Evidence-Based Tools for Screening for Patients at Risk and Monitoring for Adherence to Prescribed ER/LA Opioids

Key Principles of Managing Therapy With ER/LA Opioids

Use clinical evidence-based guidelines to:

- Screen for risk, including assessment of psychiatric comorbidities
- Establish analgesic and functional goals
- Use Patient Prescriber Agreements (PPAs) and monitor patient adherence
- Anticipate/Manage adverse effects and periodically assess benefits, health-related quality of life, the side effect frequency and intensity, and the continued need for opioid analgesics
- Reevaluate patient's underlying medical condition if clinical presentation changes over time
- Use referral sources for the treatment of abuse and addiction

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. https://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm515636.pdf. Updated May 2017. Accessed January 17, 2018.

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Realistic Individualized Goal-Setting

- Reach agreement with patient on treatment goals
- Patient-specific goals may include 1 or more of the following:
  - Pain reduction: 30% considered clinically significant
    - Explain to patient that complete pain relief rarely achieved
  - Improvement in select functional areas:
    - eg, ability to work full time at previous or modified job; play golf once a week, walk the dog daily
  - Improved mood

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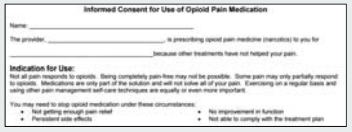
Informed Consent & Pain Agreement

Informed Consent:	Patient Provider Agreement :
➢ Use to discuss risks and benefits of opioid medication therapy ➢ Do this once ➢ Available free of charge from many sources, eg: ▪ American Academy of Pain Medicine: http://www.painmed.org/files/consent-for-chronic-opioid-therapy.pdf	➢ Contains the conditions for continued prescribing ➢ Do this yearly or with changes in pharmacy ▪ Available free of charge from many sources, eg: https://www.drugabuse.gov/sites/default/files/files/SamplePatientAgreementForms.pdf


Informed Consent for Use of Opioid Pain Medication

Name: _____

The provider: _____ is prescribing opioid pain medicine (narcotics) to you for

_____ because other treatments have not helped your pain.

Indication for Use:

Not all pain responds to opioids. Being completely pain-free may not be possible. Some pain may only partially respond to opioids. Medications are only part of the solution and will not solve all of your pain. Exercising on a regular basis and using other pain management self-care techniques are equally or even more important.

You may need to stop opioid medication under these circumstances:

- Not getting enough pain relief
- Persistent side effects
- No improvement in function
- Not able to comply with the treatment plan


Pain Management and Safety Agreement

The purpose of this agreement is to prevent misunderstandings about the medicine you will be taking for your pain. This is to help both you and your provider comply with the laws regarding these medicines. This agreement is essential to the trust and confidence necessary in a provider/patient relationship.

____ 1. I agree to obtain all pain medications from Dr _____. I will inform my provider if I establish care with any new providers or if I am prescribed any new medications.

____ 2. In the event of an emergency, I will inform the emergency providers that I have a pain management agreement with my primary care provider. I understand that if I am prescribed a small amount of pain medication, I am required to report it to my provider as soon as possible.

____ 3. I will purchase my pain medicine at _____ pharmacy, phone # _____. I understand that my provider may not be able to prescribe my pain medication through a mail order pharmacy. I may be limited to fill a 30-day supply at a time at the local pharmacy above.

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Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

Patient Prescriber Agreement (PPA)

- Clinical evidence and guidelines support use of agreements
- Any of following can be used as a PPA:
  - Informed consent documents
  - Treatment agreement documents
  - PPA available for download at no cost*
- Benefits
  - Informed decision making with patient
  - Enables clear and mutual understanding of goals and expectations and respective responsibilities of patient and clinician
  - Can be jointly signed during patient visit

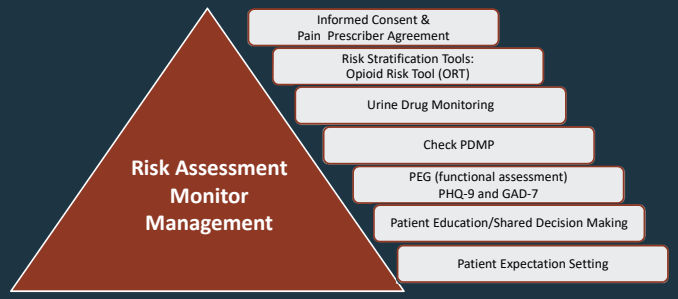
Chou R et al. *J Pain*. 2009;10(2):113-130.

What Is Typically in a Patient Prescriber Agreement (PPA)

- Understanding of risks and benefits of opioid therapy
- Taking the opioid exactly as prescribed
- **One** prescribing doctor and one designated pharmacy and whether or not refills will be called in to pharmacy without an office visit
- Urine/Serum drug testing when requested
- Pill counts at each office visit
- No early refills
- How to safeguard their opioid medication
- List of behaviors that may lead to discontinuation of opioids
- Places for signature and dating

Chou R et al. *J Pain*. 2009;10(2):113-130.

Screening and Monitoring



GAD, general anxiety disorder; PDMP, Prescription Drug Monitoring Program; PEG, pain, enjoyment, general activity; PHQ, Patient Health Questionnaire

Monitoring Patient Adherence

- Level of monitoring depends on risk stratification level determined during initial screening (using ORT or other tool)
  - State PDMPs (Prescription Drug Monitoring Programs)
  - Urine drug testing (UDT)
  - Pill counts
  - Behavioral assessment at each visit
    - If indicated, refer for substance abuse treatment

Chou R et al. *J Pain*. 2009;10(2):113-130.

Monitoring Patient Adherence: Prescription Drug Monitoring Programs (PDMPs)

- State-run electronic databases that track dispensing of controlled substances; available in all states
- Can provide clinicians with critical information about patient prescription history and identify "doctor shoppers"
- Ensure those in need for scheduled medications receive them
- Real-time data access not yet available in all states
  - Each state has its own rules and laws
  - Follow state guidelines

Dahl J. *J Pain.* April 2012;13:Abstract 245; Dahl J, et al. *J Pain.* April 2012;13:Abstract 246. PDMP TTAC. State Profiles. http://www.pdmpassist.org/content/state-profiles. Accessed November 29, 2017.

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Prescription Drug Monitoring Programs (PDMPs)

Centers for Disease Control and Prevention, National Center for Injury Prevention & Control: Opioid Overdose; Prescription Drug Monitoring Programs (PDMPs). https://www.cdc.gov/drugoverdose/pdmp/. Accessed January 11, 2017.

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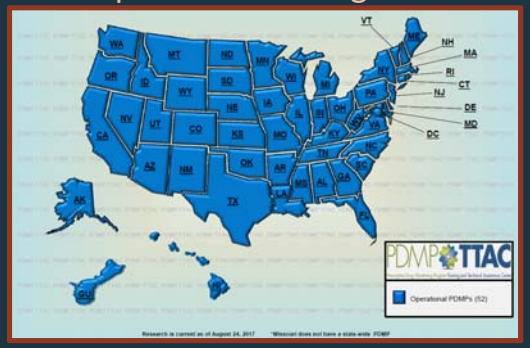
PDMPs: 2017 Operational or Legislated in All States



Centers for Disease Control and Prevention. National Center for Health Statistics. Status of Prescription Drug Monitoring Programs (PDMPs) on CDC WONDER Online Database, released 2017. http://www.pdmpassist.org/pdf/PDMP_Program_Status_20170824.pdf. Accessed January 11, 2018. Prescription Drug Monitoring Program Training and Technical Assistance Center. Waltham, MA: The Heller School for Social Policy and Management, Brandeis University.

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A Sample PDMP Report: West Virginia = Board Of Pharmacy – Patient Profile

- Date 4/15/2012 Date of Birth 12-10-1966
  Beginning Date: 04-01-11 =nbsp Ending Date: 04-15-12
- First Name: MIKE Last Name: =OWEN

First Name	Address	ZIP	Fill date	Rx no.	Product Name	Strength	Qty	Doctor Name	Doctor DEA	Pharm Name	Pharm DEA	Ph ZIP
MIKE	319 LOWER	25526	4/2/2011	11222	APAP/HYDRO	500MG-10MG	180	SMITH JOE	DH0267890	TOM'S PHARM	GF1234567	25526
MIKE	319 LOWER	25526	5/3/2011	19976	APAP/HYDRO	500MG-10MG	180	SMITH JOE	DH0267890	TOM'S PHARM	GF1234567	25526
MIKE	319 LOWER	25526	5/27/2011	23466	APAP/HYDRO	500MG-10MG	180	SMITH JOE	DH0267890	TOM'S PHARM	GF1234567	25526
MIKE	319 LOWER	25526	6/4/2011	31111	APAP/HYDRO	500MG-10MG	180	JOHN JOHN	DH0267890	BILL'S PHARM	AF1245687	25526

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Monitoring Patient Adherence: Urine Drug Testing (UDT)

- Recommended for all patients for reasons of safety and to remove the stigma associated with UDTs
- Testing does not imply a lack of trust; it is a conversation starter
- Self reports of drug use and behavioral monitoring often fail to detect abuse problems
- UDTs can identify use of prescribed opioids as well as illicit drug use

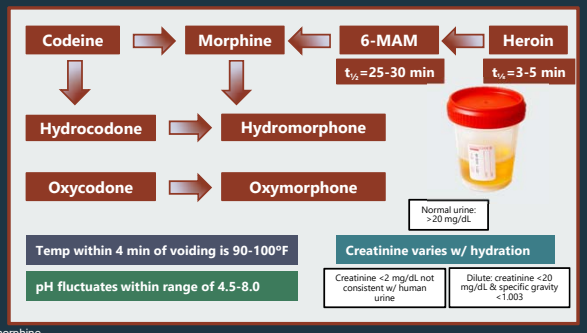
Katz NP et al. *Anesth Analg*. 2003;97(4):1097-1102; Heit HA et al. *J Pain Symptom Manage*. 2004;27(3):260-267.

Urine Drug Testing – KEY POINTS

- Know what to expect and how to interpret results
  - Parent compound and or metabolite should show up in the urine
  - Is the substance present that you expect?
  - Are there substances present that you do not expect?
  - Know what your laboratory does
- UDT frequency – expert consensus
  - Low Risk: at least annually
  - Moderate Risk: ≥2 times per year
  - High Risk: ≥3 times per year

Argoff CE et al. *Pain Med*. 2018;19(1):97-117

Metabolism of Opioids and Urine Characteristics



MAM, monoacetylmorphine.
Adapted from Gourlay DL et al. *Urine Drug Testing in Clinical Practice*. PharmaCom Group, Inc. 2010.
https://www.healthcare.uiowa.edu/familymedicine/fpinfo/Docs/Drug%20screens%202015.pdf. Accessed January 11, 2018.

Common UDT Scenarios

- Peter undergoes UDT in office and the test is negative for opioids
  - UDTs do differ
  - Certain drugs, including oxycodone, may not be detected by certain laboratory techniques
  - UDT is a conversation starter: "Why do you think your UDT is negative?"
    - Is diversion a possibility?
    - Is he bingeing and then running out of opioids?
    - Is he failing to take the prescribed drug because symptoms have abated?
    - Do you give him a 30-day Rx supply?

Heit HA et al. *J Pain Symptom Manage*. 2004;27(3):260-267.

Common UDT Scenarios (cont'd)

- Patient on LA morphine undergoes UDT. Test results positive for morphine and hydromorphone
- Possible explanations include:
  - Patient using another opioid obtained from another provider
  - Hydromorphone is a trace metabolite of morphine found only when very high morphine concentrations are present

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Common UDT Scenarios (cont'd)

- Patient being treated with hydrocodone has UDT positive for hydrocodone and hydromorphone
- After hydrocodone use, urine may be positive for:
  - Hydrocodone only
  - Hydrocodone and hydromorphone (metabolite)
  - Hydromorphone only

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Common UDT Scenarios (cont'd)

- Patient reports no relief on codeine and UDT is negative
- Possible explanations include
  - Laboratory error
  - Diversion
  - Patient is a slow metabolizer of codeine

Heit HA et al. *J Pain Symptom Manage*. 2004;27(3):260-267.

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Screening vs Confirmatory UDTs

	Screening	Confirmatory
ANALYSIS TECHNIQUE	Immunoassay	GC-MS or HPLC
SENSITIVITY (POWER TO DETECT A CLASS OF DRUGS)	Low or none when testing for semi-synthetic or synthetic opioids	High
SPECIFICITY (POWER TO DETECT AN INDIVIDUAL DRUG)	Varies (can result in false-positives or false-negatives)	High
TURNAROUND	Rapid	Slow
OTHER	Intended for a drug-free population. May not be useful in pain medicine.	Legally defensible results

GC-MS, gas chromatograph mass spectrometer; HPLC, high performance liquid chromatography.

www.opioidrisk.com.

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Anticipating and Managing Adverse Effects

Adverse Effect	Treatment
Nausea and vomiting	Anti-emetics; Switch opioids*
Sedation	Lower dose (if possible); Add nonsedating co-analgesic; Add stimulant or attention enhancer
Constipation	Treat prophylactically with stool softeners, bowel stimulants; Nonpharmacologic and pharmacologic treatment

*Opioid switching is an option for any adverse effect.

Swegle JM et al. *Am Fam Physician*. 2006;74(8):1347-1354; Chou R et al. *J Pain*. 2009;10(2):113-130.

Anticipating and Managing Adverse Effects (cont'd)

Adverse Effect	Treatment
Itching	Antipruritic therapy (eg, antihistamines)
Endocrine dysfunction/Reduced libido/Loss of menstrual period	Endocrine monitoring; Testosterone replacement; Endocrine consultation
Edema and sweating	Switch opioids*
Dizziness	Antivertigo agents
Confusion	Titrate dose

*Opioid switching is an option for any adverse effect.

Swegle JM et al. *Am Fam Physician*. 2006;74(8):1347-1354; Chou R et al. *J Pain*. 2009;10(2):113-130.

Anticipating and Managing Adverse Effects (cont'd)

- Emerging issues
  - Hyperalgesia
    - An increased response to a normally painful stimulus
    - May occur at higher doses
  - Sleep
    - Central and obstructive sleep apnea
    - Sleep architecture

Brush DE. *J Med Toxicol*. 2012;8(4):387-392; Dimsdale JE et al. *J Clin Sleep Med*. 2007;3(1):33-36.

Respiratory Depression – The Most Serious Adverse Effect

- Most serious adverse effect associated with opioids is RESPIRATORY DEPRESSION
- Occurs when
  - Initial doses are too high
  - Therapy is titrated too rapidly
  - Drug-drug interactions
  - Opioids combined with other drugs that may potentiate opioid-induced respiratory depression
    - Benzodiazepines
    - Herbals
    - OTC preparations that contain diphenhydramine
- More common in patients with sleep apnea
- Respiratory depression may be fatal

OTC, over-the-counter.

Manchikanti L et al. *Pain Physician*. 2012;15(3 suppl):S67-S116.

ER/LA Opioid Analgesics in Pregnancy

- Be aware of the pregnancy status of your patient
- There are no adequate and well-controlled studies of ER/LA opioids in pregnant women
- ER/LA opioids should be used in pregnancy only if the potential benefit justifies the risk to the fetus
- If opioid use is required, advise the patient of risk of neonatal opioid withdrawal syndrome and assure that appropriate treatment will be available

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Reevaluating the Patient's Condition

- Periodically reassess benefits and side effects of prescribed opioids and the continued need for their use
- Reevaluate underlying medical condition if presentation changes
- Continue opioid therapy if appropriate analgesia and functional status improvements are maintained
- Recognize, document, and address aberrant drug-related behavior

FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. https://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm515636.pdf. Updated May 2017. Accessed January 17, 2018.

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What to Do if Your Patient Needs Treatment for Abuse and Addiction

- Know treatment centers in your area
- Work out a plan with the center you are referring to
- With a clear indication of abuse or addiction, discontinue prescribing of opioids

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Referral Sources for Abuse and Addiction Treatment

- Balancing Pain Management and Prescription Opioid Abuse
  Available at https://www.cdc.gov/ophss/csels/dsepd/academic-partnerships/wip/primary-care.html
- Find Substance Abuse and Mental Health Treatment
  Available at www.samhsa.gov/treatment
- National Institute on Drug Abuse
  Available at www.nida.nih.gov
- American Council for Drug Education
  Available at www.acde.org
- American Academy of Addiction Psychiatry
  - Providers' Clinical Support System for Opioid Therapies: www.pcss-o.org
  - Providers' Clinical Support System for Medication Assisted Treatment: www.pcssmat.org

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Getting the Greatest Clinical Insights from Specific ER/LA Product Information Sources

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Prescribers Must Be Knowledgeable

- Before prescribing an opioid, each clinician needs to be knowledgeable about specific characteristics of each available ER/LA opioid, including:
  - Drug substance
  - Formulation
  - Strength
  - Dosing interval
  - Key instructions – reserve for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain

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Prescribing Information

- For detailed information, prescribers can refer to the prescribing information available online:
  - DailyMed at www.dailymed.nlm.nih.gov
  - drugs@fda
  - https://www.accessdata.fda.gov/scripts/cder/daf/

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Arymo ER—Morphine Sulfate

Arymo	Morphine Sulfate ER Tablets, 15 mg, 30 mg, 60 mg
Dosing Interval	**Every 8 to 12 hours**
Key Instructions	▪ Initial dose in opioid-naïve and non-tolerant patients: 15 mg every 8 to 12 hours ▪ Dose adjustment may be done every 1 to 2 days **Instruct patient:** - Take 1 tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth
Specific Drug Interactions	▪ PGP inhibitors (eg, quinidine) can increase exposure of morphine by 2x and increase risk of respiratory depressions
Use in Opioid-Tolerant Patients	A single dose of arymo ER > 60 mg or total daily dose > 120 mg is for use in opioid-tolerant patients **ONLY**
Product-Specific Safety Concerns	▪ Do not attempt to chew, crush, or dissolve. Swallow whole. ▪ Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction
Abuse Deterrence	This product is formulated with inactive ingredients that make the tablet more difficult to manipulate for misuse and abuse

PGP, P-glycoprotein
www.fda.gov

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Avinza—Morphine Sulfate ER

Avinza	Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg
Dosing Interval	**Once a day**
Key Instructions	▪ Initial dose in opioid non-tolerant patients: 30 mg ▪ Titrate in increments of not greater than 30 mg using a minimum of 3- to 4-day intervals ▪ Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid **Instruct patient:** - Swallow capsule whole (do not chew, crush, or dissolve) - May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately
Specific Drug Interactions	▪ Avoid alcoholic beverages or medications containing alcohol; may result in rapid release and absorption of potentially fatal dose of morphine ▪ PGP inhibitors (eg, quinidine) may increase absorption/exposure of morphine sulfate by approximately 2x
Use in Opioid-Tolerant Patients	Use 90 mg and 120 mg capsules in opioid-tolerant patients **ONLY**

Belbuca—Buprenorphine Buccal Film

Belbuca	Buprenorphine Buccal Film, 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg
Dosing Interval	**Every 12 hours (or once every 24 hours for initiation in opioid-naïve pts and those taking <30 mg oral morphine equivalents)** ▪ Maximum dose: 900 mcg every 12 hours due to risk of QTc prolongation
Key Instructions	▪ Initiate treatment with a 75 mcg buccal film in opioid-naïve or if prior total daily dose of opioid < 30 mg oral morphine equivalents/d ▪ Titrate in increments of 150 mcg q 12 h ▪ The minimum titration interval is 4 days ▪ In severe hepatic impairment and in oral mucositis, reduce dose by 50% ▪ Do not use if package seal is broken or film damaged in any way
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase buprenorphine levels ▪ CYP3A4 inducers may decrease buprenorphine levels ▪ Benzodiazepines may increase respiratory depression ▪ Class IA and III antiarrhythmics and other potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointes
Use in Opioid-Tolerant Patients	▪ 600 mcg, 750 mcg, and 900 mcg are for use following titration from lower doses
Product-Specific Safety Concerns	▪ QTc prolongation and torsade de pointes ▪ Hepatotoxicity
Relative Potency to Oral Morphine	▪ Equipotency to oral morphine has not been established

Butrans—Buprenorphine

Butrans	Buprenorphine Transdermal System, 5 mcg/h, 7.5 mcg/h, 10 mcg/h, 15 mcg/h, and 20 mcg/h
Dosing Interval	**One transdermal system every 7 days** ▪ Initial dose: 5 mcg/h ▪ Maximum dose: 20 mcg/h due to risk of QTc prolongation
Key Instructions	▪ When used as first opioid analgesic, initiate treatment with 5 mcg/hr ▪ If prior total daily dose of opioid < 30 mg oral morphine equivalents per day, initiate treatment with 5 mcg/h dose ▪ If prior total daily dose of opioid between 30 mg to 80 mg of oral morphine equivalents, taper patient's opioid for up to 7 days to no more than 30 mg of morphine equivalents, then initiate with 10 mcg/hrdose ▪ The minimum titration interval is 72 hours **Instruct patient** ▪ Apply only to sites indicated in full prescribing information ▪ Apply to intact/non-irritated skin ▪ Skin may be prepped by clipping hair, washing site with water only ▪ Rotate site of application; allow a minimum of 3 weeks before reapplying to same site ▪ Do not cut ▪ Avoid exposure to heat ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down toilet

Butrans—Buprenorphine (cont'd)

Butrans	Buprenorphine Transdermal System, 5 mcg/h, 7.5 mcg/h, 10 mcg/h, 15 mcg/h and 20 mcg/h
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase buprenorphine levels ▪ CYP3A4 inducers may decrease buprenorphine levels ▪ Benzodiazepines may increase respiratory depression ▪ Class IA and III antiarrythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe
Use in Opioid-Tolerant Patients	Use 7.5 mcg/h, 10 mcg/h, 15 mcg/h, and 20 mcg/h transdermal systems in opioid-tolerant patients **ONLY**
Drug-Specific Safety Concerns	▪ QTc prolongation and torsade de pointe ▪ Hepatotoxicity ▪ Application site skin reactions

Torsades de pointe (TdP) –a form of polymorphic ventricular tachycardia that may result in syncope or cardiac arrest.

Dolophine—Methadone Hydrochloride

Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg
Dosing Interval	**Every 8 to 12 hours** Initial dose in opioid non-tolerant patients: 2.5 mg to 10 mg slowly titrated to effect
Key Instructions	▪ Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death; use low doses according to table in full prescribing information (PI) ▪ High interpatient variability in absorption, metabolism, and relative analgesic potency ▪ Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program
Specific Drug Interactions	▪ Complex pharmacokinetic drug-drug interactions with methadone ▪ CYP450 inducers may increase methadone levels ▪ CYP450 inhibitors may decrease methadone levels ▪ Antiretroviral agents have mixed effects on methadone levels ▪ Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe ▪ Benzodiazepines may increase respiratory depression

Dolophine—Methadone Hydrochloride (cont'd)

Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg
Use in Opioid-Tolerant Patients	Refer to full prescribing information
Product-Specific Safety Concerns	▪ QTc prolongation and torsade de pointe ▪ Peak respiratory depression occurs later and persists longer than analgesic effect ▪ Clearance may increase during pregnancy ▪ False-positive urine drug screens possible
Relative Potency to Oral Morphine	Varies depending on patient's prior opioid experience

Duragesic—Fentanyl Transdermal System

Duragesic	Fentanyl Transdermal System, 12, 25, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/h (*these strengths available only in generic form)
Dosing Interval	Every 72 hours (3 days)
Key Instructions	▪ Use product-specific information in the full prescribing information for dose conversion from prior opioid ▪ Use 50% of the dose in mild or moderate hepatic or renal impairment; avoid use in severe hepatic or renal impairment ▪ Titrate generally using no less than 72-hour intervals; some patients may require 48-hour titration if adequate analgesia not achieved at 72-hour dose **Instruct patient:** - Apply to intact/non-irritated/non-irradiated skin on a flat surface - Skin may be prepped by clipping hair, washing site with water only - Rotate site of application - Do not cut - Avoid exposure to heat - Avoid accidental contact when holding or caring for children - Dispose used/unused patches by folding the adhesive side together and flushing down the toilet **Specific contraindications:** ▪ Patients who are not opioid-tolerant ▪ Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time ▪ Management of postoperative pain, including use after outpatient or day surgery ▪ Management of mild pain

Duragesic—Fentanyl Transdermal System (cont'd)

Duragesic	Fentanyl Transdermal System, 12, 25, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/h (*these strengths available only in generic form)
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase fentanyl drug levels and exposure ▪ CYP3A4 inducers may decrease fentanyl drug levels and exposure ▪ Discontinuation of a concomitantly used CYP3A4 inducer may result in an increase in fentanyl plasma concentration
Use in Opioid-Tolerant Patients	Indicated for use in opioid-tolerant patients **ONLY**
Product-Specific Safety Concerns	▪ Accidental exposure due to secondary exposure to unwashed/unclothed application site ▪ Increased drug exposure with increased core body temperature or fever ▪ Bradycardia ▪ Application site skin reactions
Relative Potency to Oral Morphine	See full prescribing information for conversion recommendations from prior opioid

Embeda—Morphine Sulfate ER-Naltrexone

Embeda	Morphine Sulfate ER-Naltrexone Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg
Dosing Interval	**Once a day or every 12 hours** Initial dose as first opioid: 20 mg/0.8 mg Titrate using 1- to 2-day intervals
Key Instructions	▪ **Swallow capsules whole (do not chew, crush, or dissolve)** ▪ **Instruct patient:** - Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms - If unable to swallow capsule whole, **can open capsule and sprinkle pellets on applesauce; use immediately**
Specific Drug Interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine ▪ GP inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately 2-fold
Use in Opioid-Tolerant Patients	Use 100 mg/4mg capsule in opioid-tolerant patients **ONLY**
Abuse Deterrence	This product is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse.

Exalgo—Hydromorphone Hydrochloride

Exalgo	Hydromorphone Hydrochloride Extended-Release Tablets, 8 mg, 12 mg, 16 mg, and 32 mg
Dosing Interval	**Once a day** Titrate using a minimum of 3- to 4-day intervals
Key Instructions	▪ Use conversion ratios in the full prescribing information ▪ Start patients with moderate hepatic impairment on 25% of the dose that would be prescribed for a patient with normal hepatic function ▪ Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function ▪ Do not use in patients with sulfa allergy ▪ **Instruct patient to swallow tablets whole** - **DO NOT chew, crush, or dissolve**
Specific Drug Interactions	None
Use in Opioid-Tolerant Patients	Use in opioid-tolerant patients **ONLY**
Drug-Specific Adverse Reactions	Allergic manifestations to sulfa component
Relative Potency to Oral Morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio; use conversion recommendations in the full prescribing information

Hysingla ER—Hydrocodone Bitartrate

Hysingla ER	Hydrocodone Bitartrate Extended-Release Tablets, 20, 30, 40, 60, 80, 100 mg
Dosing Interval	**Once a day (every 24 hours)** Titrate in increments of 10 mg to 20 mg every 3 to 5 days
Key Instructions	▪ In patients who are not opioid-tolerant, initiate therapy with 20 mg ▪ QTc prolongation has been observed with daily doses of 160 mg ▪ Hepatic impairment: use half the initial dose ▪ Renal impairment: use half the initial dose ▪ Instruct patients to swallow tablets whole ▪ Consider alternative analgesic in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase hydrocodone exposure ▪ CYP3A4 inducers may decrease hydrocodone exposure ▪ Concomitant use with strong laxatives may decrease hydrocodone absorption ▪ Concomitant use of MAOIs or TCAs may increase the effect of either drug
Use in Opioid-Tolerant Patients	Doses equal to or greater than 80 mg are for use in opioid-tolerant patients only
Abuse Deterrence	This product is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse.

TCAs, tricyclic antidepressants.

Hysingla ER—Hydrocodone Bitartrate (cont'd)

Hysingla ER	Hydrocodone Bitartrate Extended-Release Tablets, 20, 30, 40, 60, 80, 100 mg
Product-Specific Safety Concerns	▪ Use with caution in patients with difficulty swallowing or with underlying GI disorders that may predispose them to obstruction ▪ Esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER ▪ In nursing mothers, discontinue nursing or discontinue drug ▪ QTc prolongation has been observed with Hysingla ER following daily doses of 160 mg. Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with CHF, bradyarrhythmias, electrolyte abnormalities, or if taking medications known to prolong QTc interval. In patients who develop QTc prolongation, consider reducing the dose.
Relative Potency to Oral Morphine	See individual product information for conversion recommendations from prior opioid.

CHF, congestive heart failure.

Kadian—Morphine Sulfate

Kadian	Morphine Sulfate Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130 mg, 150 mg, and 200 mg
Dosing Interval	**Once a day or every 12 hours** Titrate using a minimum of 2-day intervals
Key Instructions	▪ Do not use as first/initial opioid (see PI) ▪ **Instruct patient:** - Swallow capsules whole • **DO NOT** chew, crush, or dissolve - If unable to swallow capsule whole, can open capsule and sprinkle pellets on applesauce; use immediately
Specific Drug Interactions	▪ Do not use with alcoholic beverages or medications containing alcohol as may result in the rapid release and absorption of a potentially fatal dose of morphine ▪ PGP inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately 2-fold
Use in Opioid-Tolerant Patients	Kadian 100 mg, 130 mg, 150 mg, and 200 mg capsules are for use in opioid-tolerant patients **ONLY**

MorphaBond ER—Morphine Sulfate

MorphaBond ER	Morphine Sulfate Extended-Release Tablets, 15 mg, 30 mg, 60 mg, 100 mg
Dosing Interval	**Every 8 hours or every 12 hours** Titrate using a minimum of 1- to 2-day intervals
Key Instructions	▪ Do not use as first/initial opioid (see PI) ▪ Instruct patient to swallow tablets whole - **Do NOT** chew, crush, or dissolve
Specific Drug Interactions	PGP inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately 2-fold
Use in Opioid-Tolerant Patients	Use MorphaBond 100 mg tablet strength in opioid-tolerant patients **ONLY**
Abuse Deterrence	MorphaBond ER is formulated with inactive ingredients that make the tablet more difficult to adulterate for misuse and abuse

MS Contin—Morphine Sulfate

MS Contin	Morphine Sulfate Controlled-Release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	**Every 8 hours or every 12 hours** Titrate using a minimum of 2-day intervals
Key Instructions	▪ Do not use as first/initial opioid (see PI) ▪ Instruct patient to swallow tablets whole - **Do NOT** chew, crush, or dissolve
Specific Drug Interactions	PGP inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately 2-fold
Use in Opioid-Tolerant Patients	Use MS Contin 100-mg and 200-mg tablet strengths in opioid-tolerant patients **ONLY**

Nucynta ER—Tapentadol

Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg
Dosing Interval	**Every 12 hours** ▪ **Use 50 mg every 12 hours as initial dose in opioid non-tolerant patients** ▪ Titrate by 50 mg increments using a minimum of 3-day intervals ▪ Maximum total daily dose is 500 mg
Key Instructions	• Dose once daily in moderate hepatic impairment with 100 mg per day maximum • **Avoid use in severe hepatic and renal impairment** • **Instruct patient :** - **Swallow tablets whole** • **Do not chew, crush, or dissolve** - Take 1 tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth
Specific Drug Interactions	▪ Do not use with alcoholic beverages or medications containing alcohol as may result in the rapid release and absorption of a potentially fatal dose of tapentadol ▪ Contraindicated in patients taking MAOIs

Nucynta ER—Tapentadol (cont'd)

Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg
Use in Opioid-Tolerant Patients	No product-specific considerations
Product-Specific Safety Concerns	▪ Risk of serotonin syndrome ▪ Angioedema
Relative Potency to Other Oral Opioids	▪ Equipotency to oral morphine not established ▪ Studies leading to its FDA approval use a dose ratio of 5:1 of tapentadol ER to Oxycodone CR
Two Indications	▪ Pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate ▪ Neuropathic pain associated with diabetic peripheral neuropathy severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Opana ER—Oxymorphone Hydrochloride

Opana ER	Oxymorphone Hydrochloride Extended-Release Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg
Dosing Interval	Every-12-hours dosing; some benefit from asymmetric (different dose given in AM than PM) dosing
Key Instructions	▪ Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance <50 mL/min) and in patients over 65 years of age ▪ Titrate using 3- to 7-day intervals ▪ Contraindicated in moderate and severe hepatic impairment **Instruct patient:** ▪ **Swallow tablets whole (do not chew, crush, or dissolve)** ▪ Take 1 tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth ▪ Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction
Specific Drug Interactions	Do not use with alcoholic beverages or medications containing alcohol as may result in absorption of a potentially fatal dose of oxymorphone
Use in Opioid-Tolerant Patients	No product specific considerations
Relative Potency to Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio

OxyContin—Oxycodone Hydrochloride

OxyContin	Oxycodone Hydrochloride Controlled-Release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	**Every 12 hours**
Key Instructions	▪ **Opioid-naïve patients: initiate treatment with 10 mg every 12 hours** ▪ Titrate using a minimum of 1- to 2-day intervals ▪ Hepatic impairment: start with one-third to one-half usual dosage ▪ Renal impairment (creatinine clearance <60 mL/min): start with one-half usual dosage ▪ **Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction** ▪ **Instruct patient:** - **Swallow tablets whole** • **DO NOT chew, crush, or dissolve** - Take 1 tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase oxycodone exposure ▪ CYP3A4 inducers may decrease oxycodone exposure

OxyContin—Oxycodone Hydrochloride (cont'd)

OxyContin	Oxycodone Hydrochloride Controlled-Release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Use in Opioid-Tolerant Patients	Single dose greater than 40 mg or total daily dose greater than 80 mg is for use in opioid-tolerant patients **ONLY**
Product-Specific Safety Concerns	▪ Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet ▪ Contraindicated in patients with GI obstruction
Relative Potency to Oral Morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio
Abuse Deterrence	OxyContin is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse
As of 8/13/2015	Indicated for opioid-tolerant pediatric patients 11 years and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent

Targiniq ER—Oxycodone HCl/Naloxone HCl

Targiniq ER	Oxycodone Hydrochloride / Naloxone Hydrochloride Extended-Release Tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg
Dosing Interval	**Every 12 hours**
Key Instructions	▪ **Opioid-naïve patients: initiate treatment with 10 mg/5 mg every 12 hours** ▪ Titrate using a minimum of 1- to 2-day intervals ▪ Do not exceed 80 mg/40 mg total daily dose ▪ Hepatic impairment: contraindicated in moderate and severe hepatic impairment. In mild hepatic impairment, start with one-third to one-half usual dosage ▪ Renal impairment (creatinine clearance <60 mL/min): start with one-half usual dosage ▪ **Instruct patient:** - **Swallow tablets whole** • DO NOT chew, crush, split or dissolve as this will release oxycodone, possibly resulting in fatal overdose, and naloxone, possibly resulting in withdrawal symptoms - Take 1 tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase oxycodone exposure ▪ CYP3A4 inducers may decrease oxycodone exposure

Targiniq ER—Oxycodone HCl/Naloxone HCl (cont'd)

Targiniq ER	Oxycodone Hydrochloride / Naloxone Hydrochloride Extended-Release Tablets, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg
Use in Opioid-Tolerant Patients	Singe dose greater than 40 mg/20 mg or total daily dose of 80 mg/40 mg are for use in opioid-tolerant patients **ONLY**
Product-Specific Safety Concerns	▪ Contraindicated in moderate and severe hepatic impairment
Relative Potency to Oral Morphine	▪ See individual product information for conversion recommendations from prior opioid
Abuse Deterrence	▪ Targiniq ER has pharmacologic properties that are expected to reduce abuse via the intranasal and intravenous routes of administration

Troxyca ER—Oxycodone HCl/Naltrexone HCl

Troxyca ER	Oxycodone Hydrochloride / Naltrexone Hydrochloride Extended-Release Capsules, 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, 80 mg/9.6 mg
Dosing Interval	**Every 12 hours**
Key Instructions	▪ **Opioid-naïve patients: initiate treatment with 10 mg/1.2 mg every 12 hours** ▪ Total daily dose may be adjusted by 20 mg/2.4 mg every 2 to 3 days as needed ▪ **Instruct patient:** - **Swallow capsule whole** • DO NOT chew, crush, split or dissolve as this will release oxycodone, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms ▪ For patients who have difficulty swallowing, Troxyca ER can be taken by sprinkling the pellets on applesauce and swallowing immediately without chewing ▪ Do not administer Troxyca pellets through a nasogastric or gastric tube
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase oxycodone exposure ▪ CYP3A4 inducers may decrease oxycodone exposure
Use in Opioid Tolerant Patients	▪ Single doses of >40 mg/4.8 mg, or a total daily dose >80mg/9.6 mg, are for use in opioid tolerant patients **ONLY**
Relative Potency to Oral Morphine	▪ See product information for conversion recommendations from prior opioid
Abuse Deterrence	▪ TROXYCA ER is formulated with a sequestered opioid antagonist, naltrexone HCl, which is released with manipulation by crushing

Vantrela ER—Hydrocodone Bitartrate

Vantrela ER	Hydrocodone Bitartrate Extended-Release Tablets 15 mg, 30 mg, 45 mg, 60 mg and 90 mg
Dosing Interval	**Every 12 hours**
Key Instructions	▪ **Opioid-naïve patients: initiate treatment with 15 mg every 12 hours** ▪ Titrate using 3- to 7-day intervals ▪ Renal impairment: start with half of recommended dose ▪ Hepatic impairment: start with half of recommended dose ▪ **Instruct patient:** - **Swallow capsules whole** • **DO NOT chew, crush, or dissolve**
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase hydrocodone exposure ▪ CYP3A4 inducers may decrease hydrocodone exposure
Use in Opioid-Tolerant Patients	Vantrela 90 mg tablets, single dose greater than 60 mg, or total daily dose greater than 120 mg are for use in opioid-tolerant patients **ONLY**
Abuse Deterrence	▪ VANTRELA ER is formulated with physicochemical properties intended to make the tablet ▪ more difficult to manipulate for misuse and abuse.

Xtampza ER—Oxycodone

Xtampza ER	Oxycodone Extended-Release Capsules, 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg
Dosing Interval	**Every 12 hours**
Key Instructions	▪ **Opioid-naïve patients: initiate treatment with 9 mg every 12 hours** ▪ Titrate using a minimum of 1- to 2-day intervals ▪ Hepatic impairment: start with one-third to one-half usual dosage ▪ Renal impairment (creatinine clearance <60 mL/min): follow a conservative approach and adjust according to clinical situation ▪ **Maximum daily dose: 288 mg** ▪ For patients who have difficulty swallowing, Xtampza ER can be opened and sprinkled on soft foods or into a cup and immediately swallowed ▪ Xtampza ER can be administered through a feeding tube ▪ Patient instructions: take with the same amount of food to ensure consistent plasma level are achieved
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase oxycodone exposure ▪ CYP3A4 inducers may decrease oxycodone exposure
Use in Opioid-Tolerant Patients	▪ A single dose >36 mg or total daily dose >72 mg
Relative Potency to Oral Morphine	▪ There are no established conversion ratios for conversion from other opioids to Xtampza ER defined by clinical trials
Abuse Deterrence	▪ XTAMPZA ER capsules contain microspheres formulated with inactive ingredients intended to make the ▪ formulation more difficult to manipulate for misuse and abuse.

Zohydro ER—Hydrocodone Bitartrate

Zohydro ER	Hydrocodone Bitartrate Extended-Release Capsules 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing Interval	**Every 12 hours**
Key Instructions	▪ **Opioid-naïve patients: initiate treatment with 10 mg every 12 hours** ▪ Titrate using 3- to 7-day intervals ▪ Renal impairment (creatinine clearance <60 mL/min): start with a low dose ▪ **Instruct patient:** - **Swallow capsules whole** • **DO NOT chew, crush, or dissolve**
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase hydrocodone exposure ▪ CYP3A4 inducers may decrease hydrocodone exposure
Use in Opioid-Tolerant Patients	▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients **ONLY**
Relative Potency to Oral Morphine	▪ Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio