Extended Release High Potency Opioids Subclass
High Potency Narcotic Analgesics

Executive Summary

- All extended release opioids (EROs) have established efficacy in the treatment of moderate to severe chronic pain.
- There is insufficient evidence to suggest that one ERO is superior to another in terms of efficacy or safety.
- EROs now have a new indication that promotes the trial of non-opioid alternative treatments prior to initiating long-term opioid treatment.
- The shared extended release/long-acting (ER/LA) Risk Evaluation Mitigation Strategy (REMS) requires that manufacturers of EROs provide education materials to prescribers and patients in an effort to reduce serious adverse events resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioids while maintaining patient access to pain medications.

Table 1: Uniform Formulary Recommendations for the Narcotic Analgesics from Previous Formulary Decisions

	Generic/brand (name)	Formulations	Generics Available
Uniform Formulary	**High-potency single analgesic agents**		
	Long-acting agents (≥12 hour duration)		
	Hydromorphone OROS (Exalgo)	tabs	no
	Fentanyl transdermal system (Duragesic)	patch	yes
	Morphine sulfate ER 24 hr (Kadian, Avinza)	cap	no
	Morphine sulfate SR 12 hr (MS Contin*, Oramorph)	tab, soln, supp, inj	yes
	Morphine sulfate ER/Naltrexone (Embeda)	caps	no
	Oxycodone ER (Oxycontin)	tabs	no
	Oxymorphone (Opana ER)	tabs	yes
	Tapentadol ER (Nucynta ER)	tabs	no
	Short-acting agents (<12 hour duration)		
	Codeine	tabs, soln, inj	yes
	Fentanyl citrate transmucosal (Actiq)	lozenges	yes
	Hydromorphone (Dilaudid)	tab, inj, liquid	yes, except for 1 mg tab
	Levorphanol (Levo-Dromoran)	tab, inj	yes
	Meperidine (Demerol)	tab, soln, inj	yes
	Meperidine/promethazine (Mepergan Fortis)	caps	yes
	Methadone (Dolophine)	tab, oral conc, soln, inj	yes
	Morphine sulfate IR*	tabs	yes
	Opium	tincture	yes
	Opium/belladonna alkaloids	supp	yes
	Oxycodone IR	caps, oral conc, soln	yes
	Oxymorphone IR (Opana)	tabs	yes
	High potency combination agents		
	Oxycodone/APAP (e.g., Percocet, Tylox, others)*	tab, cap, soln	yes
	Oxycodone/ASA (Percodan)	tabs	yes
	Low potency single analgesic agents		
	Buprenorphine (Buprenex)	inj (excludes SL tabs)	yes
	Buprenorphine transdermal system (Butrans)	patch	no
	Butorphanol (Stadol)	nasal spray, inj	yes
	Pentazocine/naloxone (Talwin NX)	tabs	yes
	Propoxyphene (Darvon)	caps, tabs	yes
	Nalbuphine (Nubain) not a controlled substance	inj	yes
	Tramadol IR (Ultram)*	tab	yes

Uniform Formulary	**Low potency combination agents**		
	Codeine/APAP (Tylenol with codeine)*	tabs, elixir, oral susp	yes
	Codeine/ASA	tabs	yes
	Codeine/ASA/carisoprodol (Soma)	tabs	yes
	Codeine/caffeine/butalbital/APAP (Fioricet with codeine)	caps	yes
	Codeine/caffeine/butalbital/ASA (Fiorinal with caffeine)	caps, tabs	yes
	Dihydrocodeine/caffeine/APAP (e.g., Panlor DC, Panlor SS)	caps, tabs	yes
	Dihydrocodeine/caffeine/ASA (Synalgos-DC)	caps	yes
	Hydrocodone/APAP (e.g., Lortab, Lorcet, Vicodin, others)	caps	yes
	Pentazocine/APAP (Talacen)	tabs	yes
	Tramadol/APAP (Ultracet)	tab	yes
Nonformulary	**Low potency single analgesic agents**		
	Tramadol extended release (Ultram ER)	tab	no
	Tramadol extended release (Ryzolt)	tab	no
	High potentcy single analgesic agents; short-acting agents (<12 hours duration)		
	Tapentadol IR (Nucynta)	tab	no
	Oxycodone IR (Oxecta)	tab	no
	Fentanyl buccal tablet (Fentora)	tab	no
	Fentanyl sublingual tablet (Abstral)	tab	no
	Fentanyl pectin nasal spray (Lazanda)	nasal spray	no
	Fentanyl sublingual spray (Subsys)	sublingual spray	no

*Basic Core Formulary (BCF) agents

Table 2: EROs—Subclass Definition

Brand	Formulation	FDA Approval	Generic Availability	Abuse Deterrence Labeling
Morphine sulfate (MS Contin)	12-hour tablets	May 29, 1987	May 29, 1987	no
Morphine ER (Avinza, Kadian)	12-24 hour capsules	Mar 20, 2002; Jul 03, 1996	Mar 20, 2002; Jul 03, 1996	no
Morphine ER/naltrexone (Embeda)	24-hour capsules	Aug 13, 2009	Aug 13, 2009	yes
Fentanyl (Duragesic)	72-hour transdermal system	Aug 07, 1990	Aug 07, 1990	no
Oxycodone (Oxycontin)	12-hour tablets	Jul 16, 2009	Jul 16, 2009	yes
Oxymorphone (Opana ER)	12-hour tablets	Jan 4, 2012	Jan 4, 2012	no*
Tapentadol (Nucynta ER)	12-hour tablets	Aug 25, 2011	Aug 25, 2011	no*
Hydrocodone (Hysingla ER)	24-hour tablets	Nov 20, 2014	Nov 20, 2014	yes
Hydrocodone (Zohydro ER)	12-hour tablets	Oct 25, 2013	Oct 25, 2013	no*
Hydromorphone (Exalgo)	24-hour tablets	Mar 1, 2010	Mar 1, 2010	no*

*Formulated with physicochemical properties aimed at reducing the likelihood of abuse though not supported by formal abuse liability studies.

FDA-Approved Indications

The EROs were previously indicated for the management of moderate to severe chronic pain. However, as of April 2014, the indication has been updated by the FDA in an effort to identify patients expected to benefit from opioids and help prevent problems associated with their use. The EROs are now indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options (non-opioid analgesics, short-acting opioids) are inadequate. Tapentadol ER (Nucynta ER) is the only ERO with an FDA-approved indication for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (DPN).

Generic Availability of Oxycontin

Table 2 shows the EROs that are commercially available in generic form. Oxycontin was reformulated in April 2010 in order to incorporate abuse deterrent properties causing an extension of its patent life. Patent settlements have now resulted in limited amounts

of generic Oxycontin becoming commercially available. As of April 2015, there has been and will continue to be a limited amount of oxycodone ER tablets, an authorized generic, available from multiple suppliers. The supply is expected to be sporadic and may not be available at every pharmacy. Purdue will manufacture the generic product and has confirmed that the following strengths will not be available in generic form: 15 mg, 30 mg, and 60 mg tablets. Patents for Oxycontin extend until March 2030.

Abuse Deterrent Formulations

EROs are more attractive for abusers than immediate release (IR) opioid formulations because of the higher dose concentrations the subject is exposed to once the formulation is manipulated. This has resulted in a national epidemic of prescription opioid abuse and associated opioid-related overdose and deaths. In an effort to combat the rising concern of opioid abuse and diversion, the FDA has supported the development of abuse-deterrent formulations of opioids, issuing specific recommendations to industry, and applying these principles to regulatory decisions. This is part of a comprehensive approach to address the issue of abuse. Claims regarding abuse-deterrent properties will appear in the product's full prescribing information when the drug has attributes intended to discourage its abuse and has undergone studies in one or more categories specified by the FDA with results showing that the drug can be expected to result in or has demonstrated a meaningful reduction in its abuse.

Four EROs have received FDA claims and three of them are commercially available. Oxycodone ER/naloxone (Targiniq) manufactured by Purdue obtained FDA approval and received claims regarding abuse deterrence in the product labeling. Purdue has decided not to launch this ERO and put their marketing force behind Oxycontin and Hysingla ER instead. See Table 2.

Previous Formulary Decisions

The narcotic analgesic drug class was last reviewed for formulary placement in February 2007. At that time, the Department of Defense (DoD) Pharmacy and Therapeutics (P&T) Committee designated morphine sulfate controlled release (MS Contin, generics) as the BCF agent. Every other ER high potency opioid was included on the Uniform Formulary (UF). Since the class review, morphine ER/naltrexone (Embeda), hydromorphone ER (Exalgo), and tapentadol ER (Nucynta ER) were added to the UF, following their evaluations as new drugs in an already reviewed class.

Summary of the Evidence

Clinical practice guidelines

- Patients with pain should be started on acetaminophen or a non-steroidal anti-inflammatory drug (NSAID). In the case of inadequate pain relief, patients should be escalated to a weak opioid and then to a strong opioid (like morphine).
- Dosing, titration, and opioid selection should be individualized considering the patient's health status, prior exposure to opioids, therapeutic goals, and anticipated or observed harms.
- Chronic pain patients with persistent pain, controlled by stable doses of short-acting opioids, should be provided 'around-the-clock' EROs with rescue dose made available for breakthrough pain
- For opioid-naïve patients, morphine is generally considered the standard starting drug of choice.
- Pure agonists are most commonly used in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone.
- In patients who require relatively high doses of chronic opioid therapy, clinicians should routinely evaluate for opioid-related adverse events, changes in health status, and adherence to the chronic opioid therapy regimen and treatment plan.
- The Centers for Disease Control and Prevention's (CDC) National Center for Injury Prevention and Control, along with other federal agencies, reviewed eight guidelines and published common elements for prescribing opioids for chronic pain. The recommendation elements found in all the guidelines include:
  - Conducting a physical exam, pain history, past medical history, and family/social history
  - Conducting urine drug testing, when appropriate
  - Considering all treatment options, weighing benefits and risks of opioid therapy, and using opioids when alternative therapies are ineffective
  - Starting patients on the lowest effective dose
  - Implementing pain treatment agreements
  - Monitoring pain and treatment progress with documentation, using greater vigilance at high doses
  - Using safe and effective methods for discontinuing opioids (e.g., tapering)

Clinical Efficacy

- The short-term efficacy of the ERO agonists for the treatment of moderate to severe pain has been well established in the literature. Data from clinical trials have demonstrated superiority over placebo in achieving pain relief for all the agents in question and were reviewed in detail as part of the review in February 2007. Head-to-head trials of EROs were also presented in 2007 and, for the most part, demonstrated similar efficacy among the individual agents evaluated.
- Since the class review and new drug evaluations, two new single entity hydrocodone ER products have come to market (Hysingla ER and Zohydro ER).

- Hysingla ER tablets incorporate abuse-deterrent technology that confer resistance to crushing, dissolving, and breaking—manipulations often employed for abuse through intranasal and intravenous routes. The FDA approved label support claims indicating Hysingla ER has physiochemical properties that are expected to create barriers and result in a meaningful reduction in abuse.
- Efficacy for Hysingla ER was demonstrated in a clinical trial of 905 patients with moderate to severe chronic low back pain. Hysingla ER 20 mg to 120 mg dosed once every 24 hours in opioid-naïve and opioid-experienced patients was superior to placebo at week 12, resulting in significantly lower "average pain over the last 24 hours" pain scores.
- Zohydro ER was initially launched in 2013 without any mechanism in place to create a barrier for abuse. The controversy surrounding its release led to the company reformulating the product, incorporating polyethylene oxide beads into the existing formulation. This excipient forms a viscous gel when crushed and dissolved in aqueous solution that is intended to deter injection of the manipulated product. No formal studies have been conducted with the reformulated product to show abuse deterrence and the FDA has not allowed for such claims to appear on the product labeling.
- Zohydro ER's efficacy was demonstrated in one clinical trial involving over 500 patients with moderate to severe chronic low back pain. Patients who had been successfully converted from their current opioid to Zohydro ER were randomized to continue active treatment at doses ranging from 20 mg to 100 mg given every 12 hours or switch to placebo in the double-blind phase. After 12 weeks, the average daily pain intensity score increased significantly more with placebo than Zohydro ER.
- Two systematic reviews conducted to evaluate the comparative efficacy of the EROs found insufficient evidence to suggest that one ERO is superior to another in adult patients with chronic non-cancer pain. The placebo-controlled trials provided no useful indirect evidence for determining the comparative efficacy of the EROs, given the heterogeneity in terms of study designs, patient populations, interventions, and assessed outcomes.

Safety

- As part of the FDA's new labeling requirement, all ERO labels must state the innate risk of addiction, abuse, and misuse even at recommended doses and include an updated warning of the risk of neonatal opioid withdrawal syndrome (NOWS) with prolonged use of EROs during pregnancy. EROs share similar black box warnings that highlight the risk of respiratory depression and the potential for accidental exposure in children, which can result in fatal overdose. Other black box warnings include cytochrome P450 3A4 interactions (applicable for fentanyl, single entity hydrocodone ER products, and Oxycontin) as well as interactions with alcohol that may result in fatal overdose (applicable for the ER morphine products, oxymorphone ER, Zohydro ER, and Nucynta ER).
- There is a shared REMS access program for all the ERO products. This shared REMS requires companies who manufacture LA opioids to make training, regarding proper prescribing practices, available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents.
- The goals of the REMS are to reduce serious adverse events resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioids while maintaining patient access to pain medications.
- All EROs are pregnancy category C.
- Only fentanyl transdermal system is approved in children (ages 2 to 17 years).
- Tapentadol is contraindicated with monoamine oxidase inhibitors, although caution should be used with any ERO given the enhanced opioid effects that can occur when combined.
- Only oxymorphone is contraindicated in severe hepatic disease.
- In general, opioid-related adverse effects are similar for all the EROs, with commonly reported effects being constipation, nausea, vomiting, dizziness, somnolence, headache, dizziness.
- Regarding harms, one systematic review evaluated evidence from observational studies that suggests being prescribed long-term opioids for chronic pain is associated with increased risk of abuse, overdose, fractures, and myocardial infarction versus not being prescribed opioids. Additionally, the risk suggested to be dose-dependent with higher doses was associated with increased risk.

Abuse Liability Studies

Outcome Measures

- Drug liking measured on a bipolar drug liking scale 0 to 100
  (0 = maximum disliking; 50 = neutral; 100 = maximum liking)
- 'Likelihood to take the drug again' measured on a unipolar scale of 0 to 100
  (0 = "definitely would not take drug again;" 100 = "definitely would take drug again")

Oxycontin

In a single-center dose crossover study evaluating the effects of various tampering methods on the exposure to oxycodone in fasting healthy subjects, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. There were five treatment arms: finely-crushed reformulated Oxycontin, coarsely-crushed

reformulated Oxycontin, finely-crushed original Oxycontin, Oxycontin powder, finely-crushed placebo. Results showed that finely-crushed and coarsely-crushed reformulated Oxycontin had lower drug liking scores than crushed original and powdered Oxycontin and higher scores than placebo. Despite the fact that intranasal reformulated Oxycontin has lower abuse potential than the original formulation, there is still evidence suggesting higher abuse potential compared to placebo.

Hysingla

A single-center, randomized, double-blind, placebo-controlled and positive-controlled crossover study in 31 nondependent opioid abusers with a history of intranasal opioid abuse was conducted to evaluate the intranasal abuse potential of Hysingla ER. The treatment arms included: fine and coarse Hysingla ER 60 mg tablets manipulated with an industrial mill and razor blade compared to hydrocodone 60 mg powder and placebo. Results showed that the intranasal administration of manipulated Hysingla ER was associated with significantly lower scores for drug liking and take drug again, compared with powdered hydrocodone. The FDA deemed both Oxycontin and Hysingla ER to have lower intranasal abuse potential than their non-abuse deterrent comparator.

Other Factors

- At equianalgesic doses, the EROs are interchangeable to a moderate degree for the treatment of moderate to severe pain. Incomplete cross-tolerance may occur when switching from one opioid to another which may lead to greater than anticipated potency in the new opioid. Also, tapentadol ER is the only ERO with an indication for neuropathic pain associated with DPN.
- In order to meet the needs of majority of patients, several options within the ERO subclass are needed on the UF, particularly to satisfy the requirement for opioid rotation when patients become tolerant and require higher doses of an ERO or experience limiting adverse effects with one opioid. There are several generic options available on the UF to potentially meet the needs of most patients.
- Besides fentanyl transdermal system, which is dosed every 72 hours, most of the EROs are dosed twice daily (oxycodone, oxymorphone, tapentadol, and Zohydro ER). Exalgo, Avinza, and Hysingla ER are dosed once daily. Kadian and Embeda may be dosed once or twice daily. MS Contin tablets are administered two to three times daily.
- Avinza and tapentadol ER are the only EROs with a maximum daily dose limit. Avinza has a maximum dose of 1600 mg due to the fumaric acid contained in the formulation, which may be renally toxic at higher doses. The maximum daily dose of tapentadol ER is 500 mg.
- Fentanyl transdermal system and Exalgo are approved for use in opioid-tolerant patients only at all doses. The other EROs have starting recommendations for opioid-naïve patients and restrict certain high doses for opioid-tolerant patients.
- While abuse deterrent formulations offer a potential barrier to abuse via intravenous and intranasal routes, they have yet to demonstrate the ability to prevent abuse altogether. Abusers can still overcome the technologies in these formulations by over consumption. Providers need to be aware of other tools available to help ensure safe opioid prescribing, as recommended by the CDC's recent publication. Training initiatives for providers within the DoD include the following:
  - "Do no harm." This mandatory training is required for all credentialed and privileged prescribing providers. It provides education on identifying patterns of prescription substance misuse and proposes potential interventions via interactive clinical scenarios.
  - Annual Pain Skills Training is hosted by the National Capital Region Pain Care Initiative.
  - Wounded Warrior Pain Care Initiative
  - Project ECHO (Extension for Community Healthcare Outcomes) is a collaborative model of medical education and patient case consultation that enables primary care providers to provide better care to patients while expanding treatment capacity.

Conclusion

- The EROs have been recognized as the mainstay of chronic pain management with well-documented evidence of their efficacy in the short term. Current guidelines do not state a preference for the use of one ERO over another for the use in moderate to severe pain.
- Conclusions from the 2007 review are still applicable with no new evidence regarding the comparative effectiveness of the EROs. Two systematic reviews concluded that there is insufficient evidence to suggest differences in efficacy and safety among the EROs.
- While abuse-deterrent opioids present a potential barrier to manipulating EROs, it is unknown what the clinical relevance is of reduced drug liking in clinical practice and what the impact of these formulations will be on rates of abuse in the community.

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Abbreviations

The following abbreviations are used in this review:

AMCP	– Academy of Managed Care Pharmacy
BCF	– Basic Core Formulary
CDC	– Centers for Disease Control and Prevention
DoD	– Department of Defense
DPN	– diabetic peripheral neuropathy
ER/LA	– extended release/long-acting
EROs	– extended release opioids
IR	– immediate release
NCCN	– National Comprehensive Cancer Network
NOWS	– neonatal opioid withdrawal syndrome
NSAID	– non-steroidal anti-inflammatory drug
P&T	– Pharmacy and Therapeutics
Project ECHO	– Extension for Community Healthcare Outcomes
REMS	– Risk Evaluation Mitigation Strategy
UF	– Uniform Formulary