ 28 day prescription supply for methadone, oxycodone ER, morphine ER or fentanyl TD	Fentanyl TD (N=1546) Methadone (N=974) Oxycodone ER (N=1866) Morphine ER (N=1298)	Adjusted HR compared to morphine ER Mortality • Fentanyl TD o 0.80 (95% CI 0.63 to 1.02) • Methadone o 0.71 (95% CI 0.46 to 1.08) • Oxycodone CR o 0.71; 95% CI 0.54 to 0.94) Oxycodone ER • Hospitalization: 23% ↓ (0.77; 95% CI 0.66 to 0.91) Noncancer pain patients risk of ED encounter Fentanyl > Morphine ER (1.27; 95% CI 1.02 to 1.59)	Adjusted HR compared to morphine ER Oxycodone ER • ED encounter or hospitalization due to AE: 55% ↓ (0.45; 95% CI 0.26 to 0.77) • Constipation: 41% ↓ (0.59; 95% CI 0.35 to 1.00) Noncancer pain patients with overdose symptoms (no differences in death) • Methadone > Morphine ER (1.57; 95% CI 1.03 to 2.40)
Allan et al, 2005[62] RCT 13 months Fair quality	680	Chronic low back pain requiring strong opioid therapy	Fentanyl TD (titrated mean dose 57 mcg/hr) Morphine sustained release (titrated mean dose 140 mg/day)	Fentanyl TD = Morphine SR (non-inferiority) • Pain score • Pain relief within 7 days • Severe pain at rest • Severe pain on movement • Severe pain during the day • Severe pain at night • Rescue opioid use • Quality of life • Loss of working days • Withdrawal due to lack of efficacy ▪	AEs leading to discontinuation • Fentanyl TD > Morphine SR (p=0.098) o Fentanyl TD – nausea 37%, vomiting 24%, constipation 11% o Morphine SR – nausea 37%, vomiting 20%, constipation 23% Constipation at endpoint • Fentanyl TD < Morphine SR (31% vs 48%, p<0.001) Use of laxatives • Fentanyl TD < Morphine SR (53% vs 66%, p<0.001)

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Allan L 2001 RCT 8 weeks	256	Chronic noncancer pain receiving continuous, opioids for at least 6 weeks with 7 days of dose stability	Crossover Trial Fentanyl TD 25 to 100 mcg/hr MS Contin 10 to 200 mg daily	Patient preference • Fentanyl TD > MS Contin (65% vs 28%; p<0.001) Better pain relief (no difference with nociceptive, neuropathic or mixed pain) • Fentanyl TD > MS Contin (35% vs 23%; p=0.002) Pain intensity score reduction • Fentanyl TD > MS Contin (P<0.001) Quality of life scores • Fentanyl TD > MS Contin Investigators' global assessment of efficacy • Fentanyl TD > MS Contin (p<0.001) Use of rescue medication during the last 3 weeks of each treatment • Fentanyl TD > MS Contin (29.4 mg vs 23.6 mg; p<0.001)	Constipation • MS Contin > Fentanyl TD (48% v 29%, P<0.001) Nausea • Fentanyl TD > MS Contin (26% vs 18%) Cutaneous reactions • Fentanyl TD 41% Withdrawals due to AEs • Fentanyl > MS Contin (10% vs 5%) Withdrawals due to AEs in morphine or fentanyl naïve patients • Fentanyl > MS Contin (11% vs 10%)
van Seventer et al[153] RCT, open-comparative 4 week trial	131	Opioid-naïve patients with moderate to severe cancer pain or non-opioid naïve patients with mild-to-moderate pain	Titrated to response with Fentanyl TD Morphine SR	Pain control • Fentanyl TD = Morphine SR Sleep quality • Fentanyl TD = Morphine SR Patient global evaluation Fewer side-effects • Fentanyl TD > Morphine SR (14% vs 36%; p=0.003) Less interruption of daily activities • Fentanyl TD = Morphine SR (88% vs 63% of patients; p = 0.012). Investigator global evaluation Side effect profile • Fentanyl TD > Morphine SR (p=0.039) Overall impression • Fentanyl TD > Morphine SR (p=0.013) • Results were similar for opioid-naïve and opioid-tolerant patients	Discontinuation • Morphine SR > Fentanyl TD (59% vs 27%; p < 0.001) Discontinuation due to AEs • Morphine SR > Fentanyl TD (36% vs 4%; p < 0.001). Constipation • Morphine SR > Fentanyl TD (27% vs 57%; p = 0.003)

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Ahmedzai et al, 1997[77] RCT 30 day	202	Cancer patients requiring strong opioid analgesia and receiving a stable dose of morphine SR	For 15 days each: Fentanyl TD every 72 hours Morphine SR every 12 hours	Pain control (patient diaries) • Fentanyl TD = Morphine SR European Organization for Research and Treatment of Cancer (EORTC) pain scores • Fentanyl TD = Morphine SR The World Health Organization (WHO) performance status and EORTC global quality of life scores • Fentanyl TD = Morphine SR Use of rescue medication • Fentanyl TD > Morphine SR (53.9% vs 41.5%, p=0.0005) Upward dosage titration (≥ change) • Fentanyl TD > Morphine SR (47.1% vs 27.4%) Patient preference Fentanyl TD > Morphine SR (p=0.037)	Constipation • Fentanyl TD < Morphine SR (p<0.001) Daytime drowsiness • Fentanyl TD < Morphine SR (p=0.015) Sleep disturbance • Fentanyl TD > Morphine SR (p=0.004) Shorter sleep duration • Fentanyl TD > Morphine SR (p=0.008) Nauseas • Fentanyl TD < Morphine SR (p=0.04)
Mitra et al, 2013[63] RCT 12 months Poor quality	46	Opioid-naïve with persistent, chronic, noncancer pain	Doses titrated over 4 weeks, then as required Fentanyl TD Buprenorphine TD	Pain intensity, pain relief, quality of life, function • Fentanyl TD = Buprenorphine TD	Discontinuations for AEs or inadequate response or skin reactions • Fentanyl TD = Buprenorphine TD
Hydrocodone ER					
Rauck RL 2014	510	Moderate to severe lower back pain	Hydrocodone ER capsules Placebo	Mean change in pain intensity at 12 weeks • Hydrocodone > PBO (p=0.008) End of treatment period responders • Hydrocodone > PBO (P<0.001) Subject global assessment of pain scores from baseline • Hydrocodone > PBO (P<0.0001)	Consistent with usual opioid AEs
Kadian					

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
`Nicholson et al, 2006[154] RCT 24 week	112	Chronic, nonmalignant, moderate to severe pain	Kadian QD OxyContin BID (at week 2 an increase to TID was allowed)	Quality of Life (Physical and Mental component summary of the SF-36v2 health survey) • Kadian + OxyContin significant vs baseline (p<0.01 for both) Pain score improvements • Kadian + OxyContin vs baseline (p<0.05 vs baseline) Patient assessment of therapy • Kadian + OxyContin significant vs baseline (p<0.01 for both) Clinician assessment of therapy • Kadian + OxyContin significant vs baseline (p<0.01 for both) Sleep score improvement • Kadian + OxyContin significant vs baseline (p<0.001 vs baseline) • Kadian > OxyContin (p<0.05) Dosing frequency • Kadian (QD 65%, BID 35%) • OxyContin (BID 56%, TID 38%, QID 6%)	Kadian = OxyContin
Methadone					
Bruera E 2004 RCT 4 weeks	103	Malignant pain poorly controlled and requiring strong opioids	Methadone 7.5 mg Q12h + methadone 5 mg Q4h PRN Morphine SR 15 mg Q12h + morphine IR 5 mg Q4h PRN	Median Dose Day 14 (range) • Methadone 17.5 mg (7.5 to 40 mg) • Morphine SR 40 mg (15 to 100 mg) Median Dose day 28 (range) • Methadone 20 mg (7.5 to 40 mg) • Morphine SR 45 mg (15 to 150 mg) Reduction in pain at day 8 and 4 weeks $\geq$ 20% • Methadone = morphine SR (75%, 95% CI, 62.0 to 89.0 vs 75.9%, 95% CI 63.0 to 89.0) Proportion of treatment responders, day 28 (49%; 95% CI, 31 to 64 vs 56%; 95% CI, 41 to 70; p=0.50) Patient reported global benefit • Methadone = morphine SR (53%; 95% CI, 38 to 68 VS 61%; 95% CI, 47 to 75; p=0.41)	Withdrawal due to opioid AEs • Methadone) > morphine SR • (22% vs 6%, p=0.019) Sedation had a delayed onset compared with morphine CR and was of greater, but non-significant magnitude.

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Krebs et al, 2011[64] Retrospective cohort Fair quality	N=108,492	VA outpatients receiving a new 28+ day supply of either methadone or morphine LA from 2000 to 2007	Methadone (n=28,554) Morphine long-acting (n=79,938) Quintile scoring by logistic regression was performed to estimate propensity for prescribing methadone.	All-cause mortality within 1st 30 days • Morphine LA 3.7% • Methadone 1.2% Overall risk of mortality (presumed from accidental ingestion and robust in all quintile validation assessments) Morphine LA > methadone (Adjusted HR 0.56; 95% CI 0.51 to 0.62)	
Morphine SR					
Mercadante et al, 2008[84] RCT 4 weeks	108	Cancer patients with moderated pain, non-responsive to opioids	(Titration) to effect Morphine SR Methadone Fentanyl TD Morphine IR for breakthrough pain during titration	Pain • Morphine SR = Methadone = Fentanyl TD Symptom intensity • Morphine SR = Methadone = Fentanyl TD Quality of life scores • Morphine SR = Methadone = Fentanyl TD Opioid escalation index • Methadone < Morphine SR or Fentanyl TD (p<0.0001) More titrations up or down were required. The authors suggest clinical expertise is required with this agent.	Opioid switching • Morphine SR 5 patients • Methadone 5 patients • Fentanyl TD 5 patients Adverse Effects Morphine SR = methadone = fentanyl TD
OxyContin Trials					
Bruera et al, 1998[155] RCT 2 weeks	32	Cancer pain receiving oral opioid therapy	Oxycodone CR (OxyContin) + Placebo Q12h for 7 days Morphine CR (MS Contin) + Placebo Q12h for 7 days	Any pain measurement at any time • OxyContin = MS Contin Average daily number of rescue doses OxyContin > MS Contin (2.3 vs 1.7, p=0.01)	Sedation • OxyContin = MS Contin Nausea • OxyContin = MS Contin
Gimbel JS 2003 Ma K 2008 Watson CPN 2003		Neuropathic pain Chronic refractory neck pain	Oxycodone CR Placebo	Pain Control Oxycodone controlled-release > Placebo	AEs Oxycodone CR 96% - typical opioid AEs
`Bruera E 1998		Cancer pain	Morphine CR Oxycodone CR	Reducing pain intensity • Oxycodone CR = Morphine CR Rescue doses used in 24 hours Oxycodone CR > Morphine CR (P=0.001)	Nausea, sedation Morphine CR = Oxycodone CR

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Salzman 1999[142] RCT 10 days Fair quality	48 57	Cancer pain Chronic, stable back pain of moderate to severe intensity despite therapy	Titrated dose cancer pain: • Oxycodone SR Q12h • Oxycodone IR QID Titrated dose back pain: • Oxycodone SR Q12h Oxycodone IR QID	Stable pain control, time to achieve pain control, degree of pain control, number of dose adjustments • Oxycodone SR = Oxycodone IR Titrated mean dose cancer pain • Oxycodone SR = oxycodone IR Titrated mean dose back pain • Oxycodone SR = oxycodone IR	AEs in cancer and noncancer pain (~10%) Oxycodone SR = oxycodone IR • Most commonly: nausea, vomiting, constipation, somnolence, dizziness, and pruritus. Withdrawal due to AEs (none serious) Cancer pain 1-CR, 2-IR Noncancer pain 6-CR, 1-IR
Oxymorphone ER Trials					
Kivitz et al, 2006[156] RCT 2 weeks	370	Osteoarthritis pain regularly taking NSAID, acetaminophen or opioid for 90 days with suboptimal response	Oxymorphone ER 10 mg Q12h Oxymorphone ER 20 mg Q12h for 7 days → 40 mg Q12h for 7 days Oxymorphone ER 20 mg Q12h for 7 days → 50 mg q12h for 7 days Placebo	Arthritis pain index score • Oxymorphone 40 mg Q12h > baseline (p=0.012) • Oxymorphone 50 mg Q12h > baseline (p=0.006)	Commonly reported AEs • Nausea (39.4%) • Vomiting (23.7%) • Dizziness (22.6%) • Constipation (22.6%) • Somnolence (17.6%) • Pruritus (16.5%) • Headache (14.7%)
Sloan et al, 2005[157] 7-days (period 2)	63	Chronic cancer pain receiving ≥ 30 mg morphine equivalent units daily	Patients were crossed from their stabilized 7 day OxyContin or MS Contin dose to an equianalgesic dose of Oxymorphone ER Oxycodone CR (OxyContin) Morphine CR (MS Contin)	Mean daily pain intensity scores • Oxymorphone ER = OxyContin = MS Contin Average total daily dose in equivalent units • Oxymorphone ER < Morphine CR or Oxycodone CR Rescue medication use Morphine CR > Oxymorphone ER (25.2% vs 13.3%; p<0.05)	Common AEs (e.g., nausea, drowsiness, somnolence) were similar for all opioids.
Hale et al, 2005[74] RCT	213	Moderate to severe chronic low back pain requiring opioid therapy.	Dose titration phase – 7 days • Oxymorphone ER Q12h • Oxycodone CR Q12h Stabilized blinded therapy • Oxymorphone ER • Oxycodone CR Placebo	Mean dose • Oxymorphone ER 10 to 110 mg • Oxycodone CR 20-220 mg Change from baseline in pain intensity • Oxymorphone ER (79.4 mg/day) > placebo • Oxycodone CR (155 mg/day) > placebo LS mean differences were -18.21 and 18.55 (95% CI, -25.83 to -10.58 and -26.12 to -10.98, respectively; P = .0001).	Oxymorphone ER = Oxycodone CR AEs at a statistically higher incidence than placebo (equivalent for both treatments) • Constipation • Sedation
Tapentadol ER Trials					

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Afilalo et al, 2010[81] RCT 12 weeks	1030	Osteoarthritis of the knee with functional capacity class I-III, requiring analgesia (morphine equivalents ≤ 160 mg daily) and dissatisfied with their current regimen	Tapentadol ER (max dose 250 mg BID) Placebo Oxycodone CR (max dose 20 mg BID	Pain relief at 12 weeks • Tapentadol ER > Placebo (least squares mean difference, -0.7 (95% CI -1.04 to -0.33) Average pain intensity rating reduction for maintenance period • Oxycodone > Placebo (least squares mean difference vs placebo, -0.3 (95% CI, -0.67 to 0.00)) Average pain intensity rating reduction at 12 weeks • Oxycodone = Placebo (least squares mean, -0.3 (95% CI,-0.68 to 0.02)) Percentage achieving ≥ 50% reduction in pain intensity at week-12 from baseline • Tapentadol ER (32.0 vs 24.3%, p=0.027) = Percentage not achieving a ≥ 50% reduction in pain intensity at week-12 from baseline • Oxycodone CR (17.3 vs 24.3%, p=0.023)	AEs • Placebo 61.1% • Tapentadol ER 75.9% • Oxycodone CR 87.4% Most common with active treatment • Nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus AEs leading to discontinuation • Placebo 6.5% • Tapentadol ER 19.2% • Oxycodone ER 42.7% (mainly GI)
Imanaka et al, 2013[158] RCT 4 weeks Japan + South Korea	343	Chronic, malignant tumor-related pain not currently taking strong opioids and dissatisfied with current treatment	Tapentadol ER 25 to 200 mg BID Oxycodone CR 5 to 40 mg BID Rescue medication: morphine IR 5 mg	Pain intensity score • Tapentadol ER = Oxycodone CR (non-inferiority) Percentage reporting pain improvement as very much, much or minimally improved • Tapentadol ER > Oxycodone CR (89.7% vs 82.7% (no statistics presented) Rescue medication: number of patients, number of doses, daily dosage • Tapentadol ER ~ Oxycodone CR	Not reported
Buynak et al, 2010[80] RCT 15 weeks	981	Non-malignant low back pain of at least 3 months unsatisfied with current analgesia regimen (if taking opioids: morphine equivalents ≤ 160 mg daily)	Randomized 1:1:1 Tapentadol ER 100-250 mg BID Oxycodone CR 20-50 mg BID Placebo	Improvements in average pain intensity scores at week-12 • Tapentadol ER > Placebo (P<0.001) • Oxycodone CR > Placebo (P<0.001) Pain intensity improvement of ≥ 30% at week-12 • Tapentadol ER > Oxycodone CR (39.7% vs 30.4%, statistically significant vs placebo only with Tapentadol ER) Pain intensity improvement of ≥ 50% at week-12 • Tapentadol ER > Oxycodone CR (27.0% vs 23.3%, statistically significant vs placebo only with Tapentadol ER)	Treatment emergent AEs • Overall: Tapentadol ER < oxycodone CR • Gastrointestinal Placebo < Tapentadol ER < Oxycodone CR (26.3% vs 43.7% vs 61.9%) included: constipation, nausea, and vomiting Odds of constipation or nausea/vomiting • Tapentadol ER < Oxycodone CR (both p < 0.001).

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
Schwartz et al, 2011[159] RCT 12 weeks	588	Patient with painful diabetic peripheral neuropathy of > 3 months, dissatisfied with their current medication regimen and average pain score of >5 of an 11 point numerical rating score.	Open-label titration over 3-weeks to therapeutic dose of tapentadol ER (100-250 mg bid) Patients (n=395) with a 1 point reduction in pain intensity were randomized 1:1 to blinded placebo or fixed dose of tapentadol ER	Mean change in average pain intensity at week 12 Placebo (1.4) > Tapentadol (0.0) least squares mean difference, -1.3; 95% CI -1.70 to -0.92; p<0.001	Treatment emergent AEs • Tapentadol > Placebo (nausea, anxiety, diarrhea, and dizziness)
Wild et al, 2010[58] RCT 12 months Fair quality	1117	Low-back pain, moderate or severe knee/hip osteoarthritis	Tapentadol ER 100-250 mg BID (N=894) • 413 completed 6 months • 227 competed 12 months Oxycodone CR 20-50 mg BID (N=223) • 78 completed 6 months • 44 completed 12 months	Pain Intensity Tapentadol ER = Oxycodone CR Global assessment of very much improved Tapentadol ER = Oxycodone CR Concomitant analgesics (NSAID, ASA, ACTM) Tapentadol ER = Oxycodone CR	Oxycodone CR > tapentadol ER • Constipation (22.6% vs 38.6% • Nausea (18.1% vs 33.2%) • Vomiting (7.0% vs 13.5%) • Pruritus (5.4% vs 10.3%) • Dizziness (14.8% vs 19.3%) Discontinuations • Tapentadol ER 53.8% 22.7% for AEs • Oxycodone CR 65.0% 36.0% for AEs
Tramadol ER Trials					
Beaulieu et al, 2007[160] Randomized, double-blind, crossover study	122	Chronic, noncancer pain of at least moderate intensity	Tramadol CR 200 mg QAM + Placebo IR tramadol 50 mg every 4 to 6 hours PRN rescue Placebo tramadol CR 200 mg QAM + active tramadol IR 50 mg every 4 to 6 hours PRN rescue. At 2 weeks Tramadol CR ↑ 400 mg Tramadol IR ↑ 100 mg	Daily tramadol dose • Tramadol CR = 2x tramadol IR Pain relief week final 2 weeks • CR > IR (mean [SD]) Visual analog scale P < 0.001 Ordinal scale P < 0.001 Patient and investigator rated effectiveness • Tramadol CR > tramadol IR (P < 0.004 and P < 0.008 respectively) Patient preference No difference	Withdrawal Rates • Tramadol CR > tramadol IR (19.7% vs 11.5%, NSS) Withdrawal due to AE • CR 30.0% vs IR 29.2% (NSS) Sleep Scores No difference

Reference Study Design	N	Patient Selection	Treatment Interventions	Results	Adverse Effects
DeLemos et al, 2011[161] RCT 12-week	801	Moderate to severe osteoarthritis pain of the hip or knee	Tramadol ER 100 mg daily Tramadol ER 200 mg daily Tramadol ER 300 mg daily Celecoxib 200 mg daily Placebo daily Celecoxib validated the model's sensitivity and was not compared to Tramadol ER for efficacy or harms.	Primary Endpoints WOMAC pain subscale • Tramadol ER 100 and 200 mg = Placebo WOMAC physical function subscale • Tramadol ER 100 and 200 mg = Placebo Patient global assessment of disease activity • Tramadol 300 mg > Placebo ($p \leq 0.05$) • Tramadol ER 100 and 200 mg = Placebo Other endpoints Patient daily pain intensity diary • Tramadol ER 200 and 300 mg > Placebo WOMAC joint stiffness subscale, physician's global assessment, arthritis pain intensity in index/non-index joint, sleep quality • Tramadol ER 300 mg > Placebo	Gastrointestinal AEs (constipation, nausea, diarrhea) • Tramadol ER > Placebo CNS AEs (dizziness, headache) • Tramadol ER > Placebo

LA – Long-acting; ER – extended release; CR – controlled release, IR – immediate release; WOMAC - Western Ontario and McMaster Universities Pain Index; HR – harms ratio