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Safe Means of Administering the Right Therapy

EXTENDED RELEASE AND LONG-ACTING OPIOIDS

PIM Postgraduate Institute for Medicine

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PROGRAM AGENDA

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Welcome, Overview, Disclosures, and Goals	5 min
MODULE 1: Assessing Patients for ER/LA Opioid Analgesic Therapy	25 min
MODULE 2: Evaluating and Initiating ER/LA Opioid Analgesic Therapy	25 min
BREAK	10 min
MODULE 3: Evaluating ER/LA Opioid Analgesic Therapy Dose Modification and Discontinuation	25 min
BREAK	10 min
MODULE 4: Managing Ongoing Therapy With ER/LA Opioid Analgesics	25 min
MODULE 5: Effectively Counseling Patients and Caregivers About the Safe Use of ER/LA Opioid Analgesics, Including Proper Storage and Disposal	10 min
MODULE 6: General and Product-Specific Drug Information About ER/LA Opioid Analgesics	25 min
Q&A and Activity Evaluation	20 min

Why Prescriber Education Is Important

WHY OPIOID REMS?

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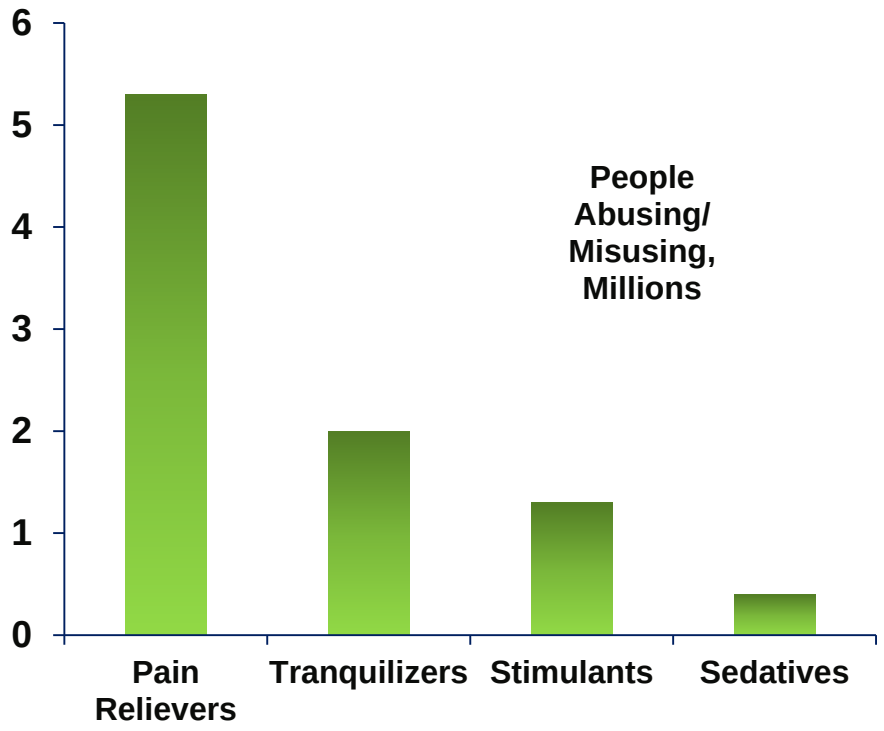
- 35 million Americans have used opioid analgesics for nonmedical purpose
- 7 million Americans misuse or abuse prescription drugs each month
- Prescription drug abuse accounts for ~25%-30% of all drug abuse
- Pain and addiction are interrelated



REMS = Risk Evaluation and Mitigation Strategies.

American College of Preventive Medicine. http://www.acpm.org/?UseAbuseRxClinRef#Prevalence. Accessed January 6, 2015; Passik SD, et al. In: Berger AM, et al (eds). *Principles and Practice of Palliative Care and Supportive Oncology.* 2nd ed. Philadelphia, PA: Lippincott William & Wilkins; 2002:593-603. National Institute on Drug Abuse. http://www.drugabuse.gov/publications/drugfacts/drug-related-hospital-emergency-room-visits. Accessed January 6, 2015.

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CDC: PARALLEL INCREASES IN OPIOID SALES, DEATHS, AND SUBSTANCE ABUSE

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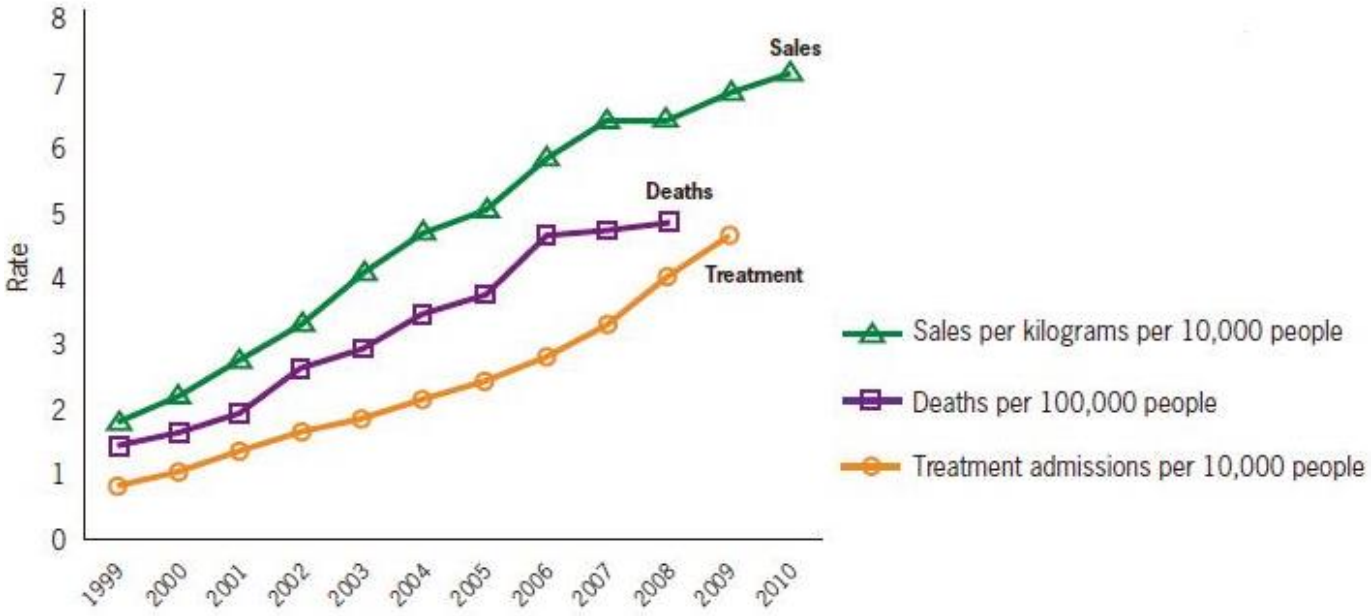
Rates of prescription painkiller sales, deaths and substance abuse treatment admissions (1999-2010)



SOURCES: National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999-2010; Treatment Episode Data Set, 1999-2009

CDC = Centers for Disease Control and Prevention.
CDC. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm. Accessed January 6, 2015.

RISKS OF OPIOID MISUSE/ABUSE

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- In 2009
  - 39,147 Americans died from drug poisoning
  - Nearly 14,800 involved prescription opioids
- For every 1 death, there are:
  - 10 treatment admissions for opioid abuse
  - 32 ED visits for misuse or abuse
  - 130 people who abused or are addicted
  - 825 nonmedical users of opioids

ED = emergency department.

Kochanek KD, et al. http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_03.pdf. Accessed January 6, 2015; CDC. http://www.cdc.gov/VitalSigns/methadoneoverdoses/index.html. Accessed January 6, 2015; Warner M, et al. http://www.cdc.gov/nchs/data/databriefs/db81.htm. Accessed January 6, 2015; National Center for Injury Prevention and Control. http://www.cdc.gov/homeandrecreationalsafety/rxbrief/. Accessed January 6, 2015.

CORE THEMES

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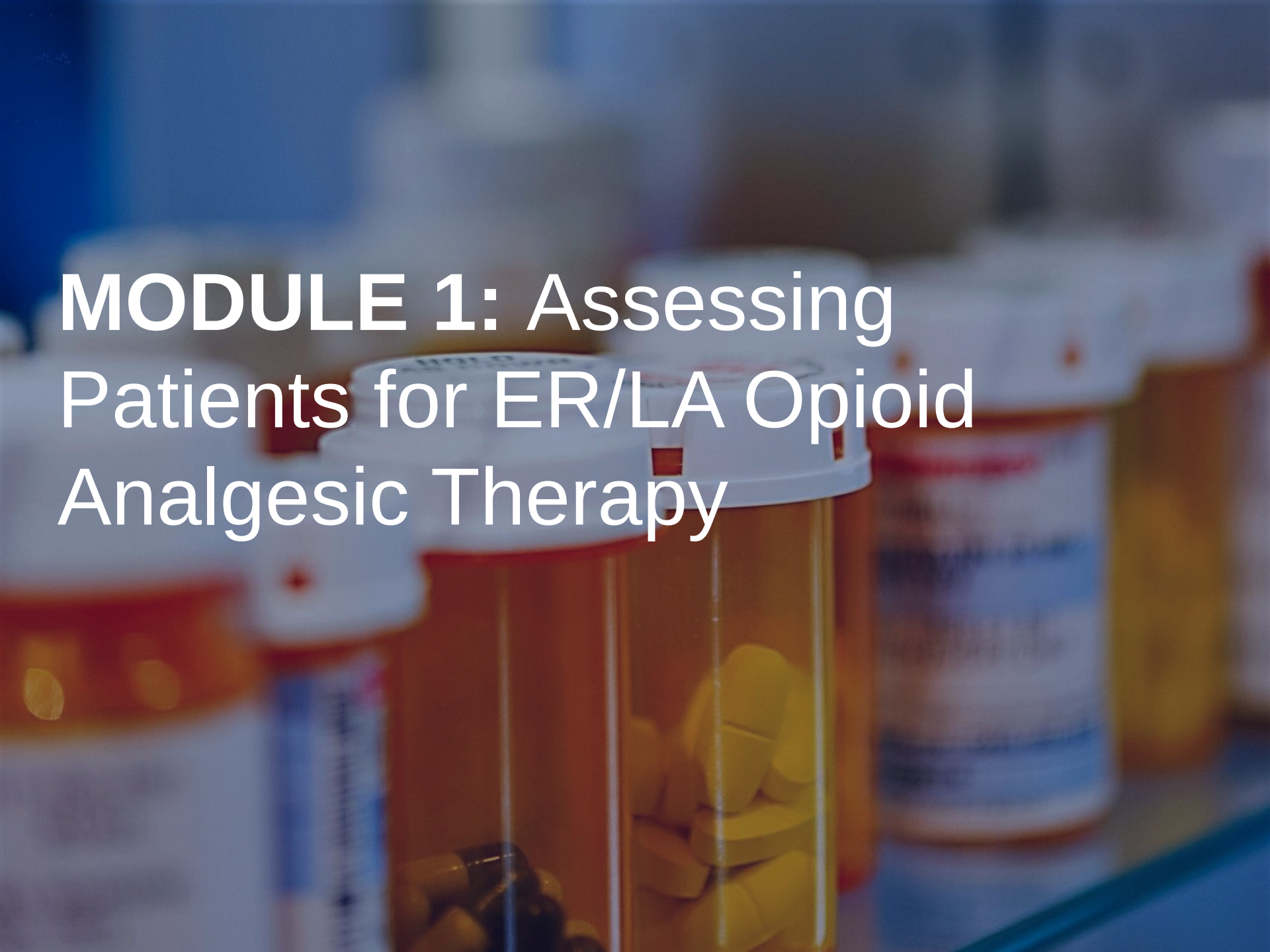
ER and LA Opioids Affected by REMS
Fentanyl
Hydromorphone
Methadone
Morphine
Oxycodone
Oxymorphone
Hydrocodone

- Assessing patients for treatment
- Initiating therapy, modifying dosing, discontinuing use
- Managing therapy
- Counseling patients and caregivers about safe use
- General drug information
- Specific drug information

Food and Drug Administration. www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf. Accessed January 6, 2015.



MODULE 1: Assessing Patients for ER/LA Opioid Analgesic Therapy

LEARNING OBJECTIVES

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- Demonstrate the ability to assess patients for treatment with ER/LA opioid analgesics

BALANCING OPIOID RISK AND BENEFIT
DUAL GOVERNMENT IMPERATIVES

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Ensure availability of opioids for patients with pain

Establish system of controls to prevent abuse, diversion

University of Wisconsin. www.medsch.wisc.edu/painpolicy/guide2003/Index/eguide2003/.pdf. Accessed January 6, 2015.

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CONSIDER THE RISKS

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- Potential risks of opioid use include:
  - Overdose
  - Abuse
  - Misuse and addiction
  - Physical dependence and tolerance
  - Interactions with other medications and substances
  - Inadvertent exposure, such as children

OPIOID MISUSE/ABUSE IS MAJOR PUBLIC HEALTH CONCERN

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- Improper use of opioids can result in serious adverse events—including overdose and death
- Risk can be greater with ER/LA opioids
  - ER opioid dosage units contain more opioid than immediate-release formulations

OPIOID-RELATED ADVERSE EVENTS: ABERRANT BEHAVIORS

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***Aberrant behavior*: Activity outside the boundaries of a treatment plan**

***Misuse*: Intentional or unintentional use of medication for medical purpose other than as directed**

***Abuse*: Use of illegal drug or intentional self-administration of medication for nonmedical purpose**

American College of Preventive Medicine. http://www.acpm.org/?UseAbuseRxClinRef#Prevalence. Accessed January 6, 2015.

REDUCING OPIOID ABUSE

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- Screen for risk of abuse
- Predict risk of abuse
- Prescriber needs to be confident in prescribing
- Monitor actual prescription of opioids
- What's missing?
  - The judgment of the clinician
  - Experience + expertise

ASSESSMENT AND DOCUMENTATION FOR OPIOID USE

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Providers must adequately document all patient interactions, assessments, test results, and treatment plans

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FSMB MODEL POLICY: CONTROLLED SUBSTANCES IN PAIN MANAGEMENT

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- Evaluation of patient
- Treatment plan
- Informed consent, agreement for treatment
- Periodic review
- Consultation
- Medical records
- Compliance with controlled substances laws and regulations

28 state medical boards have adopted model policy;
10 others have adopted guidelines with similar language

FSMB = Federation of State Medical Boards.

CLINICAL INTERVIEW: PATIENT MEDICAL HISTORY

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- Identify illnesses relevant to effects or metabolism of opioids
  - Pulmonary disease, cognitive impairment
  - Hepatic or renal disease
- Identify illnesses linked to substance abuse
  - Hepatitis, HIV, TB, cellulitis, STI, trauma/burns, cardiac disease, pulmonary disease
- Side effects
  - Constipation, nausea

STI = sexually transmitted infection.

Chou R, et al. *J Pain*. 2009;10:113-130; Zacharoff KL, et al. *Managing Chronic Pain With Opioids in Primary Care.* 2nd ed. Newton, MA: Inflexxion, Inc.; 2010; U.S. Department of Veterans Affairs, Department of Defense. VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain. 2010.

CLINICAL INTERVIEW: PAIN HISTORY

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- Describe pain
  - Location, intensity, quality, onset/duration, variations/patterns
- What relieves the pain?
- What triggers or worsens the pain?
- Functional status
  - Effects of pain on physical, emotional, psychological function
- Patient's pain and functional goals

Heapy A, et al. In: *Raj's Practical Management of Pain.* 4th ed. 2008:279-295. Zacharoff KL, et al. *Managing Chronic Pain With Opioids in Primary Care.* 2nd ed. Newton, MA: Inflexxion, Inc.; 2010.

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CLINICAL INTERVIEW: TREATMENT HISTORY

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- Past use of medications
- Current use
  - Query state prescription drug monitoring programs where available to confirm patient report
  - Contact past providers and obtain medical records
  - Conduct urine drug testing
- Dosage
  - Dose, regimen, duration
  - Determine if patient is opioid tolerant
- Effectiveness
- Nonpharmacologic strategies

ASSESSMENT AND EVALUATION OF PAIN

- Physical examination
  - General: Vital signs, appearance, posture, gait, pain behaviors
  - Neurologic exam
  - Musculoskeletal exam
  - Cutaneous or trophic findings
- Diagnostic testing
  - Appropriate to chief complaint

Lalani I, et al. In: *Raj's Practical Management of Pain*. 4th ed. 2008:177-188. Chou R, et al. *J Pain*. 2009;10:113-130.

CASE STUDY: EMILY SUMMARY

- Joint pain in hands and feet due to rheumatoid arthritis
  - Treated with combination DMARD therapy
  - No other medical or psychiatric history
- ***Reduced function***
  - Stopped playing sports
  - Has difficulty typing, holding objects
  - Walking and standing painful
- Pain did not respond to OTC medications
  - Acetaminophen
  - Naproxen

DMARD = disease-modifying antirheumatic drug; OTC = over-the-counter.

ASSESSING FOR RISK OF ABUSE

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- Complete history of current and past substance use
  - Prescription drugs, illegal substances, alcohol, and tobacco
- Substance abuse history does not prohibit treatment with ER/LA opioids; may require additional monitoring and expert consultation/referral
  - Family history of substance abuse and psychiatric disorders
  - History of sexual abuse
- Social history
  - Employment, cultural background, marital history, legal history, behavioral patterns

Chou R, et al. *J Pain.* 2009;10:113-130. SAMHSA. *Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders. Treatment Improvement Protocol (TIP) Series 54*. HHS Publication No. (SMA) 12-4671; 2011; U.S. Department of Veterans Affairs, Department of Defense. VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain. 2010.

RISK FACTORS FOR OPIOID ABUSE

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- Active alcohol or substance abuse
- Personal or family history of substance abuse
- Legal, disability issues related to pain
- Younger age
- Male sex
- Previous DUI
- Smoking
- Psychiatric, psychological disorders
- Poor social support
- Preadolescent sexual abuse
- Adverse childhood events

DUI = driving under the influence.

Dunbar SA, et al. *J Pain Symptom Manage*. 1996;11:163-171; Ives TJ, et al. *BMC Health Serv Res*. 2006;6:46; Kendler KS, et al. *Arch Gen Psychiatry*. 2000;57:953-959; Tsuang MT, et al. *Am J Med Genet*. 1996;67:473-477; Tsuang MT, et al. *Arch Gen Psychiatry*. 1998;55:967-972.

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CASE STUDY: CAL SUMMARY

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- Severe bilateral knee pain after MVA
  - Treated with oxycodone/acetaminophen immediate release
    Comorbidities: T2DM, hypertension, CAD
- ***Reduced function***
  - Trouble walking more than 2 blocks
  - Sleep disturbances
  - Pain continues to get worse – “unbearable”
- Persistent pain despite immediate-release opioid
- Yellow flags
  - Wife thinks taking more immediate-release opioids than prescribed
  - Possible depression

CAD = coronary artery disease; MVA = motor vehicle accident; T2DM = type 2 diabetes mellitus.

RISK ASSESSMENT AND SCREENING CLINICIAN-ADMINISTERED TOOLS

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Tool	Items	Goal
DIRE[1]	7	Assess whether long-term opioid therapy is appropriate in patients with CNCP
SISAP[2]	5	Predict probability of developing aberrant behavior during opioid therapy for CNCP by inquiring about alcohol, marijuana, cigarette use
POAC[3]	5	Assess criteria that suggest prescription opioid abuse in chronic pain patients
ABC[4]	20	Track addiction behaviors related to prescription opioids

ABC = Addiction Behaviors Checklist; CNCP = chronic non-cancer pain; DIRE = Diagnosis Intractability Risk Efficacy Score; POAC = Pre-Op Assessment Clinic; SISAP = Screening Instrument for Substance Abuse Potential.

1. Belgrade MJ, et al. *J Pain*. 2006;7:671-681; 2. Coambs RB, et al. *Pain Res Manage*. 1996;1:155-162; 3. Chabal C, et al. *Clin J Pain*. 1997;13:150-155; 4. Wu SM, et al. *J Pain Symptom Manage*. 2006;32:342-351.

RISK ASSESSMENT AND SCREENING PATIENT-ADMINISTERED TOOLS

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Tool	Items	Goal
ORT[1]	5	Predict, quantify potential for developing aberrant behavior during opioid therapy
SOAPP-R[2]	24	Predict potential opioid-related aberrant behavior Determine appropriateness of long-term opioid therapy for patients with CNCP
DAST[3]	28	Quantify extent of problems associated with drug abuse
CAGE-AID[4]	4	Identify misuse/addiction
STAR[5]	14	Predict, identify patients with addiction + pain
PMQ[6]	26	Assess risk for opioid medication misuse

DAST = Drug Abuse Screening Tool; ORT = Opioid Risk Tool; PMQ = Pain Medication Questionnaire; STAR = Screening Tool for Addiction Risk.

1. Webster LR, et al. *Pain Med*. 2005;6:432-442; 2. Butler SF, et al. *J Pain*. 2008;9:360-372; 3. www.drtepp.com/pdf/substance_abuse.pdf. Accessed January 6, 2015; 4. Brown RL, et al. *Wisconsin Med J*. 1995;94:135-140; 5. Li V, et al. *Pain Med*. 2001;2:245; 6. Adams LL, et al. *J Pain Symptom Manage*. 2004;27:440-459.

OPIOID RISK TOOL (ORT)

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- Administration
  - On initial visit
  - Prior to opioid therapy
- Scoring
  - 0-3: low risk (6%)
  - 4-7: moderate risk (28%)
  - ≥8: high risk (>90%)

OPIOID RISK TOOL

		Mark each box that applies	Item Score If Female	Item Score If Male
1. Family History of Substance Abuse	Alcohol	[ ]	1	3
	Illegal Drugs	[ ]	2	3
	Prescription Drugs	[ ]	4	4
2. Personal History of Substance Abuse	Alcohol	[ ]	3	3
	Illegal Drugs	[ ]	4	4
	Prescription Drugs	[ ]	5	5
3. Age (Mark box if 16 – 45)		[ ]	1	1
4. History of Preadolescent Sexual Abuse		[ ]	3	0
5. Psychological Disease	Attention Deficit Disorder, Obsessive Compulsive Disorder, Bipolar, Schizophrenia	[ ]	2	2
	Depression	[ ]	1	1
		TOTAL	———	———

Total Score Risk Category
Low Risk 0 – 3
Moderate Risk 4 – 7
High Risk ≥ 8

http://www.partnersagainstpain.com/printouts/Opioid_Risk_Tool.pdf. Accessed January 6, 2015.

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SCREENER AND OPIOID ASSESSMENT FOR PATIENTS WITH PAIN – REVISED (SOAPP-R)

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- Self-administered
  - May be completed as part of interview with clinician
- 24 items
- <10 min to complete
- Cutoff score:

  ≥18 = positive

  <18 = negative

SOAPP® Monitoring Recommendations. https://painedu.org/soapp/SOAPP_Monitoring_Recommendations.pdf. Accessed January 6, 2015; *The SOAPP® Version 1.0 Tutorial*. https://painedu.org/soapp-tutorial_01.asp. Accessed January 6, 2015.

HOW DO RISK MEASURES COMPARE? A RETROSPECTIVE STUDY

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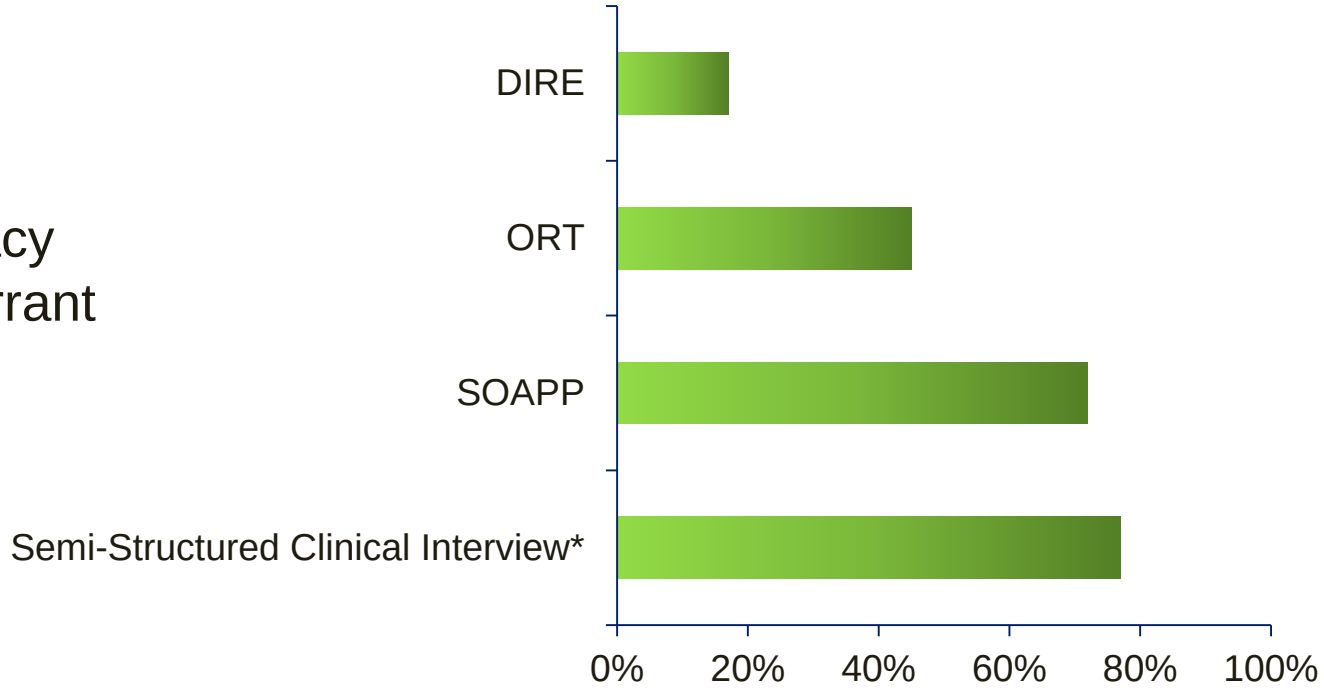
- N = 48 patients discharged from Tennessee pain practice
- Assessed accuracy in predicting aberrant drug-related behaviors



*With a psychologist who could access all other test results.

Moore TM, et al. *Pain Med*. 2008;10:1426-1433.

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TREATMENTS FOR OPIOID ADDICTION

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Buprenorphine, methadone, and naltrexone commonly used for treatment of opioid addiction

- **Buprenorphine**
  - Partial opioid agonist, approved 2002
- **Methadone**
  - Synthetic opioid used both for addiction and chronic pain
  - 2014 safety guidelines from APS
- **Naltrexone**
  - Opioid antagonist for treatment of addiction
  - Also combined with opioid to prevent tampering

APS = American Pain Society.
Substance Abuse and Mental Health Services Administration. http://buprenorphine.samhsa.gov/about.html. Accessed January 6, 2015; Taylor R, et al. *Ther Adv Drug Saf.* 2014;5:129-137; Taylor R, et al. *Ther Adv Drug Saf.* 2014;5:129-137.

METHADONE: 2014 SAFETY GUIDELINES

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- **2014 APS safety guidelines**
  - 1 in 3 opioid-related deaths associated with methadone
  - Used for addiction and, increasingly, chronic pain
  - Risk for QTc prolongation, interactions, adverse events
- **Recommendations**
  - Obtain baseline ECG in patients with risk factors for QTc prolongation or prior arrhythmia
  - Avoid in patients with QTc interval >500 ms
  - Follow-up ECG based on baseline ECG, dose changes, or other risk factors
  - Monitor neonates for abstinence syndrome – occurs in 75% of infants with prenatal methadone exposure

ECG = electrocardiogram.

Chou R, et al. *J Pain.* 2014;15:321-337.

NALTREXONE

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- Opioid antagonist – competes for opioid receptors
  - Available in tablet and intramuscular depot formulations
  - Used to prevent relapse
  - Non-addictive and not associated with withdrawal
  - Opioids must be cleared from body prior to starting
- Also coformulated with morphine (Embeda) to prevent tampering
  - Sequestered at core and released only on tampering
  - Blocks opioid agonist effects when released
  - When taken properly, no release of naltrexone

Taylor R, et al. *Ther Adv Drug Saf.* 2014;5:129-137; Ling W, et al. *Subst Abuse Rehabil.* 2011;2:181-188.

REFERRING HIGH-RISK PATIENTS

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- Elderly patients
- Children
- Pregnancy
  - Understand when to appropriately refer to pain management or addiction specialists
  - Check local state regulations for requirements

Chou R, et al. *J Pain.* 2009;10:113-130.

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ELDERLY PATIENTS

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- Presence of comorbidities that may increase risk of opioid-related adverse events
  - Higher risk for respiratory depression in elderly, cachectic, or debilitated patients
  - Altered pharmacokinetics
- Monitor closely
  - Initiating and titrating ER/LA opioids
  - Concomitant administration with drugs that depress respiration
- Reduce dose by ⅓ to ½ in opioid-naïve
- More likely to develop constipation
  - Routinely initiate bowel regimen
- Can they manage opioid therapy responsibly?

American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. *J Am Geriatr Soc.* 2009;57:1331-1346; Chou R, et al. *J Pain.* 2009;10:113-130.

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CHILDREN (<18 YEARS)

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- Safety and effectiveness of most ER/LA opioids not established
  - Pediatric analgesic trials challenging
  - Transdermal fentanyl approved ≥2 years of age
- Most studies focus on inpatient safety
  - Opioids common source of medication errors
- Opioid indications are mostly life-limiting conditions
  - Few children with chronic pain due to non–life-limiting conditions should receive opioids
- When prescribing opioids to children
  - Consult pediatric palliative care or pain specialist or refer to pain clinic

Berde CB, et al. *Pediatrics.* 2012;129:354-364; Gregoire MC, et al. *Pain Res Manag.* 2013;18:47-50; McDonnell C. *Pain Res Manag.* 2011;16:93-98; Slater ME, et al. *Pain Med.* 2010;11:207-214.

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PREGNANCY

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- No well-controlled studies of ER/LA opioid analgesics in pregnant women
- Risk of prolonged ER/LA opioid use during pregnancy is neonatal opioid withdrawal syndrome
  - Can be life-threatening if not recognized and treated

- If prolonged opioid use is needed in a pregnant woman:
  - Advise patient of the risk of neonatal opioid withdrawal syndrome
  - Ensure that appropriate treatment will be available
  - ER/LA opioids should be used during pregnancy only if the potential benefit justifies the risk to the fetus

http://www.er-la-opioidrems.com/IwgUI/rems/pdf/important_safety_information.pdf. Accessed January 6, 2015; Food and Drug Administration. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf. Accessed January 6, 2015.

SUMMARY: CLINICAL PEARLS

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- Abuse of opioids and related mortality increasing
- Assessing patients is essential
  - Assess pain and risk for abuse
  - Reduced function is key to establish need for opioids
  - Assessing abuse potential
- Clinical examination and interview, history, risk factors…use validated assessment tool
- Special considerations in elderly, children, pregnancy
  - Consider referral to pain specialist

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MODULE 2: Evaluating and Initiating ER/LA Opioid Analgesic Therapy

LEARNING OBJECTIVES

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- Demonstrate the ability to evaluate and initiate opioid therapy

FEDERAL AND STATE REGULATIONS

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FEDERAL

- Code of Federal Regulations, Title 21 Section 1306: Rules governing the issuance and filing of prescriptions pursuant to section 309 of the Act
- United States Code – Controlled Substances Act, Title 21, Section 829: Prescriptions

STATE

- Database of state statutes, regulations, and policies for pain management

U.S. Department of Justice. www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm. Accessed January 6, 2015; U.S. Department of Justice. www.deadiversion.usdoj.gov/21cfr/21usc/829.htm. Accessed January 6, 2015; Medscape. www.medscape.com/resource/pain/opioid-policies. Accessed January 6, 2015; University of Wisconsin. www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management . Accessed January 6, 2015.

FEDERAL CONTROLLED SUBSTANCE REGULATIONS FOR OPIOID THERAPY

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- Practitioner must be registered with the DEA or employed by a hospital that is registered with the DEA to prescribe controlled substances
- Follow appropriate security controls
- Time limit within which prescription must be filled (state regulations may vary)
- May issue multiple prescriptions for a patient
- Required recordkeeping: inventory and disposal
- Work in tandem with state regulations

U.S. Department of Justice. http://www.deadiversion.usdoj.gov/pubs/manuals/pract/index.html. Accessed January 6, 2015.

STATE CONTROLLED SUBSTANCE REGULATIONS FOR OPIOID THERAPY

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- Modeled after federal laws
- Some states may restrict dosage or length of valid prescription
- May require CME hours specific to pain treatment
- Most states have prescription monitoring programs
- Clinicians should be aware of both state and federal laws

O'Reilly KB. http://www.amednews.com/article/20111017/profession/310179937/2/. Accessed January 6, 2015; Medscape. http://www.medscape.com/resource/opioid/opioid-policies. Accessed January 6, 2015.

CHARACTERISTICS OF ER/LA OPIOIDS

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Benefits	Limitations
More consistent plasma concentrations	Not for as-needed use • Mild pain • Short-term pain • Acute pain
More consistent nighttime pain control	Not for routine use in headaches
Decreased number of pills may improve adherence	Not for postoperative pain

Nicholson B. *Pain Pract*. 2009;9:71-81; Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

CONTRAINDICATIONS FOR ER/LA OPIOIDS

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- Risk of respiratory depression
- Asthma in an unmonitored setting or without ability to resuscitate
- Paralytic ileus
- General hypersensitivity to opioids

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

PATIENT-PRESCRIBER AGREEMENT

Get smart
Safe Means of Administering the Right Therapy
EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Sets forth expectations of patient/clinician
  - Rationale for goals of opioid therapy
  - Responsibilities of clinician in prescribing opioids
  - Responsibilities of patient in using opioids
  - Potential adverse events
- Should be signed after assessment, before starting opioid trial

- Should reflect patient literacy
  - Assessment of 162 English-language patient-prescriber agreement submitted by APS members
    - Mean readability grade level was 13.8
    - Vocabulary not conversational
  - Low-literacy English-language version developed, validated
    - 7th-grade reading level
    - Contains 26 statements, 12 clipart illustrations

Roskos SE, et al. *J Pain*. 2007;8:753-758; Wallace LS, et al. *J Pain*. 2007;8:759-766; Zacharoff KL, et al. *Managing Chronic Pain With Opioids in Primary Care.* 2nd ed. Newton, MA: Inflexxion, Inc.; 2010.

INITIATING TREATMENT

- Initial treatment can be considered a therapeutic trial
  - May last several weeks to several months
  - Conversion to long-term therapy should be based on careful consideration of outcomes of trial
- Considerations
  - Progress toward therapeutic goals
  - Changes in underlying pain condition
  - Opioid-related adverse events
  - Changes in psychiatric or medical comorbidities
  - Aberrant drug-related behavior, addiction, or diversion

Chou R, et al. *J Pain.* 2009;10:113-130.

RESPIRATORY DEPRESSION

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Main risk of opioid agonists, including ER/LA opioids
  - May lead to respiratory arrest and death
  - Risk highest after initiation or dose increase
- Reduced urge to breathe and decreased respiration rate
  - Shallow breathing
  - CO_2 retention may worsen opioid sedating effects
- Tell patients/family to call 911

Chou R, et al. *J Pain.* 2009;10:113-130. Food and Drug Administration. www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf. Accessed January 6, 2015.

ER/LA-INDUCED RESPIRATORY DEPRESSION

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- Increased risk
  - Elderly, cachectic, or debilitated patients
  - Contraindicated in patients with respiratory depression or conditions that increase risk
  - Given concomitantly with drugs that also depress respiration
  - Obstructive sleep apnea
- Reduce risk
  - Proper dosing and titration
  - ***Do not overestimate*** dose during conversion
  - Instruct patients to swallow tablets/capsules whole

Food and Drug Administration. www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf. Accessed January 6, 2015.

OPIOID-NAÏVE PATIENTS

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Drug and dose selection critical
  - Some ER/LA opioids or forms are only recommended for ***opioid-tolerant*** patients
- Monitor closely
  - Respiratory depression
  - Especially during first 24-72 hours after initiating or increasing dose
- Titrate based on efficacy, tolerability, and adverse events
  - Check for minimum titration intervals
  - Supplement with immediate-release analgesics during dose titration

www.er-la-opioidrems.com/IwgUI/rems/pdf/important_safety_information.pdf. Accessed January 6, 2015; Chou R, et al. *J Pain.* 2009;10:113-130. Food and Drug Administration. www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf. Accessed January 6, 2015.

OPIOIDS FOR USE IN NAÏVE PATIENTS

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

Agent	Use in Opioid-Naïve Patients
Nucynta ER (tapentadol ER tablets)	Initial dose is 50 mg twice a day
Opana ER (oxymorphone HCl ER tablets)	Initiate treatment with 5 mg every 12 hours
Zohydro ER (hydrocodone bitartrate ER capsules)	Initiate treatment with 10 mg every 12 hours

HCl = hydrochloride.

PATIENT CASE: EMILY SUMMARY

- SOAPP-R: score 2 (negative)
  - Low risk for abuse
- BPI: VAS pain (0-10)
  - Worst 8
  - Least 5
  - Avg. 7
  - Now 6
- Goal for therapy
  - Improved function at work: typing and walking around office with minimal pain
- Opioid history
  - No prior use

BPI = Brief Pain Inventory; VAS = Visual Analogue Scale.

TOLERANCE

and

DEPENDENCE

(Physiological)

ADDICTION

(Psychological)

Savage SR, et al. *J Pain Symptom Manage.* 2003;26:655-667.

OPIOID TOLERANCE

- FDA definition of opioid tolerance is based on medication dosage
- Pharmacologic tolerance occurs when a higher dose is required to maintain the same effect
- Duration is also a factor in opioid tolerance

FDA = Food and Drug Administration.

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

INITIATING ER/LA OPIOIDS IN OPIOID-TOLERANT PATIENTS

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- No restrictions on which opioids can be used
- Considered tolerant if taking, for 1 week or longer, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - Equianalgesic dose of another opioid

ER/LA Opioid Analgesics REMS. www.erlaopioidrems.com/IwgUI/rems/pdf/important_safety_information.pdf. Accessed January 6, 2015.

OPIOIDS FOR USE IN TOLERANT PATIENTS
(REFER TO FULL PACKAGE INSERT)

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

Agent (oral)	Doses for Use in Opioid-Tolerant Patients Only
Avinza (morphine sulfate ER capsules)	15 mg, 30 mg, 90 mg, and 120 mg capsules
Embeda (morphine sulfate ER-naltrexone capsules)	15 mg, 30 mg, 100 mg/4 mg capsule
Kadian (morphine sulfate ER capsules)	15 mg, 30 mg, 100 mg, and 200 mg capsules
MS Contin (morphine sulfate CR tablets)	15 mg, 30 mg, 100 mg, and 200 mg tablets
OxyContin (oxycodone HCl CR tablets)	Single dose greater than 40 mg or total daily dose greater than 80 mg
Dolophine (methadone HCl tablets)	When used as first opioid analgesic, initiate therapy with small doses, no more than 2.5 mg to 10 mg every 8 to 12 hours

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

OPIOIDS FOR USE IN TOLERANT PATIENTS

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

Agent (transdermal)	Doses for Use in Opioid-Tolerant Patients Only
Butrans (buprenorphine transdermal system)	10 mcg/hr and 20 mcg/hr transdermal systems

Agent	Doses for Use in Opioid-Tolerant Patients
Duragesic (fentanyl transdermal system)	All doses
Exalgo (hydromorphone HCl ER tablets)	All doses

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

APPROPRIATE DOSING AND TITRATION

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

Avinza (morphine sulfate ER capsules)

- Once daily
- Initial dose in opioid-naïve patients is 30 mg
- Titrate using a minimum of 3-day intervals
- Maximum daily dose 1600 mg (due to risk of renal toxicity)

Butrans (buprenorphine transdermal system)

- Applied every 7 days
- Initial dose in opioid-naïve patients or patients taking <30-mg oral morphine equivalents is 5 mcg/hour
- When converting from 30-mg to 80-mg morphine equivalents, taper to 30-mg morphine equivalent, then initiate with 10 mcg/hour dose
- The minimum titration interval is 72 hours
- Maximum daily dose: 20 mcg/hour (due to risk of QTc prolongation)

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

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APPROPRIATE DOSING AND TITRATION

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Dolophine (methadone HCl tablets)	Duragesic (fentanyl transdermal system)	Embeda (morphine sulfate ER/naloxone)
• Every 8 to 12 hours • Initial dose in opioid-naïve patients is 2.5 mg to 10 mg • Conversion using equianalgesic tables can result in overdose and death • Methadone should be used cautiously by clinicians familiar with the drug	• Every 72 hours • Contraindicated in opioid non-tolerant patients • Mild or moderate hepatic or renal impairment—use 50% of original dose	• Once a day or every 12 hours • Initial dose in opioid-naïve patients is 20 mg/0.8 mg • Dosage adjustments may be done every 1 to 2 days

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

APPROPRIATE DOSING AND TITRATION

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Exalgo (hydromorphone HCl ER tablets)	Kadian (morphine sulfate ER capsules)	MS Contin (morphine sulfate CR tablets)
• Once a day • Not for use in opioid non-tolerant patients • Moderate hepatic impairment: start on 25% usual dosage • Moderate renal impairment: start on 50% usual dosage • Severe renal impairment: start on 25% usual dosage • Titrate using 3- to 4-day intervals	• Once a day or every 12 hours • Not recommended as a first opioid • Titrate using a minimum of 2-day intervals	• Every 8 or 12 hours • Not recommended as a first opioid • Titrate using a minimum of 2-day intervals

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015

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Nucynta ER (tapentadol HCl ER tablets)

- Every 12 hours
- Initial dose is 50 mg every 12 hours in opioid non-tolerant patients
- Titrate by 50-mg increments using a minimum of 3-day intervals
- Maximum total daily dose is 500 mg

Opana ER (oxymorphone HCl ER tablets)

- Every 12 hours, can use asymmetric dosing
- Initial dose is 5 mg every 12 hours in opioid non-tolerant patients
- Titrate dose at increments of 5-10 mg every 12 hours, at 3- to 7-day intervals
- Mild hepatic impairment and renal impairment (creatinine clearance <50 mL/min): start with lowest dose
- In patients older than 65 years of age: start with lowest dose

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

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OxyContin (oxycodone HCl CR tablets)	Zohydro ER (hydrocodone bitartrate ER capsules)
• Every 12 hours • Initiate with 10 mg every 12 hours in opioid non-tolerant patients • Titrate with 1- to 2-day intervals • Hepatic impairment: start with 33% to 50% of the usual dosage • Renal impairment (creatinine clearance <60 mL/min): start with 50% of the usual dosage	• Every 12 hours • Initiate with 10 mg every 12 hours in opioid non-tolerant patients • Titrate in increments of 10 mg every 12 hours every 3 to 7 days • Renal impairment: start with low dose

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

SUMMARY: CLINICAL PEARLS

Get smart
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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Know your local state laws for opioid prescribing
- Use Opioid Agreement—*before* starting opioid trial
- Identify risk factors for respiratory depression
- Certain opioids and doses of opioids can be used *only* in opioid-tolerant patients
- In general, start with low doses and titrate based on efficacy, tolerability, adverse events
- Monitor for symptoms of respiratory depression, especially after initiating or increasing dose

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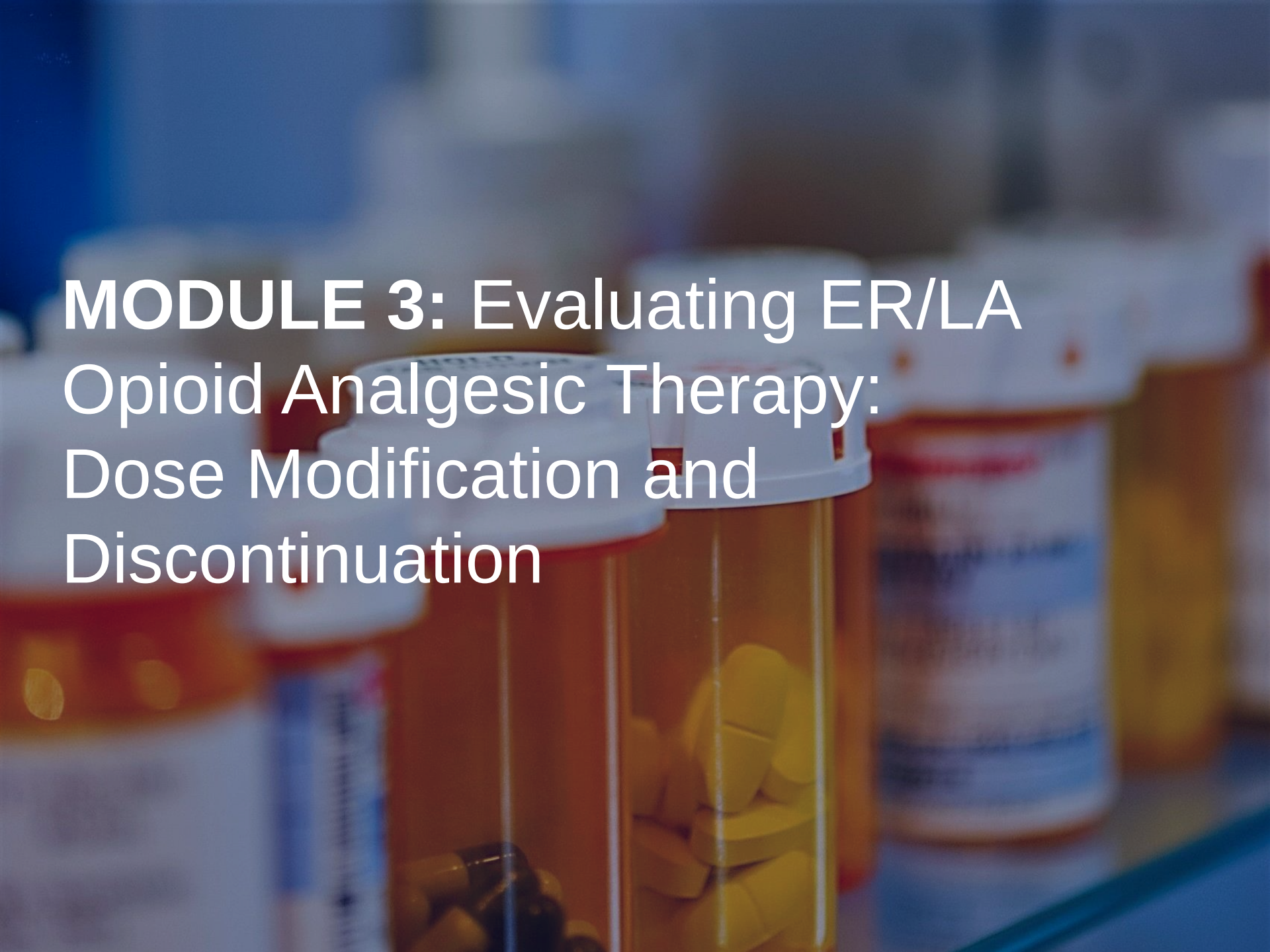

MODULE 3: Evaluating ER/LA Opioid Analgesic Therapy: Dose Modification and Discontinuation

LEARNING OBJECTIVES

Get smart
Safe Means of Administering the Right Therapy
EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Demonstrate the ability to modify dose and discontinue use of ER/LA opioid analgesics

PATIENT CASE: CAL SUMMARY

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Questionnaire responses

- ORT: score 4 (moderate risk)
- PHQ-2: positive
- BPI: VAS pain (0-10)
  - Severe, persistent pain
  - 20% relief from current pain treatments
- Opioid history
  - Oxycodone/acetaminophen IR

Goal

- Improve function at work and home
- Minimize nighttime pain and improve sleep
- Patient-prescriber agreement

IR = immediate-release; PHQ-2 = Patient Health Questionnaire-2.

OPIOID ROTATION

- Definition
  - A change from an existing opioid regimen to another opioid with the goal of improving therapeutic outcomes
- Reason
  - Lack of efficacy, AEs, reduction in dose
- Rationale
  - Effectiveness and AEs of different mu opioids vary among patients
  - Patients show incomplete cross-tolerance when rotated from one mu opioid to another
  - Patient tolerant to first opioid can have improved analgesia from second opioid at a dose lower than calculated from an equianalgesic dose table

AEs = adverse events.

Fine PG, et al. *J Pain Symptom Manage*. 2009;38:418-425; Knotkova H, et al. *J Pain Symptom Manage.* 2009;38:426-439; Pasternak GW. *Neuropharmacology*. 2004;47(suppl 1):312-323.

INCOMPLETE CROSS-TOLERANCE

- May enhance response to a new drug
  - Can heighten likelihood of therapeutic effects and AEs of another opioid
- Established among opioids
  - Should be considered whenever planning to rotate opioids

Chou R, et al. *J Pain*. 2009;10:113-130.

GENETIC POLYMORPHISMS AND RESPONSE TO OPIOIDS

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- Subtype variants of mu opioid receptor
  - Alter binding affinities
  - Change in receptor densities
- Interindividual variability in pain perception and sensitivity to analgesics
  - Efficacy
  - Side effects
  - Tolerance profiles
  - Risk of drug abuse

Landau R. *Anesthesiology.* 2006;105:235-237; Pasternak GW. *J Pain Symptom Manage.* 2005;29(5 Suppl):S2-S9; Ross JR, et al. *Pharmacogenomics J.* 2005;5:324-336.

VARIABLE OPIOID ACTIVITY AND EFFECT

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- Pharmacodynamics: drug's effect on body
  - Levels of receptor stimulation
  - Receptor-binding characteristics
- Pharmacokinetics: body's effect on drug
  - Opioid metabolism
- Genetics, race
- Medical conditions
- Role of enzyme systems

Interindividual variability: absence of benefit or occurrence of AE with one opioid does not predict similar response to another

Smith HS. *Mayo Clin Proc*. 2009;84:613-624; Trescot AM, et al. *Pain Physician*. 2008;11:S133-S153.

REASONS FOR OPIOID ROTATION

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- **Poor opioid response**
  - Dose titration yields intolerable or unmanageable AEs
  - Poor analgesic efficacy despite dose titration
- **Other potential reasons**
  - Patient desire or need to try a new formulation
  - Cost or insurance issues
  - Adherence issues
  - Concern about abuse or diversion
  - Change in clinical status requires opioid with different pharmacokinetics
  - Problematic drug-drug interactions
- **Requires equianalgesic conversion**

Fine PG, et al. *J Pain Symptom Manage.* 2009;38:418-425.

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EQUIANALGESIC CONVERSION

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Unidirectional

- Rough estimate of relative opioid potencies
  - Based on studies of opioid-naïve patients given single low-dose opioids
  - No regard for interindividual variations that play prominent role in determining real conversion
- Requires clinical consideration

Differences among available versions problematic

- Small variations in conversion ratio can lead to large differences in calculated equianalgesic doses
  - Especially at higher doses
  - Largest differences observed for oxycodone, fentanyl, methadone
  - Reported ratios for morphine, oxycodone range from 1:1 to 2:1

Müller-Busch HC, et al. *Eur J Pain*. 2005;9:571-579; Vallejo R, et al. *Pain Physician*. 2011;14:E343-E360.

CONVERSION TABLE

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Medication	Routine Dosage Equivalent	Route	Time to Effect	Duration
Morphine sulfate	10 mg 10 mg 30-60 mg	IV IM PO	5-10 min 15-30 min 30-60 min	3-6 h 3-6 h 3-6 h
Oxycodone	10-20 mg	PO	10-15 min	4-6 h
Hydrocodone	15-30 mg	PO	30-60 min	4-6 h
Fentanyl	50 mcg	IV	Immediate	1-2 h
Hydromorphone	7.5 mg 1.5 mg 1.5 mg	PO IV IM	15-30 min 15 min 15 min	4-6 h 4-6 h 4-6 h
Codeine	200 mg	PO	30-60 min	4-6 h
Nalbuphine	10 mg	IM	15 min	3-6 h

IM = intramuscular; IV = intravenous; PO = oral.
OpioidRisk. www.opioidrisk.com/node/489. Accessed January 7, 2015.

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ER/LA OPIOID CONVERSION

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- Conservative dosing recommended
  - Follow conversion instructions in PI
  - ↓ calculated comparable dose by 50%
  - Titrate new agent as needed
- Potential for underdosing during conversion
  - Use supplemental IR opioid, BTP medication until patient response known
- After steady-state of new opioid achieved, BTP medication usage known, calculate ↑ dose of new opioid

PI = package insert.

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

ER/LA OPIOID ANALGESICS RELATIVE POTENCY TO ORAL MORPHINE

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Opioid	Relative Potency to Oral Morphine
Buprenorphine	Not established
Methadone HCl	Varies depending on previous opioid experience
Fentanyl	See individual PI
Hydromorphone HCl	~5:1 (oral morphine to hydromorphone oral dose ratio); see individual PI
Tapentadol	Not established
Oxymorphone HCl	~3:1 (oral morphine to oxymorphone oral dose ratio)
Oxycodone HCl	~2:1 (oral morphine to oxycodone oral dose ratio)

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015.

METHADONE DOSE CONVERSION

- Initial dose ↓ during conversion: 75% to 90%

Advantages	Disadvantages
Low cost	Unpredictable half-life
Good oral, rectal absorption	Variable conversion ratios Morphine equivalent <30 mg, 2:1 Morphine equivalent <90 mg, 5:1 Morphine equivalent 100-299 mg, 8:1 Morphine equivalent 300-499 mg, 12:1 Morphine equivalent 500-999 mg, 15:1 Morphine equivalent 1000-1200 mg, 20:1 Morphine equivalent >1200 mg, consider consult
No active metabolites	Dose adjustments needed every 4-5 days
Low tolerance development	
Long duration of effect	

Bruera E, et al. *J Palliat Med*. 2002;5:127-138.

OPIOID ROTATION PRINCIPLES AND FUNDAMENTALS

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Opioid rotation: switching from one opioid to another to ↑ analgesia, compliance and ↓ AEs

- Appropriate in cases of poor response, intolerable AEs
  - Long-term opioid use, chronic noncancer pain, complex pain conditions
- Optimal choices unclear
- Requires calculation of approximate equianalgesic dose

Incomplete cross-tolerance: tolerance to AEs of one opioid does not imply same for another

- ↓ calculated dose of new agent by 25% to 50% at initiation
- Manage potential effects
  - Adjuvant analgesics during conversion
  - Specific treatment of AEs

Chou R, et al. *J Pain*. 2009;10:113-130; de Stoutz ND, et al. *J Pain Symptom Manage*. 1995;10:378-384; Grilo RM, et al. *Joint Bone Spine*. 2002;69:491-494; Inturrisi CE. *Clin J Pain*. 2002;18:S3-S13; Kloke M, et al. *Support Care Cancer*. 2000;8:479-486; Manchikanti L, et al. *Pain Physician*. 2012;15:S67-S116; Quang-Cantagrel ND, et al. *Anesth Analg*. 2000;90:933-937; Sinatra R. *J Am Board Fam Med*. 2006;19:165-177.

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OPIOID ROTATION SUMMARY

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- Use moderate reduction in calculated equianalgesic dose
- Rate of use varies, 10%-40%
- Optimal choices unclear
- Challenges exist in opioid rotation
  - Potential for increased cost
  - Patient preference
  - Prescriber experience and time
  - Drug availability

Chou R, et al. *J Pain*. 2009;10:113-130; de Stoutz ND, et al. *J Pain Symptom Manage*. 1995;10:378-384.

OPIOID METABOLISM MATTERS

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Opioid	Relative Risk for Drug-Drug Interactions
Fentanyl	High
Methadone	High
Oxycodone	High/intermediate
Tramadol	High/intermediate
Codeine	Intermediate
Hydrocodone	Intermediate
Hydromorphone	Minimal
Morphine	Minimal
Oxymorphone	Minimal

Zhou SF. *Curr Drug Metab*. 2008;9:310-322; Zhou SF, et al. *Ther Drug Monit*. 2007;29:687-710.

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FOLLOW-UP DURING DOSE ADJUSTMENTS

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- Monitor closely to evaluate effectiveness of analgesia, tolerability of AEs
- Anticipate subsequent dose adjustments, rotations
  - ≥1 rotation often necessary; sometimes 3-4
- Recognize that dose ratios in conversion tables may be more accurate for single-dose opioid administration than for chronic opioid dosing

Cherny NJ, et al. *Cancer*. 1995;76:1283-1293; Cherny NJ, et al. *J Clin Oncol*. 2001;19:2542-2554; Galer BS, et al. *Pain*. 1992;49:87-91; Quang-Cantagrel ND, et al. *Anesth Analg*. 2000;90:933-937.

MANAGING BTP

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

Patients on stable opioid therapy may have BTP

- Disease progression or a new or unrelated pain

Therapies

- Directed at cause of BTP or precipitating factors
- Nonspecific symptomatic therapies to lessen impact of BTP

Consider adding

- As needed IR opioid trial based on analysis of benefit versus risk
- Nonopioid drug therapies
- Nonpharmacologic treatments

NEVER use ER/LA opioids for BTP

Chou R, et al. *J Pain.* 2009;10:113-130.

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SUPPLEMENTING ER/LA OPIOIDS: PHARMACEUTICAL TREATMENT

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Therapeutic Alternative	Treatment Option	
Employ nonopioid analgesics	→ Acetaminophen or NSAIDs	Antidepressants and anticonvulsants
Alter dose of ER/LA opioid	→ Continue with higher dose if no treatment-limiting effects	Reduce dose if treatment-limiting effects persist
Utilize short-acting opioids	→ Requires continual analysis	

Zeppetella G. *Curr Opin Support Palliat Care*. 2009;3:1-6; Chou R, et al. *J Pain.* 2009;10:113-130; Burton AW. www.medscape.org/viewarticle/506124. Accessed January 5, 2015; Rhiner MI, et al. *J Support Oncol.* 2010;8:232-238.

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IR VERSUS ER/LA OPIOIDS

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	Pros	Cons
IR	Onset of effect 30-40 min	Duration of action 2-4 h Decreased absorption after full meal Affect limbic system rapidly (pleasure center)
ER/LA	Duration of action 6-72 h Less effect on limbic system More predictable serum levels, analgesic effect Avoids mini-withdrawals Easier to use; greater compliance, patient satisfaction Less reinforcement of drug-taking behavior; may be more appropriate if known or expected high risk Patients report being in control of pain, tend not to dose-escalate	Cost Increased dosage for potential diversion

Sinatra R. *J Am Board Fam Med*. 2006;19:165-177; Von Korff M, et al. *Pain*. 2011;152:1256-1262.

CONSIDERATIONS WHEN SUPPLEMENTING ER/LA OPIOIDS WITH IR OPIOIDS

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- Requires patient education regarding additional treatment options
- ER/LA opioid dose may be increased by 25%
  - May require shortening dosage interval
- Short-acting opioids must be selected based on current ER/LA opioids
  - Dose and dose timing should be individualized based on daily activity, pain severity, duration, and patient tolerance

Burton AW. http://www.medscape.org/viewarticle/506124. Accessed January 5, 2015.

CONSIDERATIONS WHEN SUPPLEMENTING ER/LA OPIOIDS WITH NONOPIOIDS

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- NSAIDs may have dose-limiting toxicities or slow onset
- Antidepressant use may be limited by comorbidities such as cardiovascular disease
  - AEs can limit patient adherence
- Anticonvulsants may also produce AEs
  - Benefits have been shown in clinical trials

Wu WT, et al. *Neuropsychiatr Dis Treat*. 2013;9:1023-1028; Bouloux GF. *J Oral Maxillofac Surg*. 2011;69:1885-1891; Gilron I. *Can J Anaesth*. 2006;53:562-571; Burton AW. http://www.medscape.org/viewarticle/506124. Accessed January 5, 2015.

SUPPLEMENTING ER/LA OPIOIDS: NONPHARMACOLOGIC TREATMENT

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Requires patient education
- Appropriate pacing
- Cognitive-behavioral interventions
- Heating pads or ice packs
- Starting or continuing a limited exercise program
- Psychosocial interventions
  - Relaxation techniques
  - Biofeedback

Rhiner MI, et al. *J Support Oncol*. 2010;8:232-238; Burton AW. http://www.medscape.org/viewarticle/506124. Accessed January 5, 2015.

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REASONS FOR DISCONTINUING ER/LA OPIOIDS

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No progress toward therapeutic goals

Intolerable & unmanageable AEs

Pain level decreases in stable patients

Nonadherence or unsafe behavior

- 1 or 2 episodes of increasing dose without prescriber knowledge
- Sharing medications
- Unapproved opioid use to treat another symptom (such as insomnia)

Aberrant behaviors suggestive of addiction and/or diversion

- Use of illicit drugs or unprescribed opioids from multiple outside services
- Prescription forgery
- Multiple episodes of prescription loss

Chou R, et al. *J Pain*. 2009;10:113-130; Department of Veterans Affairs, Department of Defense. http://www.healthquality.va.gov/guidelines/Pain/cot/. Accessed January 6, 2015.

TAPERING AND DISCONTINUING ER/LA OPIOID ANALGESICS

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- Do not suddenly discontinue ER/LA opioids
  - May result in withdrawal
  - Look for physical signs and refer to patient history
- May use range of approaches
  - Slow 10% dose reduction per week
  - More rapid 25% to 50% reduction every few days
  - Tailor to individual patient, opioid, and treatment history

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 6, 2015; Chou R, et al. *J Pain*. 2009;10:113-130; Suttner J, et al. *Adv Pharmacol Pharmacy*. 2013;1:42-57.

SUMMARY: CLINICAL PEARLS

Get smart
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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Opioid administration varies for opioid-tolerant patients
- Lack of efficacy can be addressed through opioid rotation or supplementing ER/LA opioids with other opioids or with nonopioid treatments
- Be conservative and thoughtful when dosing
  - When initiating, titrating, and rotating opioids
  - First calculate equianalgesic dose, then reduce dose appropriately
- Discontinue ER/LA opioids slowly and safely

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MODULE 4: Managing Ongoing Therapy With ER/LA Opioid Analgesics

LEARNING OBJECTIVES

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Demonstrate the ability to manage ongoing therapy with ER/LA opioid analgesics

COMPLIANCE MONITORING PURPOSE AND TECHNIQUES

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Purpose
  - Identify previous, current drug use
  - Determine basis of treatment
  - Decrease drug abuse, misuse
  - Implement adequate pain management strategies
- Techniques
  - Screening tests
  - Patient-prescriber agreement
  - Patient education
  - State PDMP
  - Medication reconciliation
  - UDT
  - Combination of above

Manchikanti L, et al. *Pain Physician*. 2008;11:S155-S180.

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INFORMED CONSENT

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Before initiating a trial of opioid analgesic therapy, confirm patient understanding of informed consent

Establish:

- Goals of treatment
- Expectations
- Potential risks
- Alternative treatments

Potential for and how to manage:

- Common opioid-related AEs
- Other serious risks (eg, abuse, respiratory depression)
- AEs after long-term or high-dose therapy (eg, hyperalgesia, endocrine dysfunction)

Chou R, et al. *J Pain*. 2009;10:113-130; Department of Veterans Affairs, Department of Defense. http://www.healthquality.va.gov/guidelines/Pain/cot/. Accessed January 7, 2015.

PATIENT-PRESCRIBER AGREEMENT (PPA)

Get smart
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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Use of a PPA has been supported by clinical evidence and is also in guidelines for pain management
- PPAs can consist of:
  - Informed consent documents
  - Treatment agreement documents
- Initiated at time opioid is prescribed
  - Recommend obtaining patient's signature

Chou R, et al. *J Pain*. 2009;10:113-130.

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COMPONENTS OF A PPA

Get smart
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Description of expectations for benefits and AEs associated with ER/LA opioids
Designate one pharmacy for filling prescriptions
Explain the importance of using one clinician
The importance of taking the opioid as prescribed, and the consequences of deviating from the established prescription
Frequency with which prescriptions will be filled
Compliance monitoring
Safeguarding ER/LA opioids
Why and how to discontinue opioids
Places for signature and dating

Chou R, et al. *J Pain*. 2009;10:113-130.

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THE FOUR A's: MONITOR PATIENTS DURING OPIOID THERAPY

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- Analgesia
- Adverse events
- Activities of daily living
- Aberrant behavior

Also consider Assessment, Affect, and Action

Passik SD, et al. *Adv Ther.* 2000;17:70-83; Manchikanti L, et al. *Pain Physician.* 2012;15(3 suppl):S67-S116.

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MONITOR PATIENTS DURING OPIOID THERAPY

Get smart
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Therapeutic risks and benefits are not static

- Affected by change in underlying pain condition, coexisting disease, and/or psychological/social circumstances

Identify patients

- Who are benefiting from opioid therapy
- Who might benefit from additional services or restructuring of treatment
- Risks outweigh benefits of treatment

Periodically assess need for opioid analgesic

- Re-evaluate underlying medical condition if clinical presentation changes

Chou R, et al. *J Pain.* 2009;10:113-130; Department of Veterans Affairs, Department of Defense. http://www.healthquality.va.gov/guidelines/Pain/cot/. Accessed January 7, 2015.

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MONITOR PATIENTS DURING OPIOID THERAPY

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Periodically evaluate

- Pain control
  - Document pain intensity, pattern, and impact
- Functional outcomes
  - Document level of function
  - Assess progress toward goals
- Health-related QoL
- AEs frequency and severity
- Adherence

Patients requiring more frequent monitoring

- High-risk patients
  - Such as elderly persons, children, and pregnant women
- Patients taking high doses of opioids

QoL = quality of life.

Chou R, et al. *J Pain*. 2009;10:113-130; Department of Veterans Affairs, Department of Defense. http://www.healthquality.va.gov/guidelines/Pain/cot/. Accessed January 7, 2015.

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ANTICIPATE AND TREAT COMMON OPIOID AEs

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Constipation	The most common AE of opioid therapy Initiate bowel regimen Increase fluid & fiber intake, stool softeners, laxatives Opioid antagonists may prevent/treat
Nausea and vomiting	Tend to diminish over days or weeks Oral and rectal antiemetic therapies as needed
Drowsiness and sedation	Tend to diminish over time Counsel patients about driving, work & home safety Describe risks of concomitant exposure to other substances with sedating effects
Pruritus and myoclonus	Tend to diminish over days or weeks Treatment strategies are anecdotal

Chou R, et al. *J Pain*. 2009;10:113-130.

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ANTICIPATE AND TREAT COMMON OPIOID AEs

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Respiratory depression	Most serious AE Occurs when initial doses are too high, during rapid titration, or interaction with other drugs (eg, benzodiazepines, herbals, diphenhydramine) Risk increased by sleep apnea or other underlying pulmonary conditions
Hyperalgesia	Heightened response to pain Higher doses may enhance hyperalgesia May be occurring if pain seen in other areas Controversial
Sleep disruptions	Sleep apnea increases risk of AE

Brush DE. *J Med Toxicol*. 2012;8:387-392; Dimsdale JE, et al. *J Clin Sleep Med*. 2007;3:33-36; Manchikanti L, et al. *Pain Physician*. 2012;15(3 suppl):S67-S116; Chou R, et al. *J Pain*. 2009;10:113-130.

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MONITOR PATIENT ADHERENCE AND ABERRANT BEHAVIOR

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Develop monitoring strategy based on established risk

- State PDMPs
- UDTs
- Pill counts
- Frequently assess behavior
  - Refer for substance abuse treatment if necessary

Chou R, et al. *J Pain*. 2009;10:113-130.

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ADDRESS ABERRANT DRUG-RELATED BEHAVIOR

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Less indicative of aberrant behavior:

- Unsanctioned dose escalation or other noncompliance with therapy on 1 or 2 occasions
- Unapproved use of the drug to treat another symptom
- Openly acquiring similar drugs from other medical sources

More indicative of aberrant behavior:

- Multiple dose escalations or other noncompliance with therapy despite warnings
- Prescription forgery
- Obtaining prescription drugs from nonmedical sources

Fleming MF, et al. *Pain Med.* 2008;9:1098-1106; Passik SD, et al. *J Pain Symptom Manage.* 2011;41:116-125; Portenoy RK. *J Law Med Ethics.* 1996;24:296-309; Passik SD, et al. *Clin J Pain.* 2006;22:173-181; Chou R, et al. *J Pain*. 2009;10:113-130.

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SCREENING FOR SUBSTANCE ABUSE

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- Four C's:
  - Adverse **C**onsequences/harm from use
  - Impaired **C**ontrol over use
  - **C**ompulsive use
  - Preoccupation with use due to **C**raving
- Clinicians must also consider sleep and work patterns, failure to improve functioning, and mood when assessing patient for opioid misuse or abuse
- High risk for misuse decreases likelihood of pain control

Holmes CP, et al. *Pain Pract*. 2006;6:74-88; Morasco BJ, et al. *J Gen Intern Med.* 2011;26:965-971.

INCREASE MONITORING

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Seeking early refills
- Misusing alcohol or illicit drugs
- Taking larger doses than prescribed
- Insisting that higher doses are needed
- Deteriorating functioning
- Obtaining opioids illegally
- Prescribed opioids not present on UDT
- Not adhering to nonpharmacologic treatments

Substance Abuse and Mental Health Services Administration. *Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders.* Treatment Improvement Protocol (TIP) Series 54. HHS Publication No. (SMA) 12-4671. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2011.

PDMPs

- Electronic database provides clinicians with information about prescription history
- No national standards
  - PDMPs are state run and have been adopted in almost all states
  - Regulations differ among states
  - Not all states offer real-time data access
- In some states, reports are automatically generated on patients who cross certain thresholds when filling prescriptions
- Information may be available through electronic medical records

Dahl J. *J Pain.* April 2012;13:Abstract 245; Dahl J, et al. *J Pain.* April 2012;13:Abstract 246.

PDMPs OPERATIONAL OR LEGISLATED IN 49 STATES, 1 TERRITORY

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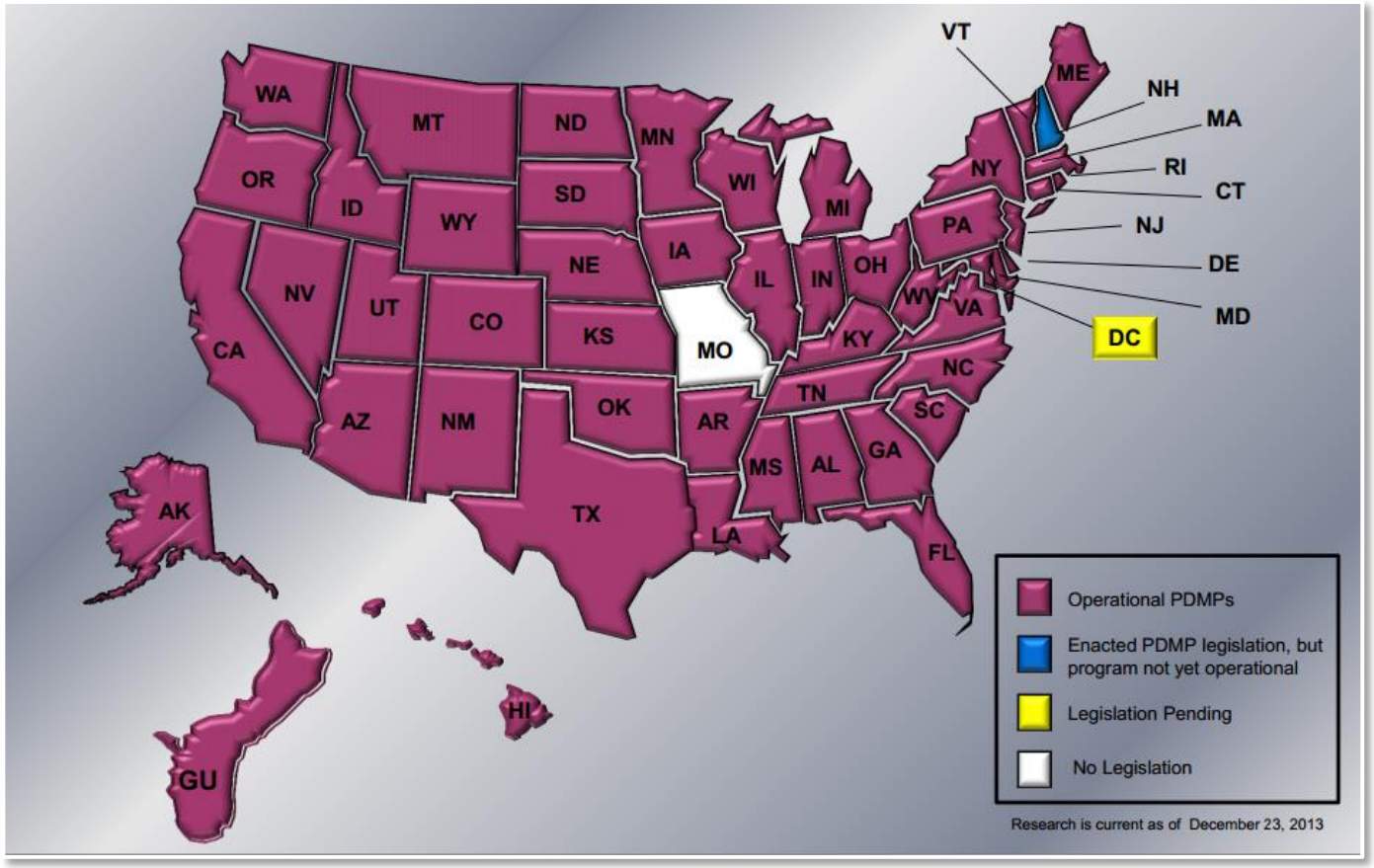

Alliance of States With Prescription Drug Monitoring Programs. http://www.pdmpassist.org/pdf/pmpprogramstatus2013_a.pdf. Accessed January 7, 2015.
NOTE: Graphic borrowed from other presentation (Michael Brennan, MD).

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BENEFITS OF PDMPs

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- Review records of patients' controlled substance prescriptions
  - Some are available online 24/7
  - Provides opportunity to discuss with patient
- Provide warnings of potential misuse/abuse
  - Existing prescriptions not reported by patient
  - Multiple prescribers or pharmacies
  - Drugs that increase overdose risk when taken together
  - Patient pays cash for drugs of abuse
- Prescribers can review their own prescribing histories

URINE DRUG TESTING

Get smart
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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Patient self-reports may not provide adequate information to identify misuse or abuse
- UDTs should be used in all patients
- Use UDTs to identify both prescription and illicit drugs
- Can be used to assess adherence to opioid therapy
- Use UDTs to initiate a discussion

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

INTERPRETING UDT RESULTS

- Know which compounds should appear in the UDT result
  - Either parent drug or metabolite
- Identify presence of expected and unexpected drugs
  - Positive result
    - Demonstrates recent use
    - Does not diagnose addiction, dependence, or impairment
    - Does not tell you exposure time, dose, or frequency of use
  - Negative result
    - Does not identify diversion
    - May be due to maladaptive drug-taking behavior (eg, bingeing)
- Know what your laboratory can and cannot do

Gourlay DL, et al. http://www.pharmacomgroup.com/udt/udt5.pdf. Accessed January 7, 2015.

LIMITATIONS OF UDTs

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- Most drug screening involves a monoclonal antibody
- Negative results may be caused by:
  - No drug
  - Drug is present below detection threshold
  - Assay binds weakly to the drug
  - Interference with assay by other medications
- Possibility of false-positives or false-negatives

Reisfield G, et al. *Ann Clin Lab Sci*. 2007;37:301-314.

DIFFERENCES IN TYPES OF UDTs

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Screening UDT
Immunoassay analysis
Low or no sensitivity to synthetic or semi-synthetic opioids
Variable specificity—can result in false-negatives or false-positives
Rapid turnaround

Confirmatory UDT
Analyzed with GC-MS or HPLC
High sensitivity
High specificity and can detect individual drugs
Slow turnaround
Results are legally defensible

GC-MS = gas chromatograph mass spectrometer; HPLC = high performance liquid chromatography.
Adapted from Urine Drug Testing. http://www.nhms.org/sites/default/files/Pdfs/Urine DrugTestingguide.pdf. Accessed January 7, 2015.

SCREENING TECHNIQUES

- Assess misuse or abuse with:
  - PDMPs
  - UDTs
  - Pill counts
- Can help identify:
  - Presence of unprescribed medications
  - If the patient is no longer taking the medication
  - Potential interactions
  - If the patient is taking the medication incorrectly

OpioidRisk – Improving Provider Skills in Reducing the Risk of Opioid Therapy. http://www.opioidrisk.com/node/3130. Accessed January 7, 2015.

IDENTIFYING REFERRAL SOURCES

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- Substance Abuse and Mental Health Services Administration (SAMHSA)
  http://www.samhsa.gov/treatment
- Balancing Pain Management and Prescription Opioid Abuse
  http://www.cdc.gov/primarycare/materials/opoidabuse/index.html
- National Institute on Drug Abuse
  http://www.nida.nih.gov
- American Council for Drug Education
  http://www.acde.org
- American Academy of Addiction Psychiatry
  - Providers' Clinical Support System for Opioid Therapies
    http://www.pcss-o.org
  - Providers' Clinical Support System for Medication Assisted Treatment
    http://www.pcssmat.org

SUMMARY: CLINICAL PEARLS

Get smart
Safe Means of Administering the Right Therapy
EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Goals of opioid therapy are to improve pain control, daily functioning, QoL
- PPA establishes goals and compliance
- PDMPs can help clinicians understand a patient's prescription history and aberrant behavior
- UDTs can establish prescription drug and illicit drug use, but have limitations
- Monitor the four A's: **A**nalgesia, **A**Es, **A**ctivities of daily living, and **A**berrant behavior

MODULE 5: Counseling Patients and Caregivers About the Safe Use of ER/LA Opioid Analgesics

LEARNING OBJECTIVES

Get smart
Safe Means of Administering the Right Therapy
EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Participants will demonstrate the ability to perform effective counseling with patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal

PATIENT COUNSELING DOCUMENT (PCD)

Get smart
Safe Means of Administering the Right Therapy
EXTENDED RELEASE AND LONG-ACTING OPIOIDS

Patient Counseling Document used to help counsel patients:

- **"DOs"** and "**DON'Ts**" of ER/LA opioid analgesics
- When to seek emergency services
- Issues that warrant clinician attention
- Patient-specific information
- Drug-specific information

Download: http://www.er-la-opioidrems.com/IwgUI/rems/pdf/patient_counseling_document.pdf

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics

Patient Name:

The DOs and DON'Ts of Extended-Release / Long - Acting Opioid Analgesics

DO:

- Read the **Medication Guide**
- Take your medicine exactly as prescribed
- Store your medicine away from children and in a safe place
- Flush unused medicine down the toilet
- Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Call 911 or your local emergency service right away if:

- You take too much medicine
- You have trouble breathing, or shortness of breath
- A child has taken this medicine

Talk to your healthcare provider:

- If the dose you are taking does not control your pain
- About any side effects you may be having
- About all the medicines you take, including over-the-counter medicines, vitamins, and dietary supplements

DON'T:

- **Do not** give your medicine to others
- **Do not** take medicine unless it was prescribed for you
- **Do not** stop taking your medicine without talking to your healthcare provider
- **Do not** break, chew, crush, dissolve, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.
- **Do not** drink alcohol while taking this medicine

For additional information on your medicine go to: **dailymed.nlm.nih.gov**

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics

Patient Name:

Patient Specific Information

Take this card with you every time you see your healthcare provider and tell him/her:

- Your complete medical and family history, including any history of substance abuse or mental illness
- The cause, severity, and nature of your pain
- Your treatment goals
- All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements
- Any side effects you may be having

Take your opioid pain medicine exactly as prescribed by your healthcare provider.

ER/LA Opioid Analgesics REMS. http://www.er-la-opioidrems.com/IwgUI/rems/pcd.action. Accessed January 7, 2015.

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UNDERSTANDING THE "DOs" IN THE PCD

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The "DOs": What to Tell Your Patients
Read medication guide from dispensing pharmacy
Take your medicine exactly as prescribed
Store your medicine away from children and in a safe place
Flush unused medicine down the toilet
Call your healthcare clinician for medical advice about side effects and report them to the FDA

ER/LA Opioid Analgesics REMS. http://www.er-la-opioidrems.com/IwgUI/rems/pcd.action. Accessed January 7, 2015.

UNDERSTANDING THE "DON'Ts" IN THE PCD

Get smart
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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

The "DON'Ts": What to Tell Your Patients
Do not give your medicine to others
Do not take medicine unless it was prescribed for you
Do not stop taking your medicine without talking to your healthcare clinician
Do not break, chew, crush, dissolve, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare clinician
Do not drink alcohol while taking this medicine

ER/LA Opioid Analgesics REMS. http://www.er-la-opioidrems.com/IwgUI/rems/pcd.action. Accessed January 7, 2015.

INCLUDING THE PCD IN CLINICAL PRACTICE

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Clinicians utilize the PCD at the time of prescribing and at follow-up visits
- Incorporate the PCD when discussing a patient-prescriber agreement
- Patient and caregiver education strategies should ensure that patients understand their specific medication

ER/LA Opioid Analgesics REMS. http://www.er-la-opioidrems.com/IwgUI/rems/pcd.action. Accessed January 7, 2015.

COUNSEL PATIENTS ABOUT PROPER USE OF ER/LA OPIOID ANALGESICS

Get smart
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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

Explain:

- Product characteristics that are found in the medication guide
  - Product-specific adverse events
  - Specific drug-delivery system
- How to take as prescribed
- Importance of adherence, handling, and missed doses, contacting prescriber if pain not controlled

Instruct Patients/Caregivers:

- Read **medication guide** every time an ER/LA opioid is dispensed
- Identify all medications they take **at every** medical appointment

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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IMPROVING OPIOID ADHERENCE

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- 60% of patients adhere to a patient-prescriber agreement
- **Lack of communication** between patients and clinicians can lead to incorrect usage

Factors That Influence Adherence
Dosing frequency
Depression
Side effects
Perceived benefit
Realistic treatment expectations
Knowledge of the disease

Hariharan J, et al. *J Gen Intern Med.* 2007;22:485-490; Lewis E, et al. *Pain Med.* 2010;11:861-871; Graziottin A, et al. *Pain Pract.* 2011;11:574-581.

THE ER/LA OPIOID MEDICATION GUIDE

Get smart
Safe Means of Administering the Right Therapy
EXTENDED RELEASE AND LONG-ACTING OPIOIDS

Medication guides provide essential information for patients to take ER/LA opioids safely:

- When they should take or not take the medication
- What they need to tell their healthcare clinician
- How they should take the medication
- What they should not do while taking ER/LA opioids
- Possible AEs

Medication Guides are available at www.ER-LA-opioidREMS.com.

ER/LA Opioid Analgesics REMS. www.er-la-opioidrems.com/IwgUI/rems/products.action. Accessed January 7, 2015.

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WARN PATIENTS: DO NOT TAMPER WITH ER/LA OPIOIDS

Get smart
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Oral ER/LA opioids must be swallowed whole
Never break, chew, crush, or dissolve an oral ER/LA tablet or capsule
Never cut or tear patches prior to use; never chew, swallow, or use in way other than indicated

- May lead to rapid release of ER/LA opioid, potentially causing overdose and death
- When a patient cannot swallow a tablet or capsule whole, use an ER/LA formulation that can be opened and sprinkled on pudding or applesauce
- For transdermal systems: external heat, fever, exertion can ↑ opioid absorption, potentially leading to fatal overdose
- Metallic backings on some products not safe during magnetic resonance imaging

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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MANAGING A PATIENT WHO HAS DIFFICULTY SWALLOWING OPIOID

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Refer to product information to determine if the contents of a capsule can be sprinkled on applesauce

- Avinza (morphine sulfate ER)
- Kadian (morphine sulfate ER)
- Embeda (morphine sulfate ER/naltrexone)

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

WARN PATIENTS: OPIOID USE WITH CNS DEPRESSANTS

Get smart
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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Use of CNS depressants or alcohol with ER/LA opioids can cause overdose and death
- Opioids account for 25% of overdoses related to CNS depressants
- CNS depressants contribute to a significant number of opioid-related overdoses

- Use with alcohol may result in rapid release and absorption of a potentially fatal dose
- Other CNS depressants include alcohol, benzodiazepines (eg, diazepam, lorazepam), illegal drugs (eg, heroin), and other sedative-hypnotics and anxiolytics

CNS = central nervous system.

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015; Hoyert DL, et al. *Natl Vital Stat Rep*. 2012;61; Jones CM, et al. *JAMA*. 2013;309:657-659.

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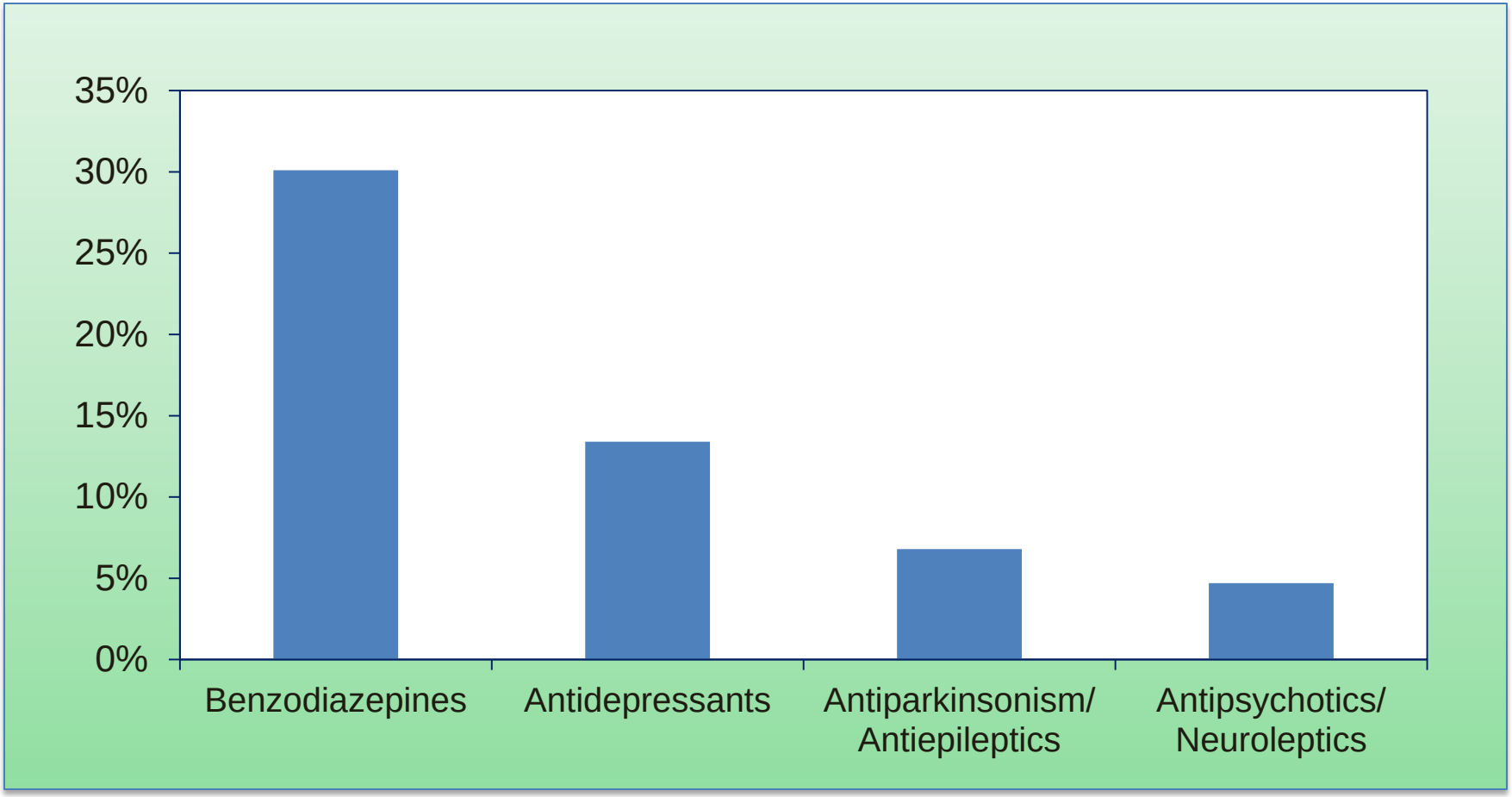
CNS DEPRESSANTS IN OPIOID OVERDOSES



Jones CM, et al. *JAMA*. 2013;309:657-659.

DISCONTINUING ER/LA OPIOIDS

Get smart
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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Abruptly discontinuing ER/LA opioids can result in withdrawal syndrome
- Discuss when and how to taper opioid dose if the patient wishes to discontinue the therapy
  - For example, decrease original dose by 10% per week to taper

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

WITHDRAWAL SYNDROME

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

Withdrawal syndrome is rarely fatal

Withdrawal Symptoms	
Stomach cramps	Increased blood pressure
Diarrhea	Irritability
Rhinorrhea	Dysphoria
Sweating	Hyperalgesia
Tachycardia	Insomnia

Miller N, et al. *Am Fam Physician.* 1998;58:139-146.

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ER/LA OPIOID SIDE EFFECTS

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- Opioids may decrease psychomotor performance
  - Driving
  - Operating heavy machinery
- Reporting opioid-related adverse events
  - Prescriber
  - Product manufacturer
  - FDA MedWatch Reporting System (800) 332-1088 (800-FDA-1088)
  - www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm

Common Adverse Events
Sedation
Dizziness
Nausea
Vomiting
Constipation
Respiratory depression
Endocrine dysfunction
Allergic reaction

Benyamin R, et al. *Pain Physician*. 2008;11(2 Suppl):S105-S120; Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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OPIOID OVERDOSE

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Signs of Opioid Overdose
Altered level of consciousness
Hypoventilation
Reduced bowel motility
Miosis

- With ER/LA opiates, this may be gradual
  - Can be reversed by naloxone
- Risk greatest with dose escalation, rotation, and early in "month," and methadone

Williams RH, et al. *Lab Med.* 2000;31:334-342.

PROTECT FAMILY AND COMMUNITY: ER/LA OPIOID STORAGE

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Caution Patients

- Store medications safely and securely away from family, visitors, and pets
- Protect from theft
- Dispose of ER/LA opioids when no longer needed

Monitor

- Take inventory of all drugs in home
- Note how many pills in each prescription bottle
- Keep track of refills
- Make sure family members are aware of risks

Secure

- Do not store opioids in medication cabinet
- Keep in safe place (eg, locked cabinet)

Dispose

- Discard expired or unused drugs

http://www.asam.org/docs/default-source/education-docs/asam-3-hour-v2-0-handouts--color.pdf?sfvrsn=10. Accessed January 7, 2015.

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FDA RECOMMENDATIONS FOR DISPOSAL

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- Dispose of ER/LA opioids when they are no longer needed
- FDA safe disposal method recommendations:
  - Drug take-back programs
  - Drug drop boxes in some local police departments
  - Flush down the toilet—includes transdermal patches (folded in half)
- It is not recommended to throw opioids in the trash, even when combined with coffee grounds or some other unpalatable substance

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015; Food and Drug Administration. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalofMedicines/ucm186188.htm. Accessed January 7, 2015.

SUMMARY: CLINICAL PEARLS

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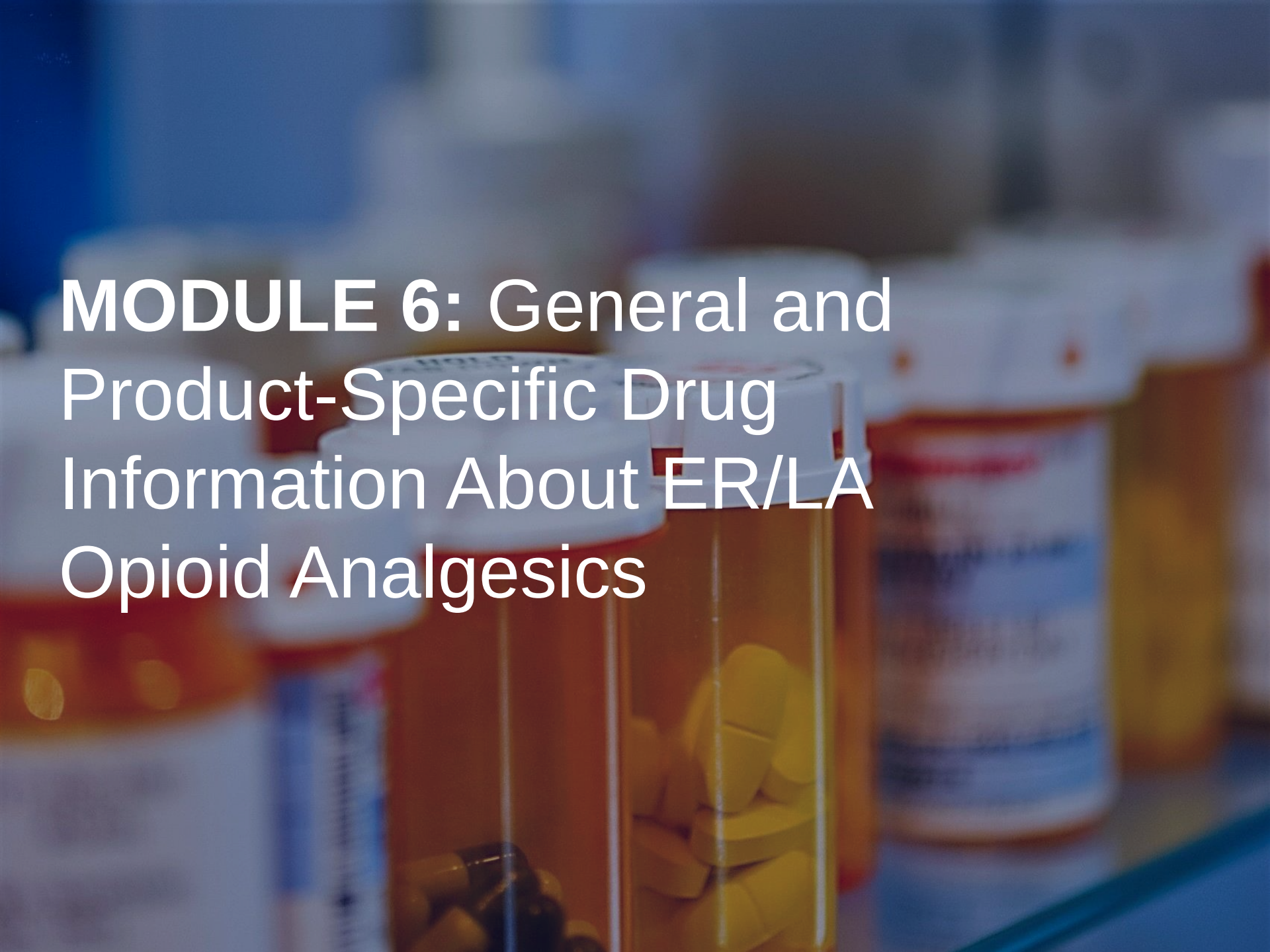
- Use PCD to outline “DOs” and “DON’Ts” of opioids and establish patient goals
- Counsel patients about proper use and:
  - Adverse events of opioids, particularly respiratory depression
  - Nonadherence, which can lead to possible overdose or inadequate pain control
  - Overdoses are more likely when opioids are combined with other CNS depressants
- Appropriate disposal of opioids is essential



MODULE 6: General and Product-Specific Drug Information About ER/LA Opioid Analgesics

LEARNING OBJECTIVES

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- Participants will demonstrate the ability to identify general and product-specific drug information concerning ER/LA opioid analgesics

GENERAL ER/LA OPIOID DRUG INFORMATION

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Prescribers should be knowledgeable about the characteristics, toxicities, and drug-drug interactions for ER/LA opioid products

Controlled Substances

ER/LA opioid products are scheduled under the Controlled Substances Act

- Can be misused and abused

Adverse Events

Respiratory depression is the most serious adverse event

- Can be life-threatening
- Constipation is the most common long-term adverse event
- Should be anticipated

Drug-Drug Interactions

- CNS depressants
- Alcohol
- MAOIs
- Diuretics
- QTc prolongation
- P450 interactions

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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CONTROLLED SUBSTANCES ACT

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Schedule Class	Description	Examples
I	No accepted medical use; high potential for abuse; potentially severe psychological or physical dependence	Heroin, marijuana, ecstasy, methaqualone, peyote, LSD
II	High potential for abuse (less than schedule I); potentially severe psychological or physical dependence	**Opioids (including hydrocodone combination products),** cocaine, methamphetamine, methylphenidate
III	Moderate to low risk of dependence; less abuse potential than schedule I or II	Ketamine, **buprenorphine**, anabolic steroids, **less than 90 mg of codeine per dose**
IV	Low potential for dependence; low potential for abuse	Alprazolam, carisoprodol, diazepam, lorazepam, pentazocine, zolpidem
V	Lower potential for abuse than schedule IV; limited quantities of certain narcotics	Cough medicine with less than 200 mg codeine, pregabalin, diphenoxylate/atropine, attapulgite

LSD = lysergic acid diethylamide.

Drug Enforcement Administration. http://www.justice.gov/dea/druginfo/ds.shtml. Accessed January 7, 2015.

MANAGING CONSTIPATION: THE MOST COMMON ADVERSE EVENT

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- Occurs in 40% to 95% of patients
- Unlikely to improve over time
- May be severe enough to reduce dose or discontinue opioid use
- Rotating opioids or route of administration can be effective
- Can also be treated with stool softeners, laxatives, nonpharmacologic methods
  - Monotherapy with stool softeners is considered ineffective

Swegle J, et al. *Am Fam Physician.* 2006;74:1347-1354.

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WARNING SIGNS OF RESPIRATORY DEPRESSION

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- Most serious potential adverse event
- Can be immediately life-threatening
- Rescue with naloxone

Increased Risk
Obesity
Lung disease
Sleep-related breathing disorders
Older adults

Warning Signs
Bradypnea
Tachypnea
Mental status change
Hypercarbia
Hypoxia

Dahan A, et al. *Pain Phys*. 2013;16:E85-E94; American Nurse Today. http://www.americannursetoday.com/assets/0/434/436/440/ 8364/8366/8368/8392/5110ee64-04bf-4aac-acc1-f6f20807d1fb.pdf. Accessed January 7, 2015.

PATHOPHYSIOLOGY OF DRUG-DRUG INTERACTIONS

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PHARMACODYNAMICS

- How the drug affects the body
  - May be influenced by pharmacokinetic interaction
  - Levels of receptor stimulation
  - Receptor-binding characteristics

PHARMACOKINETICS

- How the body affects the drug
  - Inhibition or induction of opioid metabolism
    - Age, sex, ethnicity
    - Hepatic and renal impairment
    - Role of active metabolites

Smith HS. *Mayo Clin Proc*. 2009;84:613-624; Trescot AM, et al. *Pain Physician*. 2008;11:S133-S153.

DRUG-DRUG INTERACTIONS: CNS DEPRESSANTS

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Common CNS depressants include:

Can have potentiating effect on sedation and respiratory depression

Can reduce initial dose if opioids and CNS depressants must be taken concomitantly

Opioids in overdose deaths for CNS depressants:

- Benzodiazepines: **77%**
- Antiepileptic and antiparkinsonism drugs: **65%**
- Antidepressants: **57%**

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationby drugclass/ ucm277916.pdf. Accessed January 7, 2015; Jones CM, et al. *JAMA*. 2013;309:657-659.

PRODUCT-SPECIFIC CNS DEPRESSANT INTERACTIONS

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Opioid	Warning
Butrans (buprenorphine) Dolophine (methadone)	***Benzodiazepines may increase respiratory depression***

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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DRUG-DRUG INTERACTIONS: ALCOHOL

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Discuss product-specific information with patients
Warn patients not to drink alcohol

Alcohol involved in 18.3% of emergency department visits associated with opioids

Alcohol may result in a dose dump or increased drug levels without dose dump

Substance Abuse and Mental Health Services Administration. http://www.samhsa.gov/data/2k13/DAWN2k11ED/DAWN2k11ED.htm#4.1. Accessed January 7, 2015;
Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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PRODUCT-SPECIFIC ALCOHOL INTERACTIONS

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Opioid	Warning
Avinza (morphine sulfate) Kadian (morphine sulfate) Embeda (morphine sulfate-naloxone) Nucynta (tapentadol) Opana (oxymorphone HCl)	***Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of morphine***

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

DRUG-DRUG INTERACTIONS: MONOAMINE OXIDASE INHIBITORS

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- Coadministration with opioids may increase respiratory depression
- MAOIs contraindicated with tapentadol
- Serotonin syndrome is a risk with certain opioids, such as methadone and fentanyl

Symptoms of Serotonin Syndrome
Cognitive or mental status changes ▪ Agitation, confusion, hallucinations, hyperactivity
Neuromuscular abnormalities ▪ Clonus, restlessness, tremor, hyperreflexia
Autonomic hyperactivity symptoms ▪ Diarrhea, fever, flushing, hypo- or hypertension, tachycardia

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015; Brown CH. http://www.uspharmacist.com/content/d/feature/c/23707/. Accessed January 7, 2015.

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DRUG-DRUG INTERACTIONS: DIURETICS

- Can affect renal function
  - Dependent on type of opioid receptor involved
- Opioids may reduce efficacy of diuretics by inducing release of antidiuretic hormone (ADH)

Mercadante S, et al. *J Pain.* 2004;5:2-9; Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

DRUG-DRUG INTERACTIONS: QTC INTERVAL

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- Some opioids may prolong QTc interval
- Correlation between methadone dose and risk for QTc prolongation

Opioid	Warning
Butrans (buprenorphine)	Class IA and III antiarrhythmics, and other potentially arrhythmogenic agents, may increase risk for QTc prolongation and TdP
Dolophine (methadone)	Potentially arrhythmogenic agents may increase risk for QTc prolongation and TdP

TdP = torsade de pointes, a form of polymorphic ventricular tachycardia that may result in syncope or cardiac arrest.

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ ucm277916.pdf. Accessed January 7, 2015; Mayet S, et al. *Drug Alcohol Rev.* 2011;30:388-396.

DRUG-DRUG INTERACTIONS: CYTOCHROME P450 ENZYMES

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- Polymorphisms in CYP450 can alter opioid metabolism
- Many drugs act as inducers or inhibitors
  - Interactions may be enzyme-specific

CYP450 Potent Inducers	CYP450 Potent Inhibitors
Carbamazepine	Amiodarone
Phenobarbital	Cimetidine
Phenytoin	Ciprofloxacin
Rifampin	Clarithromycin
	Fluoxetine
	Fluvoxamine
	Metronidazole
	Paroxetine
	Ritonavir

Mikus G, et al. *Ann Acad Med Singapore.* 1991;20:9-12; Ogu CC, et al. *Proc (Bayl Univ Med Cent).* 2000;13:421-423; Lynch T, et al. *Am Fam Physician.* 2007;76:391-396.

OPIOID TOLERANCE

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Patients must be opioid tolerant before using:

- Any strength of transdermal fentanyl or hydromorphone ER
- Certain strengths or daily doses of other ER products

Tolerance to the sedating and respiratory-depressant effects of opioids is essential to ensure the safe use of certain ER/LA opioid products, dosage unit strengths, or doses

Opioid-tolerant patients are those taking at least:

- 60 mg oral morphine/day
- 25 mcg transdermal fentanyl/day
- 30 mg oral oxycodone/day
- 8 mg oral hydromorphone/day
- 25 mg oral oxymorphone/day
- An equianalgesic dose of another opioid

Blueprint specifies 25 mcg transdermal fentanyl/hour

FOR 1 WEEK OR LONGER

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

ORAL OPIOID DOSES FOR OPIOID-TOLERANT PATIENTS ONLY

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Oral Agent	Selected Doses for Use in Opioid-Tolerant Patients Only
Avinza (morphine sulfate ER capsules)	15 mg, 30 mg, 90 mg, 100 mg, and 120 mg capsules
Embeda (morphine sulfate ER-naltrexone capsules)	15 mg, 30 mg, and 100 mg/4 mg capsules
Kadian (morphine sulfate ER capsules)	15 mg, 30 mg, 100 mg, and 200 mg capsules
MS Contin (morphine sulfate CR tablets)	15 mg, 30 mg, 100 mg, and 200 mg tablets
OxyContin (oxycodone HCl CR tablets)	Single dose greater than 40 mg or total daily dose greater than 80 mg
Dolophine (methadone HCl tablets)	When used as first opioid analgesic, initiate therapy with small doses, no more than 2.5 mg to 10 mg every 8 to 12 hours

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf Accessed January 7, 2015.

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TRANSDERMAL OPIOID DOSES FOR OPIOID-TOLERANT PATIENTS ONLY

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Transdermal Agent	Doses for Use in Opioid-Tolerant Patients Only
Butrans (buprenorphine transdermal system)	15 mg, 30 mg, 10 mcg/hour and 20 mcg/hour transdermal systems
Duragesic (fentanyl transdermal system)	All doses indicated for use in opioid-tolerant patients only
Exalgo (hydromorphone HCl ER tablets)	All doses indicated for use in opioid-tolerant patients only

Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

FOLLOWING ER/LA OPIOID ADMINISTRATION INSTRUCTIONS

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Tablet or Capsule
Swallow whole
Do not cut, break, chew, crush, or dissolve because the drug will be released and absorbed rapidly; may lead to overdose and death
Consult product labeling to determine other administration methods if patient unable to swallow intact capsule

Transdermal Patches
Do not cut, tear, damage, chew, swallow, or use in any way other than indicated
External heat, fever, exertion can increase opioid absorption; may lead to overdose and death
Metal foil backings on some products are not safe for use in magnetic resonance imaging
Rotate location of application

Food and Drug Administration. www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf. Accessed January 7, 2015; www.er-la-opioidrems.com/IwgUI/rems/pdf/important_safety_information.pdf. Accessed January 7, 2015.

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Specific ER/LA Opioid Product Information

MORPHINE SULFATE ER (AVINZA)

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Avinza	Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg
Dosing interval	• Once a day • Initial dose in opioid non-tolerant patients: 30 mg • Maximum daily dose: 1600 mg due to risk of renal toxicity
Key instructions	• Titrate using minimum of 3-day intervals (4-day intervals in opioid non-tolerant patients) • **Swallow capsules whole (DO NOT chew, crush, or dissolve)** • If unable to swallow, capsule can be opened and pellets sprinkled on applesauce
Specific drug interactions	• Avoid alcoholic beverages or medications containing alcohol; may result in increased dose release and absorption of potentially fatal dose of morphine • P-gp 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

P-gp = P-glycoprotein.

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

BUPRENORPHINE (BUTRANS)

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Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr
Dosing interval	One transdermal system every 7 days • Initial dose: 5 mcg/hr • Maximum dose: 20 mcg/hr due to risk of QTc prolongation
Key instructions	• If prior total daily dose of opioid <30 mg oral morphine equivalents per day, initiate treatment with 5 mcg/hr dose • Initial dose in patients with mild to moderate hepatic impairment is 5 mcg/hr • If prior total daily dose of opioid between 30 mg and 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/hr dose • The minimum titration interval is 72 hours **Application Instructions** • Apply only to sites indicated in full PI • Apply to intact/non-irritated skin • Skin may be prepped by clipping hair and 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

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

BUPRENORPHINE (BUTRANS)

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Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, and 20 mcg/hr
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, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and TdP
Use in opioid-tolerant patients	Use 10 mcg/hr and 20 mcg/hr transdermal systems in opioid-tolerant patients ONLY
Drug-specific safety concerns	• QTc prolongation and TdP • Hepatotoxicity • Application site skin reactions
Relative potency to oral morphine	Not established

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

METHADONE HCL (DOLOPHINE)

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Dolophine	Methadone HCl 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 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 drug-drug interactions • 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 TdP • Benzodiazepines may increase respiratory depression

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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METHADONE HCL (DOLOPHINE)

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Dolophine	Methadone HCl Tablets, 5 mg and 10 mg
Use in opioid-tolerant patients	Refer to full PI
Product-specific safety concerns	• QTc prolongation and TdP • Peak respiratory depression occurs later and persists longer than analgesic effect • Clearance may increase during pregnancy • False-positive urine drug tests possible
Relative potency to oral morphine	Varies depending on patient's prior opioid experience

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

FENTANYL (DURAGESIC)

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Duragesic	Fentanyl Transdermal System, 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr
Dosing interval	Every 72 hours
Key instructions	• Refer to full PI 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 using no less than 72-hour intervals • 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 analgesics for a short period of time • Management of postoperative pain • Management of mild pain

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

FENTANYL (DURAGESIC)

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Duragesic	Fentanyl Transdermal System, 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr
Specific drug interactions	• CYP3A4 inhibitors may increase fentanyl drug levels • CYP3A4 inducers may decrease fentanyl drug levels
Use in opioid-tolerant patients	All doses 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 PI for conversion recommendations from prior opioid

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

MORPHINE SULFATE ER/NALTREXONE (EMBEDA)

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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
Key instructions	• Titrate using 1- to 2-day intervals • **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
Specific drug interactions	• Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine • P-gp inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately two-fold
Use in opioid-tolerant patients	Use 100 mg/4 mg capsule in opioid-tolerant patients ONLY

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

HYDROMORPHONE HCL (EXALGO)

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Exalgo	**Hydromorphone HCl ER 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 PI • 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 • **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 PI

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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MORPHINE SULFATE (KADIAN)

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

Kadian	**Morphine Sulfate ER Capsules, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 80 mg, 100 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) • **Swallow capsules whole (DO NOT chew, crush, or dissolve)** • Instruct patient: - 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 this may result in the rapid release and absorption of a potentially fatal dose of morphine • P-gp inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately two-fold
Use in opioid-tolerant patients	Kadian 100-mg and 200-mg capsules are for use in opioid-tolerant patients ONLY

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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MORPHINE SULFATE (MS CONTIN)

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MS Contin	Morphine Sulfate CR 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) • **Swallow tablets whole (DO NOT chew, crush, or dissolve)**
Specific drug interactions	P-gp inhibitors (eg, quinidine) may increase the absorption/exposure of morphine sulfate by approximately two-fold
Use in opioid-tolerant patients	Use 100-mg and 200-mg tablet strengths in opioid-tolerant patients ONLY

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf Accessed January 7, 2015.

TAPENTADOL (NUCYNTA ER)

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Nucynta ER	Tapentadol ER 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 • **Swallow tablets whole (DO NOT chew, crush, or dissolve)** • Instruct patient: - 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 this may result in the rapid release and absorption of a potentially fatal dose of tapentadol • Contraindicated in patients taking MAOIs

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

TAPENTADOL (NUCYNTA ER)

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Nucynta ER	Tapentadol ER 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 oral morphine	Equipotency to oral morphine not established

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

OXYMORPHONE HCL (OPANA ER)

Get smart
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Opana ER	**Oxymorphone HCl** **ER 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 older than 65 years • Titrate using 3- to 7-day intervals • Contraindicated in moderate and severe hepatic impairment • **Swallow tablets whole (DO NOT chew, crush, or dissolve)** • Instruct patient to take 1 tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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OXYMORPHONE HCL (OPANA ER)

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Opana ER	**Oxymorphone HCl ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg**
Specific drug interactions	Do not use with alcoholic beverages or medications containing alcohol, as this 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

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

OXYCODONE HCL (OXYCONTIN)

Get smart
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OxyContin	**Oxycodone HCl CR 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 gastrointestinal disorders that may predispose them to obstruction** • **Swallow tablets whole (DO NOT chew, crush, or dissolve)** • Instruct patient to 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

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

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OXYCODONE HCL (OXYCONTIN)

Get smart
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OxyContin	Oxycodone HCl CR 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 gastrointestinal obstruction
Relative potency to oral morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio
New as of 4/16/2013	This product has abuse-deterrent properties. The tablet is more difficult to crush, break, or dissolve. It forms a viscous hydrogel and cannot be easily prepared for injection.

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

HYDROCODONE BITARTRATE (ZOHYDRO)

Get smart
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Zohydro ER	Hydrocodone Bitartrate ER Capsules 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 50 mg
Dosing interval	Every 12 hours
Key instructions	• Not indicated for use as an as-needed analgesic • Coingestion with alcohol may result in increased plasma levels and a potent fatal overdose of hydrocodone • CYP3A4 isoenzymes play a major role in metabolism of hydrocodone
Specific drug interactions	• Drugs that inhibit CYP3A4 activity may decrease clearance of hydrocodone, leading to an increase in plasma concentrations • Drug interaction with CNS depressants and may increase risk for respiratory depression, hypotension, profound sedation, coma, or death • When combined with a CNS depressant, dose of one or both agents should be reduced
	• Use of Zohydro ER with MAOIs or tricyclic antidepressants may increase the effect of either the antidepressant or Zohydro ER (hydrocodone bitartrate)

Food and Drug Administration. www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf. Accessed January 7, 2015.

SUMMARY: CLINICAL PEARLS

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EXTENDED RELEASE AND LONG-ACTING OPIOIDS

- Understand adverse events and potential drug interactions:
  - Respiratory depression is the most serious and constipation the most common adverse event
  - Opioids interact with CNS depressants, MAOIs, diuretics, and CYP450 enzymes and may prolong the QTc interval
- Certain formulations and doses should be used only in opioid-tolerant patients
- It is important not to tamper with opioid formulations
- Know the specific characteristics of each opioid and tailor therapy to individual patients