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CO*RE COLLABORATION FOR REMS EDUCATION PRESENTS

Pain Management and Opioids:

Balancing Risks and Benefits

UPDATED IN 2018

4:1

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CHAPTER 1

WELCOME

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Faculty Information

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Chairman, Department of Geriatrics
Philadelphia College of Osteopathic Medicine

DISCLOSURE:
Dr. Galluzzi has nothing to disclose.

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CO*RE ORGANIZATIONS

AAPA · ASAM American Society of Addiction Medicine · American Pain Society · AANP American Association of Nurse Practitioners · AOA · aahpm American Academy of Hospice and Palliative Medicine · California Academy of Family Physicians Strong Medicine for California · NPWHF · Medscape · IPMA · Healthcare Performance Consulting

NO CO*RE PARTNER HAS ANY CONFLICTS OF INTEREST TO REPORT (APPENDIX 2)

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ACKNOWLEDGEMENT

Presented by the American Osteopathic Association, a member of the Collaborative for Risk Evaluation and Mitigation Strategy (REMS) Education (CO*RE), eleven interdisciplinary organizations working together to improve pain management and prevent adverse outcomes.

This educational activity is supported by an independent educational grant from the Extended-Release/Long-Acting (ER/LA) Opioid Analgesic REMS Program Companies. Please see **this document** for a listing of the member companies. This activity is intended to be fully compliant with the ER/LA Opioid Analgesic REMS education requirements issued by the US Food and Drug Administration.

PRODUCTS COVERED BY THIS REMS

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BRAND NAME PRODUCTS

- Arymo ER morphine sulfate ER tablets
- Avinza® morphine sulfate ER capsules
- Belbuca® buprenorphine buccal film
- Butrans® buprenorphine transdermal system
- Dolophine® methadone hydrochloride tablets
- Duragesic® fentanyl transdermal system
- Embeda® morphine sulfate/naltrexone ER capsules
- Exalgo® hydromorphone hydrochloride ER tablets
- Hysingla® ER hydrocodone bitartrate ER tablets
- Kadian® morphine sulfate ER capsules
- MorphaBond® morphine sulfate ER tablets
- MS Contin® morphine sulfate CR tablets
- Nucynta® ER tapentadol ER tablets
- Opana® ER oxymorphone hydrochloride ER tablets
- OxyContin® oxycodone hydrochloride CR tablets
- Targiniq™ ER oxycodone hydrochloride/naloxone hydrochloride ER tablets
- Troxyca ER oxycodone hydrochloride/naltrexone capsules
- Vantrela ER hydrocodone bitartrate ER tablets
- Xtampza ER oxycodone ER capsules
- Zohydro® hydrocodone bitartrate ER capsules

GENERIC PRODUCTS

- Fentanyl ER transdermal systems
- Methadone hydrochloride tablets
- Methadone hydrochloride oral concentrate
- Methadone hydrochloride oral solution
- Morphine sulfate ER tablets
- Morphine sulfate ER capsules
- Oxycodone hydrochloride ER tablets

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CHAPTER 2

WHY ARE WE HERE?

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Optional Slide

OPIOID DEATHS, TREATMENT ADMISSIONS AND PRESCRIBING

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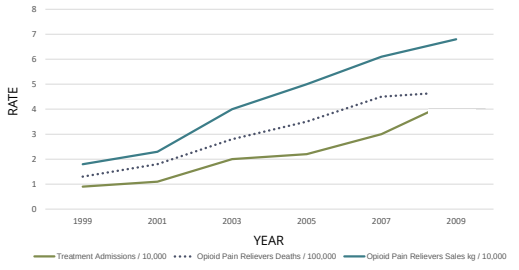

SOURCE: MMWR, November 2, 2011/60(43);1487-1492
https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm

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OVERDOSE DEATHS INVOLVING OPIOIDS, U.S, 2000-2016

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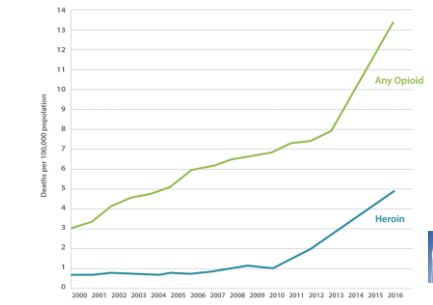

CDC

SOURCE: MMWR, January 1, 2016/64(50);1378-82
https://www.cdc.gov/drugoverdose/data/analysis.html

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Drugs Involved in U.S. Overdose Deaths 2000-2016

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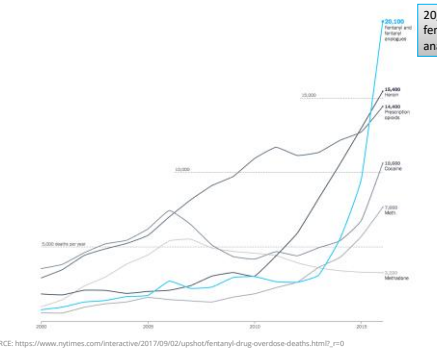

SOURCE: https://www.nytimes.com/interactive/2017/09/02/upshot/fentanyl-drug-overdose-deaths.html?_r=0

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Fentanyl and Fentanyl Analogues

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OD deaths from fentanyl and fentanyl analogues, such as carfentanil, have increased 540% in three years

Street fentanyl is illegally manufactured – generally NOT diverted pharmaceutical product

Two causes of fentanyl OD death: Opioid-induced **respiratory depression** and **rigid chest wall syndrome**; higher or repeated doses of naloxone required to reverse fentanyl overdose

Fentanyl has either contaminated or replaced all heroin across the U.S., also found in cocaine and methamphetamine

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PRESCRIBING PATTERNS – WE PLAY A ROLE

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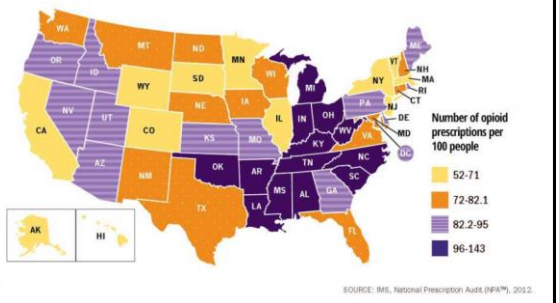

SOURCE: https://www.cdc.gov/drugoverdose/data/prescribing.html

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OPIOID PRESCRIBING - THE PENDULUM SWINGS

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PRESCRIBING BEHAVIORS	RESULTING OUTCOMES
Under-Prescribing	Unresolved Pain
Over-Prescribing	Adverse Outcomes
Appropriate Prescribing	Adequate Analgesia

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BENEFITS VS. RISKS

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BENEFITS

- Analgesia
  - Adequate pain control
  - Continuous, predictable (with ER/LAs)
- Improved function
- Quality of life

RISKS

- Overdose, especially as ER/LA formulations contain more opioids than Immediate Release
- Life-threatening respiratory depression
- Abuse by patient or household contacts
- Misuse, diversion, and addiction
- Physical dependence and tolerance
- Interactions with other meds and substances
- Risk of neonatal opioid withdrawal syndrome
- Inadvertent exposure/ingestion by household contacts especially children

SOURCE: Nicholson, B. Pain Pract. 2009;9(1):71-81. http://onlinelibrary.wiley.com/doi/10.1111/j.1533-2500.2008.00232.x/abstract

SOURCE OF MOST RECENT RX OPIOIDS AMONG PAST-YEAR MISUSERS 2015

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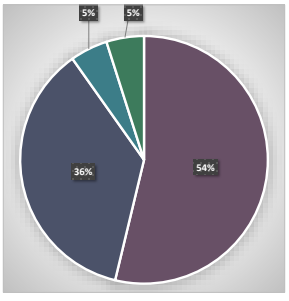

Source where pain relievers were obtained for most recent misuse among 12.5 million people aged 12 or older who misused prescription pain relievers in the past year: percentages, 2015

- 54% - Given by, bought from, or taken from a friend or relative
- 36% - Through a prescription or stolen from healthcare provider
- 5% - Bought from a dealer or stranger
- 5% - Some other way

SOURCE: Prescription Drug Use and Misuse in the United States: Results from the 2015 National Survey on Drug Use and Health, Sept 2016 https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.htm

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FIRST SPECIFIC DRUG ASSOCIATED WITH INITIATION OF ILLICIT DRUG USE 2013

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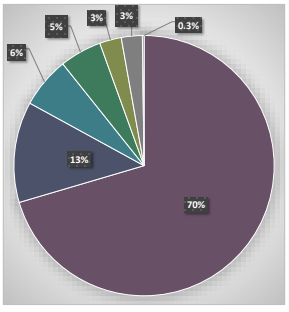

2.8 million initiates of illicit drugs

- 70.3% - Marijuana
- 12.5% - Pain Relievers
- 6.3% - Inhalants
- 5.2% - Tranquilizers
- 2.7% - Stimulants
- 2.6% - Hallucinogens
- 0.3% - Sedatives and Cocaine

SOURCE: SAMHSA Annual National Survey on Drug Use and Health, June 2015 https://www.drugabuse.gov/publications/drugfacts/nationwide-trends

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THE FEDERAL PLAYERS

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Many agencies involved

SURGEON GENERAL

CDC

Office of National Drug Control Policy

NIH National Institute on Drug Abuse

SAMHSA

WE ARE HERE BECAUSE OF …

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REMS: RISK EVALUATION AND MITIGATION STRATEGY

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FDA

- On July 9, 2012, the Food and Drug Administration (FDA) approved a Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER) and long-acting (LA) opioid medications
- First time FDA has ever used accredited CE/CME as part of a REMS

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CO*RE STATEMENT

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Misuse, abuse, diversion, addiction, and overdose of opioids has created a serious public health epidemic in the U.S.

When prescribed well and used as prescribed, opioids can be valuable tools to effectively treat pain.

This course does not advocate for or against the use of Immediate Release (IR) or Extended-Release/Long-Acting (ER/LA) opioids. Our purpose is to provide proper education about safe prescribing practices along with effective patient education.

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LEARNING OBJECTIVES

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- Accurately assess patients with pain for consideration of an opioid trial
- Establish realistic goals for pain management and restoration of function
- Initiate opioid treatment (IR and ER/LA) safely and judiciously, maximizing efficacy while minimizing risks
- Monitor and re-evaluate treatment continuously; discontinue safely when appropriate
- Counsel patients and caregivers about use, misuse, abuse, diversion, and overdose
- Educate patients about safe storage and disposal of opioids
- Demonstrate working knowledge and ability to access general and specific information about opioids, especially those used in your practice

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You and Your Team *can* have an immediate and positive impact on this crisis while also caring for your patients appropriately.

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CHAPTER 3

PAIN

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THE NEUROPSYCHOBIOLOGY OF PAIN

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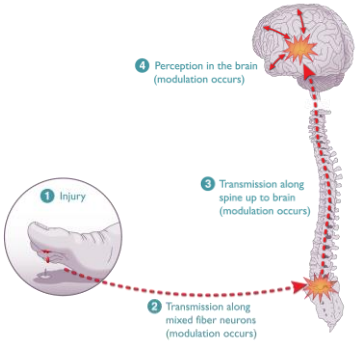

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OPIOID SITES OF ACTION IN THE BRAIN

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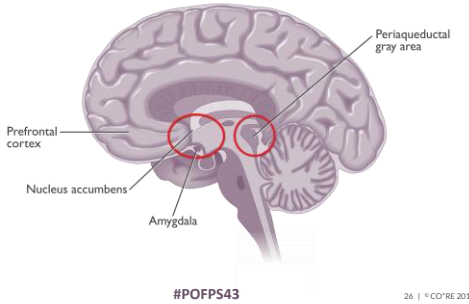

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UNDERSTANDING PAIN

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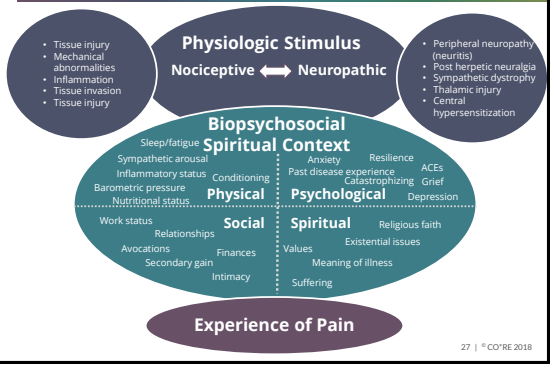
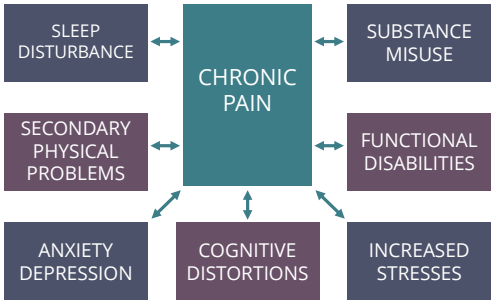


THE IMPACT OF PAIN



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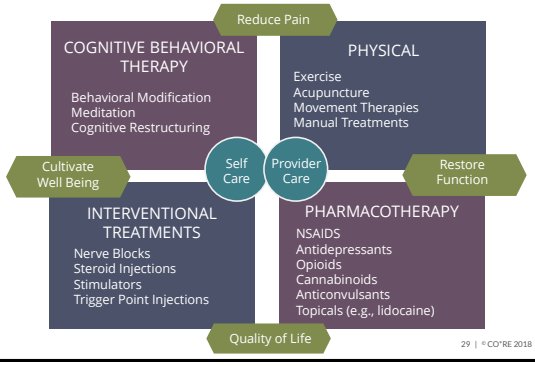
PAIN MANAGEMENT GOALS AND TREATMENT OPTIONS: A MULTI-MODAL APPROACH



CHAPTER 3 - PEARLS FOR PRACTICE

- Explain neurophysiology of pain processing to patients
- When patients understand, their concerns are validated
- Pain has biological, psychological, social, and spiritual components

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CHALLENGE: THE EARLY REFILL

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RED FLAG:
Is this misuse? Abuse?

Your patient requests an early refill for the second time in six months. Took extra medications for headache and again for toothache. Prescription is for lower back pain.

Action:

Evaluate potential misuse. Confirm patient's understanding of each medication's dosage, time of day, and maximum daily dose. Ask him/her to repeat these instructions back to you. Avoid clinical terms such as "prn". Review treatment goals and expectations. Select and document a therapy plan that is compatible with patients' individual needs, is safe, effective and balanced. Screen for risk with Current Opioid Misuse Measure (COMM) and, if indicated, refer to addiction specialist for treatment.

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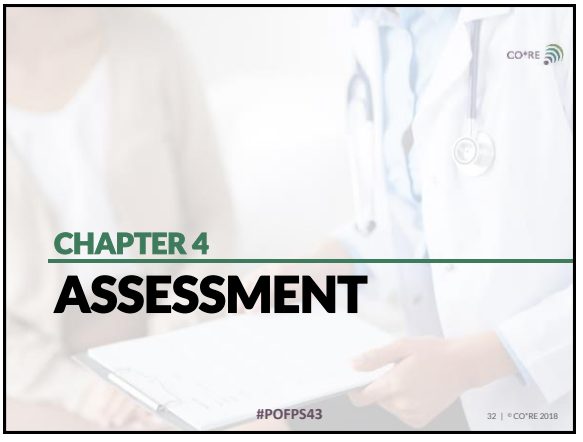

PAIN ASSESSMENT

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DESCRIPTION OF PAIN

- Location
- Intensity
- Quality
- Onset/ Duration
- Variations/ Patterns/Rhythms

WHAT RELIEVES THE PAIN?

WHAT CAUSES OR INCREASES PAIN?

EFFECTS OF PAIN ON PHYSICAL, EMOTIONAL, AND PSYCHOSOCIAL FUNCTION

PATIENT'S CURRENT PAIN AND FUNCTION

SOURCE: Heapy A, Kerns RD. Psychological and Behavioral Assessment. In: Raj's Practical Management of Pain, 4th ed. 2008;279-95. Zacharoff KL, et al. Managing Chronic Pain with Opioids in Primary Care. 2nd ed. Newton, MA: Inflexion, Inc., 2010.

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TREATMENT HISTORY

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NON-PHARMACOLOGIC STRATEGIES AND EFFECTIVENESS

PHARMACOLOGIC STRATEGIES AND EFFECTIVENESS

PAST USE

CURRENT USE

- Query state Prescription Drug Monitoring Program **(PDMP)** to confirm patient report

DOSAGE

- For opioids currently prescribed: opioid, dose, regimen, and duration
  - Important to determine if patient is **opioid tolerant**

GENERAL EFFECTIVENESS

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PAST MEDICAL HISTORY

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ILLNESS RELEVANT TO (1) EFFECTS OR (2) METABOLISM OF OPIOIDS

1. Pulmonary disease, constipation, nausea, cognitive impairment
2. Hepatic, renal disease

ILLNESS POSSIBLY LINKED TO SUBSTANCE USE DISORDER (SUD):

- Hepatitis
- HIV
- Tuberculosis
- Cellulitis
- STIs
- Trauma/Burns
- Cardiac Disease
- Pulmonary Disease

SOURCE: Chou R, et al. *J Pain*. 2009;10:113-30. Zacharoff KL, et al. *Managing Chronic Pain with Opioids in Primary Care*. 2nd ed. Newton, MA: Inflexion, Inc., 2010. Department of Veterans Affairs, Department of Defense. *VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain*. 2010.

OBTAIN A COMPLETE HISTORY OF CURRENT AND PAST SUBSTANCE USE

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RISK FACTORS FOR OPIOID ABUSE

- Controlled medications: prescribed or non-prescribed
- Alcohol and tobacco
- History of sexual abuse
- Family history of substance abuse and psychiatric disorders
- Age (16-45 YO)

Substance abuse history does not prohibit treatment with ER/LA opioids but may require additional monitoring and expert consultation/referral

SOCIAL HISTORY

Employment, cultural background, social network, marital history, legal history, and other behavioral patterns

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PHYSICAL EXAM AND ASSESSMENT

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Seek objective confirmatory data → Components of patient evaluation for pain → Order diagnostic tests (appropriate to complaint)

- General: vital signs, appearance, and pain behaviors
- Neurologic exam
- Musculoskeletal exam
  - Inspection
  - Gait and posture
  - Range of motion
  - Palpation
  - Percussion
  - Auscultation
  - Provocative maneuvers
- Cutaneous or trophic findings

SOURCE: Lalani I, Argoff CE. History and Physical Examination of the Pain Patient. In: *Raj's Practical Management of Pain*. 4th ed. 2008;177-88. Chou R, et al. *J Pain*. 2009;10:113-30.

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RISK ASSESSMENT TOOLS

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TOOL	# OF ITEMS	ADMINISTERED BY
PATIENTS CONSIDERED FOR LONG-TERM OPIOID THERAPY		
ORT Opioid Risk Tool	5	patient
SOAPP® Screener and Opioid Assessment for Patients with Pain	24, 14, & 5	patient
DIRE Diagnosis, Intractability, Risk, and Efficacy score	7	clinician
CHARACTERIZE MISUSE ONCE OPIOID TREATMENT BEGINS		
PMQ Pain Medication Questionnaire	26	patient
COMM Current Opioid Misuse Measure	17	patient
PDUQ Prescription Drug Use Questionnaire	40	clinician
NOT SPECIFIC TO PAIN POPULATIONS		
CAGE-AID Cut Down, Annoyed, Guilty, Eye-Opener tool, Adapted to Include Drugs	4	clinician
RAFFT Relax, Alone, Friends, Family, Trouble	5	patient
DAST Drug Abuse Screening Test	28	patient
SBIRT Screening, Brief Intervention, and Referral to Treatment	Varies	clinician

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OPIOID RISK TOOL (ORT)

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Mark each box that applies	Female	Male
1 Family history of substance abuse		
Alcohol	☐ 1	☐ 3
Illegal drugs	☐ 2	☐ 3
Prescription drugs	☐ 4	☐ 4
2 Personal Hx of substance abuse		
Alcohol	☐ 3	☐ 3
Illegal drugs	☐ 4	☐ 4
Prescription drugs	☐ 5	☐ 5
3 Age between 16 and 45 yrs	☐ 1	☐ 1
4 Hx of preadolescent sexual abuse	☐ 3	☐ 0
5 Psychologic disease		
ADD, OCD, bipolar, schizophrenia	☐ 2	☐ 2
Depression	☐ 1	☐ 1
Scoring Totals:		

ADMINISTER
On initial visit
Prior to opioid therapy

SCORING (RISK)
0-3: low
4-7: moderate
≥8: high

SOURCE: Webster LR, Webster RM. *Pain Med*. 2005;6:432-42.

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SCREENER AND OPIOID ASSESSMENT FOR PATIENTS WITH PAIN (SOAPP)®

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Identifies patients as high, moderate, or low risk for misuse of opioids prescribed for chronic pain

HOW IS SOAPP® ADMINISTERED?

Usually self-administered in waiting room, exam room, or prior to an office visit	May be completed as part of an interview with a nurse, physician, or psychologist	Prescribers should have a completed and scored SOAPP® while making opioid treatment decisions

SOURCE: SOAPP® Monitoring Recommendations. https://painedu.org/soapp/SOAPP_Monitoring_Recommendations.pdf
The SOAPP® Version 1.0 Tutorial. https://painedu.org/soapp-tutorial_01.asp

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SOAPP®: 4 FORMATS AVAILABLE TO ASSESS MISUSE RISK

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SOAPP® 1.0 24Q VERSION (ORIGINAL)	14Q VERSION	5Q (SHORT-FORM) VERSION	SOAPP-R 24Q VERSION (REVISED)
24 questions (14 used to score tool)	14 questions*	5 questions*	24 questions
Add ratings for 14 "screening" questions	Add ratings for each question		
Score ≥12: high risk 8-11: moderate risk <8: low risk	Score ≥12: high risk 8-11: moderate risk <8: low risk	Score ≥4: increased risk	Score ≥22: high risk 10-21: moderate risk ≤9: low risk
<10 min. to complete 10 "unscored" questions provide background	<8 min. to complete	<5 min. to complete	<10 min. to complete

*Questions from SOAPP V.1.0 Patients rate all questions on scale of 0-4

SOURCE: SOAPP® *Monitoring Recommendations*. painedu.org/soapp/SOAPP_Monitoring_Recommendations.pdf The SOAPP® Version 1.0 Tutorial. painedu.org/soapp-tutorial_01.asp SOAPP® *Frequently Asked Questions*. painedu.org/soapp-development.asp painedu.org. *SOAPP® Version 1.0-5Q*. painedu.org *SOAPP® Version 1.0-14Q*. painedu.org *SOAPP®-R*. painedu.org

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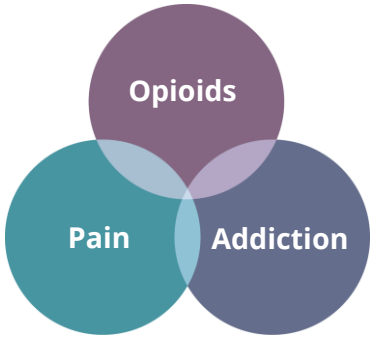

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Opioids

WHAT IS THE RISK FOR MY PATIENT?

- Risk of opioid use disorder in patients on chronic opioid therapy (COT) for chronic non-cancer pain (CNCP) is up to 30%
- Always highest with past history of substance use disorder (SUD) or psychiatric comorbidity
- Recognize that patient needs and patterns shift with age

SOURCE: Boscarino, J. Journal of Addictive Diseases, 30:3,185-194 http://www.tandfonline.com/doi/abs/10.1080/10550887.2011.581961

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PAIN AND ADDICTION

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PAIN – 5 A'S	ADDICTION – 5 C'S
Analgesia	Control, loss of
Activities/Function	Compulsive use
Aberrant Behavior	Craving drug
Adverse Effects	Continued use
Affect	Chronic problem

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RISK AND PAIN ASSESSMENT TOOL BOXES

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PAIN ASSESSMENT TOOL BOX	RISK ASSESSMENT TOOL BOX
• Pain Assessment Tools (BPI, etc.) • Functional Assessment (SF 36, PPS, geriatric assessment, etc.) • **P**ain intensity, **E**njoyment of life, **G**eneral activity (PEG)	• PDMP • UDT • Risk Assessment Tools (ORT or SOAPP®)

Mental Health Tools (PHQ9, GAD7, etc.)

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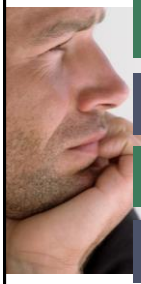
CONSIDER A TRIAL OF AN OPIOID?



- POTENTIAL BENEFITS ARE LIKELY TO OUTWEIGH RISKS
- FAILED TO ADEQUATELY RESPOND TO NON-OPIOID & NONDRUG INTERVENTIONS
- PAIN IS MODERATE TO SEVERE
- INITIATE TRIAL OF IR OPIOIDS

SOURCE: Chou R, et al. *J Pain.* 2009;10:113-30. Department of Veterans Affairs, Department of Defense. *VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain.* 2010.

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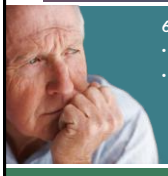
WHEN TO CONSIDER A TRIAL OF AN OPIOID



60-YR-OLD WITH CHRONIC DISABLING OA PAIN

- Non-opioid therapies not effective
- No psychiatric/medical comorbidity or personal/family drug abuse history
  - High potential benefits relative to potential risks
  - Could prescribe opioids to this patient in most settings with routine monitoring

30-YR-OLD WITH FIBROMYALGIA AND RECENT ALCOHOL USE DISORDER

- High potential risks relative to benefits (opioid therapy not first line for fibromyalgia)
- Requires intensive structure, monitoring, and management by clinician with expertise in both addiction & pain

Not a good candidate for opioid therapy

SOURCE: Chou R, et al. *J Pain.* 2009;10:113-30.

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INITIATING OPIOIDS: CDC GUIDELINE (2016)

- Begin with IR
- Prescribe the lowest effective dosage
- Use caution at any dosage, but particularly when
  - Increasing dosage to ≥50 morphine milligram equivalents (MME)/day and carefully justify a decision to titrate dosage to ≥90 MME/day
- For acute pain, prescribe lowest effective dose of IRs, no more than needed
- Re-evaluate risks/benefits within 1 - 4 weeks of initiation or dose escalation
- Re-evaluate risks/benefits every 3 months; if benefits do not outweigh harms optimize other therapies, work to taper and discontinue
- Link to the Guideline: https://www.cdc.gov/drugoverdose/prescribing/providers.html

Cancer pain, hospice, and palliative care patients are not covered by CDC Guideline

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INFORMED CONSENT

When initiating a trial of opioid analgesic therapy, confirm patient understanding of informed consent to establish:

- ANALGESIC AND FUNCTIONAL GOALS OF TREATMENT
- EXPECTATIONS
- POTENTIAL RISKS
- ALTERNATIVES TO OPIOIDS

HOW TO MANAGE

- Common Adverse Effects (AEs) (e.g., constipation, nausea, sedation)
- Risks (e.g., abuse, addiction, respiratory depression, overdose)
- AEs with long-term therapy (e.g., hyperalgesia, low testosterone, irregular menses or sexual dysfunction)

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PATIENT-PRESCRIBER AGREEMENT (PPA)

Document signed by both patient and prescriber at time an opioid is prescribed

- CLARIFY TREATMENT PLAN AND GOALS OF TREATMENT WITH PATIENT, PATIENT'S FAMILY, AND OTHER CLINICIANS INVOLVED IN PATIENT'S CARE
- ASSIST IN PATIENT EDUCATION
- DISCUSS MEDICATION SAFE HANDLING, STORAGE, AND DISPOSAL
- DOCUMENT PATIENT AND PRESCRIBER RESPONSIBILITIES

#POFPS43

PATIENT PROVIDER AGREEMENT (PPA)

REINFORCE EXPECTATIONS FOR APPROPRIATE AND SAFE OPIOID USE

- One prescriber
- Consider one pharmacy
- Safeguard
  - Do not store in medicine cabinet
  - Keep locked (medication safe)
  - Do not share or sell
- Instructions for disposal when no longer needed
- Prescriber notification for any event resulting in a pain medication prescription
- Follow-up
- Monitoring
  - Random UDT and pill counts
- Refills
- Identify behaviors for discontinuation
- Exit strategy

#POFPS43

MONITOR ADHERENCE AND ABERRANT BEHAVIOR

CO*RE

ROUTINELY MONITOR PATIENT ADHERENCE TO TREATMENT PLAN

- Recognize and document aberrant drug-related behavior
  - In addition to patient self-report also use:
    - State PDMPs
    - UDT
      - Positive for non-prescribed drugs
      - Positive for illicit substance
      - Negative for prescribed opioid
- Family member or caregiver interviews
- Monitoring tools such as the COMM, PADT, PMQ, or PDUQ
- Medication reconciliation (e.g., pill counts)

PADT=Pain Assessment and Documentation Tool

#POFPS43

ADDRESS ABERRANT DRUG-RELATED BEHAVIOR

CO*RE

Behavior outside the boundaries of agreed-on treatment plan:

Unsanctioned dose escalations or other noncompliance with therapy on 1 or 2 occasions	Multiple dose escalations or other noncompliance with therapy despite warnings
Unapproved use of the drug to treat another symptom	Prescription forgery
Openly acquiring similar drugs from other medical sources	Obtaining prescription drugs from nonmedical sources

Any of these behaviors merit **investigation**, proceed with caution

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CO*RE

Adequately **DOCUMENT** all patient interactions, assessments, test results, and treatment plans.

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CHAPTER 4 – PEARLS FOR PRACTICE

- Conduct a comprehensive and pain-focused history and physical
- Assess for risk of abuse and for mental health issues
- Determine if a therapeutic trial is appropriate
- Establish realistic goals for pain management and function
- Document EVERYTHING

#POFPS43

Optional Slide

CHALLENGE: THE DELAYED SURGERY

RED FLAG:
Patient may be stalling to continue an opioid regimen

Ms. Jones says she needs opioids to manage her pain until she can have surgery. She reports continued delays in getting to surgery. You phone the surgeon and discover that no date has been set and that she has cancelled several appointments.

Action:
Set a time limit and expectation. Offer non-pharmacologic methods and non-opioid interventions for pain management. Communicate with the surgeon and advise patient to make appointment with surgeon for discussion of treatment plan.

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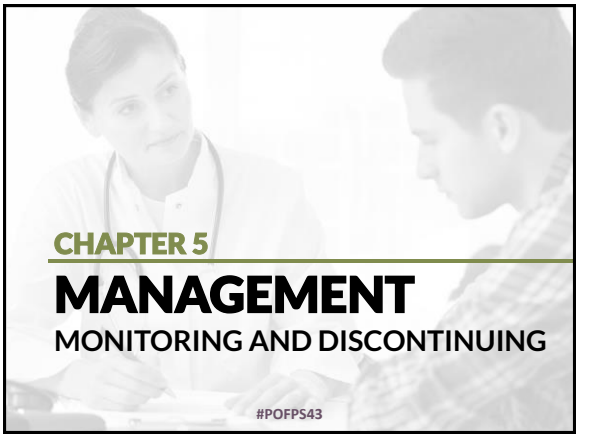

CHAPTER 5

MANAGEMENT

MONITORING AND DISCONTINUING

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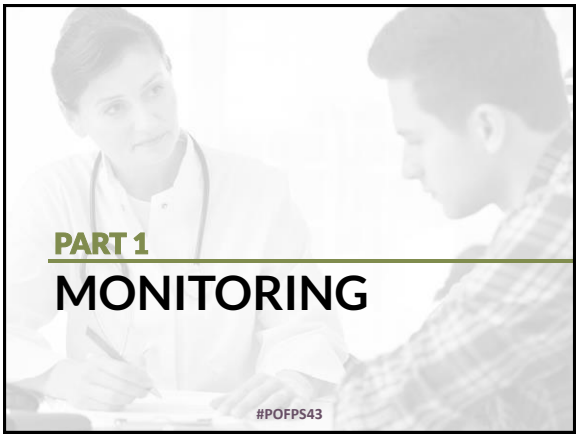

OPIOID SIDE EFFECTS

CO•RE

- Respiratory depression – most serious
- Opioid-Induced Constipation (OIC) – most common
- Sedation, cognitive impairment
- Falls and fractures
- Sweating, miosis, urinary retention
- Hypogonadism
- Tolerance, physical dependence, hyperalgesia
- Addiction in vulnerable patients

FDA

Prescribers should report serious AEs to the FDA:
www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf
or 1-800-FDA-1088

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OPIOID-INDUCED RESPIRATORY DEPRESSION

CO•RE

Chief hazard of opioid agonists, including ER/LA opioids

- If not immediately recognized and treated, may lead to respiratory arrest and death
- Greatest risk: initiation of therapy or after dose increase

Manifested by reduced urge to breathe and decreased respiration rate

- Shallow breathing
- CO_2 retention can exacerbate opioid sedating effects

Instruct patients/family members to call 911

Managed with

- Close observation
- Supportive measures
- Opioid antagonists
- Depending on patient's clinical status

SOURCE: Chou R, et al. *J Pain.* 2009;10:113-30.
FDA. *Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics.* 01/2017.
https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM515636.pdf

OPIOID-INDUCED RESPIRATORY DEPRESSION

CO•RE

MORE LIKELY TO OCCUR	REDUCE RISK
• In elderly, cachectic, or debilitated patients – **Contraindicated** in patients with respiratory depression or conditions that increase risk • If given concomitantly with other drugs that depress respiration • Patients who are opioid-naïve or have just had a dose increase	• Proper dosing and titration are essential • **Do not overestimate** dose when converting dosage from another opioid product – Can result in fatal overdose with first dose • Instruct patients to swallow tablets/capsules whole – Dose from cut, crushed, dissolved, or chewed tablets/capsules may be fatal, particularly in opioid-naïve individuals

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WHEN TO MOVE FROM IR TO ER/LA OPIOIDS

CO•RE

PRIMARY REASONS	OTHER POTENTIAL REASONS
• Maintain stable blood levels (steady state plasma) • Longer duration of action • Multiple IR doses needed to achieve effective analgesia • Poor analgesic efficacy despite dose titration • Less sleep disruption	• Patient desire or need to try a new formulation • Cost or insurance issues • Adherence issues • Change in clinical status requires an opioid with different pharmacokinetics • Problematic drug-drug interactions

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CONSIDERATIONS FOR CHANGE FROM IR TO ER/LA OPIOIDS

CO•RE

DRUG AND DOSE SELECTION IS CRITICAL	MONITOR PATIENTS CLOSELY FOR RESPIRATORY DEPRESSION	INDIVIDUALIZE DOSAGE BY TITRATION BASED ON EFFICACY, TOLERABILITY, AND PRESENCE OF AEs
Some ER/LA opioids or dosage forms are only recommended for opioid-tolerant patient • ANY strength of transdermal fentanyl or hydromorphone ER • Certain strengths/ doses of other ER/LA products (check drug prescribing information)	Especially within 24-72 hours of initiating therapy and increasing dosage	Check ER/LA opioid product PI for minimum titration intervals Supplement with IR analgesics (opioids and non-opioid) if pain is not controlled during titration

SOURCE: The ER/LA Opioid Analgesics Risk Evaluation & Mitigation Strategy. *Selected Important Safety Information. Abuse potential & risk of life-threatening respiratory depression.* www.er-la-opioidrems.com/wgUI/rems/pdf/Important_safety_information.pdf. 2012. Chou R, et al. *J Pain.* 2009;10:113-30. FDA. *Blueprint for Prescriber Education for ER/LA Opioid Analgesics.* 05/2013. www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf

OPIOID TOLERANCE

If opioid tolerant caution should still be used at higher doses

Patients considered opioid tolerant are taking 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
- An equianalgesic dose of another opioid

FOR 1 WEEK OR LONGER

IMPORTANT

Still requires caution when rotating a patient on an IR opioid to a different ER/LA opioid

SOURCE: The ER/LA Opioid Analgesics Risk Evaluation & Mitigation Strategy. *Selected Important Safety Information. Abuse potential & risk of life-threatening respiratory depression.* www.er-la-opioidrems.com/lwgUI/rems/pdf/important_safety_information.pdf. 2012.

OPIOID ROTATION

DEFINITION

Change from an existing opioid regimen to another opioid with the goal of improving therapeutic outcomes or to avoid AEs attributed to the existing drug (e.g., myoclonus)

RATIONALE

Differences in pharmacologic or other effects make it likely that a switch will improve outcomes

- Effectiveness and AEs of different mu opioids vary among patients
- Patients show incomplete cross-tolerance to new opioid
  - Patient tolerant to first opioid can have improved analgesia from second opioid at a dose lower than calculated from an Equianalgesic Dosing Table (EDT)

SOURCE: Fine PG, et al. *J Pain Symptom Manage*. 2009;38:418-25. Knotkova H, et al. *J Pain Symptom Manage*. 2009;38:426-39. Pasternak GW. *Neuropharmacol*. 2004;47(suppl 1):312-23.

EQUIANALGESIC DOSE TABLES (EDT)

Many different versions:

PUBLISHED	ONLINE
ONLINE INTERACTIVE	SMART-PHONE APPS

Vary in terms of:

EQUIANALGESIC VALUES	WHETHER RANGES ARE USED

Which opioids are included: May or may not include transdermal opioids, rapid-onset fentanyl, ER/LA opioids, or opioid agonist-antagonists

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EXAMPLE OF AN EDT FOR ADULTS

	Equianalgesic Dose		Usual Starting Doses	
DRUG	SC/IV	PO	PARENTERAL	PO
Morphine	10 mg	30 mg	2.5-5 mg SC/IV q3-4hr (1.25-2.5 mg)	5-15 mg q3-4hr (IR or oral solution) (2.5-7.5 mg)
Oxycodone	NA	20 mg	NA	5-10 mg q3-4 (2.5 mg)
Hydrocodone	NA	30 mg	NA	5 mg q3-4h (2.5 mg)
Hydromorphone	1.5 mg	7.5 mg	0.2-0.6 mg SC/IV q2-3hr (0.2 mg)	1-2 mg q3-4hr (0.5-1 mg)

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Optional Slide

MU OPIOID RECEPTORS AND INCOMPLETE CROSS-TOLERANCE

MU OPIOIDS BIND TO MU RECEPTORS

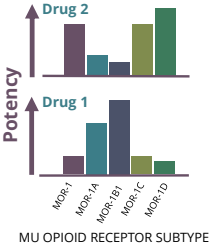
MANY MU RECEPTOR SUBTYPES:

Mu opioids produce **subtly different** pharmacologic response based on distinct activation profiles of mu receptor subtypes

MAY HELP EXPLAIN:

Inter-patient variability in response to mu opioids

Incomplete cross-tolerance among mu opioids



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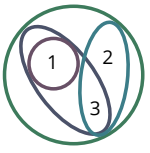
INCOMPLETE CROSS-TOLERANCE

Drug	Receptor Subtype Selectivity
A	1+3
B	2+3
C	1
D	1+2+3



CHALLENGE DRUG:

CROSS-TOLERANCE IF TOLERANT TO DRUG:	A	B	C	D
A	-	Partial	Partial	Yes
B	Partial	-	No	Yes
C	Yes	No	-	Yes
D	Partial	Partial	Partial	-

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GUIDELINES FOR OPIOID ROTATION

CO•RE

Calculate equianalgesic dose of new opioid from EDT

REDUCE CALCULATED EQUIANALGESIC DOSE BY 25%-50%*

SELECT % REDUCTION BASED ON CLINICAL JUDGMENT

CLOSER TO 50% REDUCTION IF PATIENT IS	CLOSER TO 25% REDUCTION IF PATIENT
• Receiving a relatively high dose of current opioid regimen • Elderly or medically frail	• Does not have these characteristics • Is changing route of administration

*75%-90% reduction for methadone

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GUIDELINES FOR OPIOID ROTATION *(continued)*

CO•RE

IF SWITCHING TO METHADONE:

- Standard EDTs are less helpful in opioid rotation to methadone
- In opioid tolerant patients, methadone doses should **not** exceed 30-40 mg/day upon rotation
  - Consider inpatient monitoring, including serial EKG monitoring
- In opioid-naïve patients, methadone should **not** be given as an initial drug

IF SWITCHING TO TRANSDERMAL:

- **Fentanyl**, calculate dose conversion based on equianalgesic dose ratios included in the PI
- **Buprenorphine**, follow instructions in the PI

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GUIDELINE FOR OPIOID ROTATION: SUMMARY

CO•RE

VALUES FROM EDT*	PATIENT OPIOID VALUES	"SOLVE" FOR X	AUTOMATICALLY REDUCE DOSE
Value of Current Opioid / Value of New Opioid	24 Hr Dose of Current Opioid / X Amount of New Opioid	Equianalgesic 24 Hr Dose of New Opioid	By 25%-50%†

Frequently assess initial response	Titrate dose of new opioid to optimize outcomes	Calculate supplemental rescue dose used for titration at 5%-15% of total daily dose‡

* If switching to transdermal fentanyl, use equianalgesic dose ratios provided in PI
† If switching to methadone, reduce dose by 75%-90%
‡ If oral transmucosal fentanyl used as rescue, begin at lowest dose irrespective of baseline opioid

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BREAKTHROUGH PAIN (BTP)

CO•RE

PATIENTS ON STABLE ATC OPIOIDS MAY EXPERIENCE BTP

- Disease progression or a new or unrelated pain
  - Target cause or precipitating factors
- Dose for BTP: using an IR is 5%-15% of total daily opioid dose, administered at an appropriate interval
- Never use ER/LA for BTP

CONSIDER ADDING

- PRN IR opioid trial based on analysis of benefit versus risk
  - Risk for aberrant drug-related behaviors
  - High-risk: only in conjunction w/ frequent monitoring & follow-up
  - Low-risk: w/ routine follow-up & monitoring
- Non-opioid drug therapies
- Non-pharmacologic treatments

ATC = Around the Clock

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BE READY TO REFER

CO•RE

SUBSTANCE USE DISORDER

SAMHSA substance abuse treatment facility locator

SAMHSA mental health treatment facility locator

https://findtreatment.samhsa.gov/locator/home

HIGH-RISK/COMPLEX PATIENTS

Refer to pain management, check state regulations for requirements

SAMHSA = Substance Abuse and Mental Health Service Administration

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RATIONALE FOR URINE DRUG TESTING (UDT)

CO•RE

- Urine testing is done **FOR** the patient not **TO** the patient
- Help to identify drug misuse/addiction
- Assist in assessing and documenting adherence

UDT FREQUENCY IS BASED ON CLINICAL JUDGMENT AND STATE REGULATIONS

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TYPES OF UDT METHODS

CO*RE

Be aware of what you are testing and not testing

IMMUNOASSAY (IA) DRUG PANELS

- Either lab-based or point of care
- Identify substance as present or absent according to cutoff
- Many do not identify individual drugs within a class
- Subject to cross-reactivity and variability

GC/MS OR LC/MS

- Identify the presence and quantity of substance(s)
- Identify drugs not included in IA tests
- When results are contested

GC/MS=gas chromatography/mass spectrometry - LC/MS=liquid chromatography/mass spectrometry

SOURCE: Melanson,S. Ptolemy, A., Wasan, A. Professionalism and Commentary: Optimizing Urine Drug Testing for Monitoring Medication Compliance in Pain Management, In Pain Medicine, December 2013 14(12):1813-1820

Optional Slide

SPECIFIC WINDOWS OF DRUG DETECTION

CO*RE

How long a person excretes drug and/or metabolite(s) at a concentration above a cutoff

DETECTION TIME OF DRUGS IN URINE

Governed by various factors; e.g., dose, route of administration, metabolism, fat solubility, urine volume and pH	For most drugs it is 1-3 days	Chronic use of lipid-soluble drugs increases detection time; e.g., marijuana, diazepam, ketamine

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SPECIFIC WINDOWS OF DRUG DETECTION *(continued)*

CO*RE

Drug	How soon after taking drug will there be a positive drug test?	How long after taking drug will there continue to be a positive drug test?
Marijuana/Pot	1-3 hours	1-7 days
Crack (Cocaine)	2-6 hours	2-3 days
Heroin (Opiates)	2-6 hours	1-3 days
Speed/Uppers (Amphetamine, methamphetamine)	4-6 hours	2-3 days
Angel Dust/PCP	4-6 hours	7-14 days
Ecstasy	2-7 hours	2-4 days
Benzodiazepine	2-7 hours	1-4 days
Barbiturates	2-4 hours	1-3 weeks
Methadone	3-8 hours	1-3 days
Tricyclic Antidepressants	8-12 hours	2-7 days
Oxycodone	1-3 hours	1-2 days

Source: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/DrugsofAbuseTests/ucm125722.htm

Optional Slide

URINE SPECIMEN INTEGRITY

CO*RE

SPECIMEN COLOR RELATED TO CONCENTRATION

Concentrated samples more reliable than dilute samples

TEMP WITHIN 4 MINUTES OF VOIDING IS 90-100°F

PH FLUCTUATES WITHIN RANGE OF 4.5-8.0

CREATININE VARIES WITH HYDRATION

Normal urine: >20 mg/dL	Dilute: creatinine <20 mg/dL and specific gravity <1.003	Creatinine <2 mg/dL not consistent with human urine

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INTERPRETATION OF UDT RESULTS

CO*RE

POSTIVE RESULT

Demonstrates recent use
- Most drugs in urine have detection times of 1-3 days
- Chronic use of lipid-soluble drugs: test positive for ≥1 week

Does not diagnose
- Drug addiction, physical dependence, or impairment

Does not provide enough information to determine
- Exposure time, dose, or frequency of use

NEGATIVE RESULT

Does not diagnose diversion
- More complex than presence or absence of a drug in urine

May be due to maladaptive drug-taking behavior
- Binging, running out early
- Other factors: e.g., cessation of insurance, financial difficulties

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EXAMPLES OF METABOLISM OF OPIOIDS

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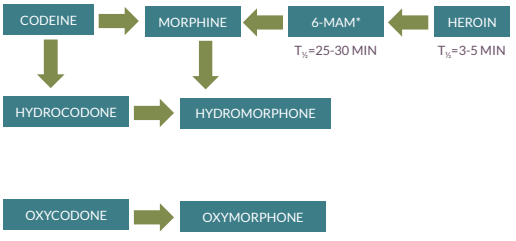

*6-MAM=6-MONOACETYLMORPHINE

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Optional Slide

CHALLENGE: THE OFFENDED PATIENT

CO*RE

RED FLAG:

You decide not to request routine risk assessment for fear of creating conflict

Mrs. Lane and her family have been your patients for years. She has chronic headache and back pain treatment. When you ask her to take a UDT, she becomes upset and accuses you of not trusting her. You decide against further risk assessments because you are concerned about damaging the relationship.

Action:

Require all patients receiving opioids to follow a treatment plan and adhere to defined expectations. Create office policy for performing UDT for patients receiving opioids beyond two weeks. Practice universal precautions. Explain to patient that you must meet the standards of care that include evaluation of risk in all patients, use of PPAs, and other tools.

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REASONS FOR DISCONTINUING OPIOIDS

CO*RE

PAIN LEVEL DECREASES IN STABLE PATIENTS	INTOLERABLE AND UNMANAGEABLE AEs	NO PROGRESS TOWARD THERAPEUTIC GOALS

MISUSE	ABERRANT BEHAVIORS
• 1 or 2 episodes of increasing dose without prescriber knowledge • Sharing medications • Unapproved opioid use to treat another symptom (e.g., insomnia)	• Use of illicit drugs or unprescribed opioids • Repeatedly obtaining opioids from multiple outside sources • Prescription forgery • Multiple episodes of prescription loss • Diversion

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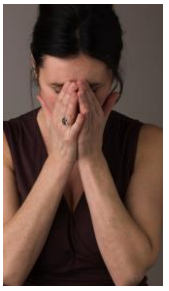
TAPER DOSE WHEN DISCONTINUING

- Minimize withdrawal symptoms in opioid-dependent patient, consider medications to assist with withdrawal
- May use a range of approaches from slow 10% dose reduction per week to more rapid 25%-50% reduction every few days
- If opioid use disorder or a failed taper, refer to addiction specialist or consider opioid agonist therapy
- Counseling and relaxation strategies needed



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CHAPTER 5 – PEARLS FOR PRACTICE

- Establish informed consent and PPA at the beginning
- Educate the whole team: ***patients, families, caregivers***
- Refer if necessary
- Anticipate opioid-induced respiratory depression and constipation
- Follow patients closely during times of dose adjustments
- Periodically evaluate functional outcomes
- Discontinue opioids slowly and safely

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Optional Slide

CHALLENGE: IS THIS A LAB ERROR?

RED FLAG:
The questionable Urine Drug Test

Donald has been prescribed oxycodone for six months to treat back pain. His UDT at six months comes back negative in all areas. He tells you that he is taking his meds.

Action:
Do not discharge the patient as the first action. Contact the lab and discuss the test and any metabolite or specimen integrity issues. Ask: Is this the right lab test? Repeat the UDT and document everything. Discuss with the patient.

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Optional Slide

CHALLENGE: PATIENTS WHO ARE NOT WHO THEY APPEAR

CO*RE

RED FLAG:

Patient wants to control their pill mg dose and taper plan

Tom has back pain. He is managed by taking oxycodone (40 mg BID) but wants to decrease his dose when he can, thus he requests only 20 mg pills. He often brings in unused meds to show how he is trying to reduce his dose. He resists any change.

Action:

Do not allow patient to taper on their own. Create an endpoint for the taper. See patient once a week with a seven-day supply for the tapering until they are off opioids. Document teaching, patient's comments about the plan, UDT, pill counts, non-pharmacological modalities for pain management, and their adherence to this plan.

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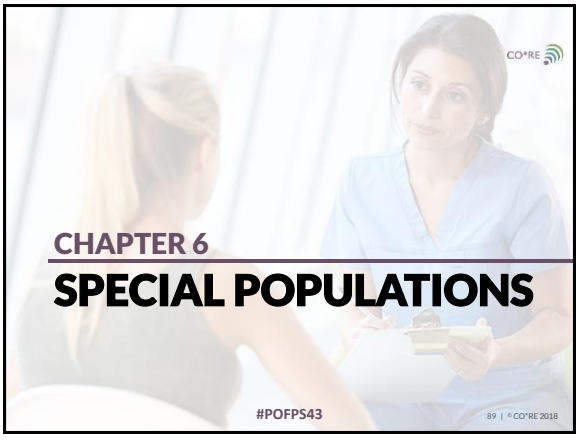

CO*RE

CHAPTER 6

SPECIAL POPULATIONS

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OLDER ADULTS

CO*RE

RISK FOR RESPIRATORY DEPRESSION

- Age-related changes in distribution, metabolism, excretion; absorption less affected

MONITOR

- Initiation and titration
- Concomitant medications (polypharmacy)
- Falls risk, cognitive change, psychosocial status

- Reduce starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients
- Start low, go slow, but GO
- Patient and caregiver reliability/risk of diversion

ROUTINELY INITIATE A BOWEL REGIMEN

SOURCE: American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. *J Am Geriatr Soc.* 2009;57:1331-46. Chou R, et al. *J Pain.* 2009;10:113-30.

WOMEN WITH CHILDBEARING POTENTIAL

CO•RE

KNOW THE REPRODUCTIVE PLANS AND PREGNANCY STATUS OF YOUR PATIENTS

- 40% of women with childbearing potential are prescribed opioids
- Opioid exposure during pregnancy causes increased risk for fetus
- Most women do not know they are pregnant in first few weeks
- Therefore all women of childbearing age are at risk
- No adequate nor well-controlled studies of opioids for pain in pregnancy

SOURCE: Ailes, E., Dawson, A., Lind, J., Bilboa, S., Frey, M., Broussard, C., Honein, M., MMWR 64(2015)"Opioid Prescripiton Claims Among Women of Reproductive Age – United Sates, 2008-2012

THE PREGNANT PATIENT

CO•RE

Potential risk of opioid therapy to the newborn is neonatal opioid withdrawal syndrome

GIVEN THESE POTENTIAL RISKS, CLINICIANS SHOULD:

- Counsel women of childbearing potential about risks and benefits of opioid therapy during pregnancy and after delivery
- Encourage minimal/no opioid use during pregnancy, unless potential benefits outweigh risks to fetus
- Refer to a high risk OB/Gyn who will ensure appropriate treatment for the baby

- If chronic opioid therapy is used during pregnancy, anticipate and manage risks to the patient and newborn
- If using opioids on a daily basis, consider methadone or buprenorphine

SOURCE: Chou R, et al. *J Pain.* 2009;10:113-30.

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CHILDREN AND ADOLESCENTS: HANDLE WITH CARE

CO•RE

JUDICIOUS USE OF IR FOR BRIEF THERAPY

SAFETY AND EFFECTIVENESS OF MOST ER/LA OPIOIDS UNESTABLISHED

- Pediatric analgesic trials pose challenges
- Transdermal fentanyl approved in children aged ≥2 yrs
- Oxycodone ER dosing changes for children ≥11 yrs

ER/LA OPIOID INDICATIONS ARE PRIMARILY LIFE-LIMITING CONDITIONS

WHEN PRESCRIBING ER/LA OPIOIDS TO CHILDREN:

- Consult pediatric palliative care team or pediatric pain specialist or refer to a specialized multidisciplinary pain clinic

SOURCE: Berde CB, et al. *Pediatrics.* 2012;129:354-64. Gregoire MC, et al. *Pain Res Manag.* 2013;18:47-50. Mc Donnell C. *Pain Res Manag.* 2011;16:93-8. Slater ME, et al. *Pain Med.* 2010;11:207-14.

Optional Slide

CHALLENGE: VULNERABILITY IN CO-DEPENDENT OLDER ADULTS

CO*RE

RED FLAG:
Questionable family diversion

78-year-old Thelma comes into clinic, accompanied by grandson, who is in the exam room with you and Thelma. Thelma says her oxycodone 10 mg tablets q 4 hours is no longer working for her back pain. She asks for more medicine. You ask grandson to leave the exam room so you can examine her privately.

Action: Based on exam findings and her request for more medication:

- UDT and PDMP check
- Discuss whether or not it is possible her grandson, or another family member, might be using her medications.
- Patient education: Do not give opioids to another person. Store in secure place – locked. Let you know if medications are not secure or if she feels any pressure about sharing medications.

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CHAPTER 7
KNOW YOUR FEDERAL AND STATE LAWS

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FEDERAL AND STATE REGULATIONS

CO*RE

Comply with federal and state laws and regulations that govern the use of opioid therapy for pain

FEDERAL

- Code of Federal Regulations, Title 21 Section 1306: rules governing the issuance and filling of prescriptions pursuant to section 309 of the Act (21 USC 829)
  www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm
- United States Code (USC) - Controlled Substances Act, Title 21, Section 829: prescriptions
  www.deadiversion.usdoj.gov/21cfr/21usc/829.htm

STATE

- Database of state statutes, regulations, and policies for pain management
  www.medscape.com/resource/pain/opioid-policies
  www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management

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PRESCRIPTION DRUG MONITORING PROGRAMS (PDMPs)

CO*RE

NOT ALL FEDERALLY LICENSED FACILITIES REPORT TO PDMPS

Link to state PDMP sites

INDIVIDUAL STATE LAWS DETERMINE

- Who has access to PDMP information
- Which drug schedules are monitored
- Which agency administers the PDMP
- Whether prescribers are required to register with the PDMP
- Whether prescribers are required to access PDMP information in certain circumstances
- Whether unsolicited PDMP reports are sent to prescribers
- Bordering states may be available
- Designated surrogates may have access

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PDMP BENEFITS

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Provides full accounting of prescriptions filled by patient

RECORD OF A PATIENT'S CONTROLLED SUBSTANCE PRESCRIPTIONS

- Some are available online 24/7
- Opportunity to discuss with patient

PROVIDE WARNINGS OF POTENTIAL MISUSE/ABUSE

- Existing prescriptions not reported by patient
- Multiple prescribers/pharmacies
- Drugs that increase overdose risk when taken together
- Patient pays with cash (vs insurance) for controlled meds

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Opioid Prescribing:
Safe Practice, Changing Lives

State Specific Information

Pennsylvania

www.health.pa.gov

Created: August 2016

Updated: April 2018

The CO*RE State Information Hub is updated three times per year. Since opioid prescribing policies, laws, and regulations change rapidly, please check your state's regulations for the most up-to-date information.

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Content Outline

- Opioid Prescribing Rates and Overdose Deaths
- Prescription Drug Monitoring Program (PDMP)
- Prescribing Limits, Status and Education Requirements
- Naloxone Regulation
- Medical and Recreational Marijuana Status

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Opioid Prescribing Rates & Overdose Deaths

Prescribing Rates (per 100 people)

	2012	2014	2016
PA	83	80	70

2016 Opioid Overdose Deaths

PA	2235	US	42,249

https://www.cdc.gov/drugoverdose
https://www.kff.org/state-category/health-status/opioids/

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PDMP: Prescription Drug Monitoring Program

General	• **PA PDMP Program** www.doh.pa.gov/pdmp • Administered by **Department of Health** • **Schedule II-V** are monitored • **Dispensers and prescribers are required** to register and input data • Before prescribing, there **is an obligation** to review under certain circumstances
Access	• **Prescribers, dispensers, law enforcement, judicial officers, patients, medical examiner, licensing boards, Department of Drug and Alcohol Programs** • Prescribers **can authorize** a registered delegate
Reporting	• Must be entered into PDMP **by the next business day** after dispensing • Unsolicited reports/alerts **are sent** to law enforcement and licensing boards • Pennsylvania **does share** data with other states' PDMP • Out-of-state pharmacies **are required** to report to the patient's home state • Patient **will be notified** if their record has been accessed

http://www.namsdl.org/prescription-drug-monitoring-programs-maps.cfm Jan. 2018

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Prescribing Limits, Status and Education Requirements

CO*RE

Initial prescribing limits for acute pain: Adults-None Minors-7 days

	Physician	Physician Assistant	Advanced Practice Nurse
Prescriber Status	Licensed	Schedule II-V	Schedule II-V
Education Requirements	2 hrs./2 yrs.	2 hrs./2 yrs.	4 hrs. initially, then 2 hrs./2 yrs.

www.netce.com/ce-requirements/

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Naloxone Regulation

CO*RE

Effective date	• **December 2014**
Criminal Immunity	• Prescribers: **Yes** • Dispensers: **Yes** • Lay People: **Yes**
Also Available	• Without Prescription: **Yes** • To 3rd Party: **Yes** • By Standing Order: **Yes**
Carried by First Responders	• **Yes**

https://www.networkforphl.org/_asset/qz5pvn/legal-interventions-to-reduce-overdose.pdf July 2017
www.pdaps.org

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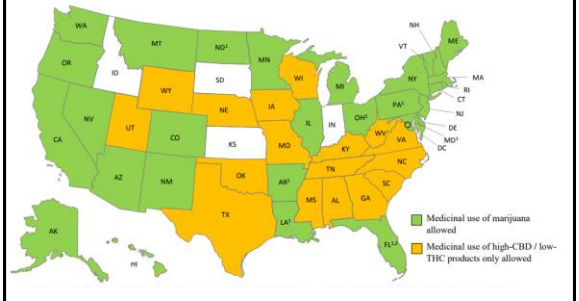
Marijuana Status

CO*RE

Medical



Recreational | **Not legal for recreational use in Pennsylvania**

Optional Slide

CANNABIS

CO*RE

- DEA Schedule 1 ("high abuse potential") yet state laws and regulations vary
- There is evidence that cannabis or selective cannabinoids (cannabidiol) are effective for chronic pain treatment in adults
- More research is needed
- Concern for high risk groups: children, adolescents, pregnant women

SOURCE: The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. A National Academy of Science publication (2017)

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Optional Slide

CONSIDERATIONS FOR CLINICIANS

CO*RE

- Use available scientific evidence, advise patients
  - Inform about potential effects; AEs mostly mild and well tolerated (cough, anxiety)
  - Screen for potential misuse/abuse, diversion
- Set treatment goals, use PPA
- Encourage patients to keep notes, discuss with them
- Document everything
- Regular re-evaluation
- Consider periodic UDTs
- Discontinue if not helpful moving toward goals
- Edibles are the fastest growing delivery system
- No well controlled studies on the combined use of opioids and cannabis

SOURCE: The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. A National Academy of Science publication (2017)

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Optional Slide

CHALLENGE: THE HIGH RISK PATIENT

CO*RE

RED FLAG:

Proceed with caution, but treat the high risk patient

18-year-old with a recurrent wound in the antecubital fossa secondary to intravenous injection. This is her third wound debridement and she is in more pain than before. She tells you if she cannot get relief from you, she will go to the street for meds.

Action:

With a drug abuse history, proceed with caution and use extra safety measures. Patient may require admission to either hospital or treatment facility while managing pain. This history does not mean you should discharge or avoid treating the patient's pain.

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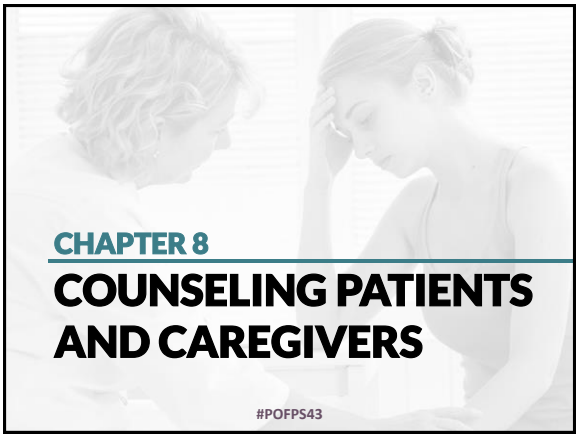
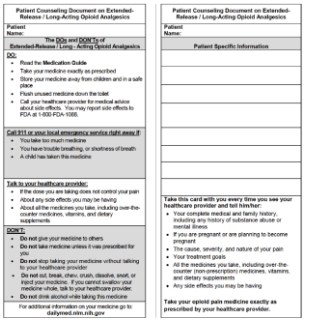


USE PATIENT COUNSELING DOCUMENT

CO•RE

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

ORDER HARD COPIES:
www.minneapolis.cenveo.com/pcd/SubmitOrders.aspx



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'Ts
- 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 cut, break, chew, crush, dissolve, snort, 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
- If you are pregnant or are planning to become pregnant
- 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.

SOURCE: FDA. Extended-release (Er) And Long-acting (La) Opioid Analgesics Risk Evaluation And Mitigation Strategy (Rems). Modified 06/2015 www.fda.gov/downloads/ Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf

COUNSEL PATIENTS ABOUT PROPER USE

CO•RE

EXPLAIN	INSTRUCT PATIENTS/ CAREGIVERS TO
• Product-specific information about the IR or ER/LA opioid (especially when converting) • Take opioid as prescribed • Adhere to dose regimen • How to handle missed doses • Notify prescriber if pain not controlled • Call prescriber for options on side effect management	• Read the ER/LA opioid **Medication Guide** received from pharmacy **every time** an ER/LA opioid is dispensed

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COUNSEL PATIENTS ABOUT PROPER USE *(continued)*

CO•RE

EXPLAIN	OPIOIDS CAN CAUSE DEATH EVEN WHEN TAKEN PROPERLY
• Inform prescriber of ALL meds being taken • Warn patients not to abruptly discontinue or reduce dose • Risk of falls • Caution with operating heavy machinery and when driving • Sharing or selling opioids can lead to others' deaths and is against the law	• Signs/symptoms are respiratory depression, gastrointestinal obstruction, allergic reactions

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COUNSEL PATIENTS ABOUT PROPER USE *(continued)*

CO•RE

EXPLAIN	OPIOIDS SHOULD BE STORED IN A SAFE AND SECURE PLACE
• Tell patients and caregivers, medications must be kept in a locked container • Will periodically assess for benefits, side effects, and continued need for IR/ER/LA opioids • Need for re-evaluation of underlying medical condition if the clinical presentation changes over time	• Away from children, family members, visitors, and pets • Safe from theft Opioids are scheduled under Controlled Substances Act and can be misused and abused

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WARN PATIENTS

CO•RE

Never break, chew, crush, or snort an oral ER/LA tablet/capsule, or cut or tear patches prior to use

- May lead to rapid release of ER/LA opioid causing overdose and death
- If unable to swallow a capsule whole, refer to PI to determine if appropriate to sprinkle contents on applesauce or administer via feeding tube

Use of CNS depressants or alcohol with ER/LA opioids can cause overdose & death

- Use with alcohol may result in rapid release and absorption of a potentially fatal opioid dose – "dose dumping"
- Other depressants include sedative-hypnotics and anxiolytics, illegal drugs

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OVERDOSE POISONING, CALL 911

- Person cannot be aroused or awakened or is unable to talk
- Any trouble with breathing, heavy snoring is warning sign
- Gurgling noises coming from mouth or throat
- Body is limp, seems lifeless; face is pale, clammy
- Fingernails or lips turn blue/purple
- Slow, unusual heartbeat or stopped heartbeat

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NALOXONE

Naloxone:
- An opioid antagonist administered by injection or intranasally, or IV
- Reverses acute opioid-induced respiratory depression but will also reverse analgesia

Available as:
- Naloxone kit (with syringes, needles)
- Injectable
- Nasal spray

What to do:
- Discuss an 'overdose plan'
- Involve and train family, friends, partners, and/or caregivers
- Check with pharmacy if they are prescribing
- Check expiration dates and keep a viable dose on hand
- In the event of known or suspected overdose, administer naloxone and **call 911**

Consider offering a naloxone prescription to all patients prescribed IR and ER/LA opioids

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SOURCE: http://prescribetoprevent.org/wp2015/wp-content/uploads/CA_Detailing_Provider_final.pdf 2015

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Optional Slide

ABUSE-DETERRENT FORMULATION/TAMPER RESISTANT (ADF/TR) OPIOIDS

- Response to growing non-medical use problem
- An ER/LA opioid with physical barrier to *deter* extraction
  - Less likely to be crushed, injected, or snorted
- Consider as one part of an overall strategy
- Mixed evidence on the impact of ADF/TR on misuse
- Remember overdose is still possible if taken orally in excessive amounts

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Optional Slide

TALK WITH YOUR PATIENTS WHO ARE PARENTS

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- Consider the behavior you are modeling
- 45% of parents have taken pain medications without a prescription at some point
- 14% have given their children pain medications without a prescription
- Teens report that their parents do not talk with them about prescription drug risks
  - Evidence suggests that pre-college parental conversation helps reduce high-risk substance abuse among college students

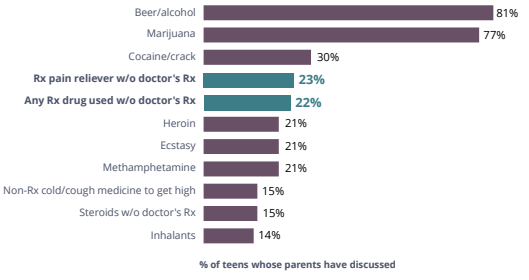
SOURCE: Turris,R., Mallett,K. Cleveland,M., Varvil-Weld,L., Abar,C., Scaglione N., Hultgren,B. J Stud Alcohol Drugs 74 (2013) "Evaluation of timing and dosage of a parent-based intervention to minimize college students' alcohol consumption" https://www.ncbi.nlm.nih.gov/pubmed/23200148

Optional Slide

SUBSTANCES PARENTS HAVE DISCUSSED WITH TEENS*

CO*RE

*As reported by teens



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Optional Slide

REMEMBER...

CO*RE

STEP 1: MONITOR
- Note how many pills in each prescription
- Keep track of dosage and refills
- Make sure everyone in the home knows

STEP 2: SECURE
- Keep meds in a safe place (locked cabinet)
- Encourage parents of your teen's friends to secure their prescriptions

STEP 3: DISPOSE
- Discard expired or unused meds
- Consult PI for best disposal

SOURCE: McDonald E, Kennedy-Hendrick, A, McGinty E, Shields W, Barry C, Gielen A AAP News, Pediatrics February 2017

RX OPIOID DISPOSAL

CO*RE

New "Disposal Act" expands ways for patients to dispose of unwanted/expired opioids

DECREASES AMOUNT OF OPIOIDS INTRODUCED INTO THE ENVIRONMENT, PARTICULARLY INTO WATER

Collection receptacles
Call DEA Registration Call Center at **1-800-882-9539** to find a local collection receptacle

Mail-back packages
Obtained from authorized collectors

Voluntarily maintained by:
- Law enforcement
- Authorized collectors, including:
  - Manufacturer
  - Distributor
  - Reverse distributor
  - Retail or hospital/clinic pharmacy
    - Including long-term care facilities

Look for local take-back events
- Conducted by Federal, State, tribal, or local law enforcement
- Partnering with community groups

SOURCE: DEA. *Federal Register*. 2014; 79(174):53520-70. Final Rule. Disposal of Controlled Substances. [Docket No. DEA-316] www.deadiversion.usdoj.gov/fed_regs/rules/2014/2014-20926.pdf. DEA. Disposal Act: General Public Fact Sheet. www.deadiversion.usdoj.gov/drug_disposal/fact_sheets/disposal_public.pdf

OTHER METHODS OF OPIOID DISPOSAL

CO*RE

IF COLLECTION RECEPTACLE, MAIL-BACK PROGRAM, OR TAKE-BACK EVENT UNAVAILABLE, THROW OUT IN HOUSEHOLD TRASH

- Take drugs out of original containers
- Mix with undesirable substance
- Place in sealable bag, can, or other container
- Remove identifying info on label

Source: https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/EnsuringSafeUseofMedicine/SafeDisposalof

FDA: PRESCRIPTION DRUG DISPOSAL

CO*RE

FLUSH DOWN SINK/TOILET IF NO COLLECTION RECEPTACLE, MAIL-BACK PROGRAM, OR TAKE-BACK EVENT AVAILABLE

- As soon as they are no longer needed
- Includes transdermal adhesive skin patches
  - Used patch (3 days) still contains enough opioid to harm/kill a child
  - Dispose of used patches immediately after removing from skin
- Fold patch in half so sticky sides meet, then flush down toilet
- Do NOT place used or unneeded patches in household trash
  - Butrans (buprenorphine transdermal system)
    exception: can seal in Patch-Disposal Unit provided and dispose of in the trash

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CHAPTER 8 – PEARLS FOR PRACTICE

- Use formal tools (PPAs, counseling document) to educate patients and caregivers
- Emphasize safe storage and disposal to patients and caregivers
- Consider co-prescribing naloxone

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Optional Slide

CHALLENGE: THE DAUGHTER'S PARTY

RED FLAG:

Patients do not safeguard their opioid medications correctly

Your patient's daughter stole her father's opioids from his bedside drawer to take to a "fishbowl party." Her best friend consumed a mix of opioids and alcohol and died of an overdose.

Action:

Always counsel patients about safe drug storage; warn patients about the serious consequences of theft, misuse, and overdose. Tell patients that taking another person's medication, even once, is against the law.

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CHAPTER 9

DRUG CLASS CONSIDERATIONS

#POFPS43

FOR SAFER USE: KNOW DRUG INTERACTIONS, PK, AND PD

CO•RE

- CNS depressants can potentiate sedation and respiratory depression
- Some ER/LA products rapidly release opioid (dose dump) when exposed to alcohol
  - Some drug levels may increase without dose dumping
- Use with MAOIs may increase respiratory depression
  - Certain opioids with MAOIs can cause serotonin syndrome
- Can reduce efficacy of diuretics
  - Inducing release of antidiuretic hormone
- Methadone and buprenorphine can prolong QTc interval
- Drugs that inhibit or induce CYP enzymes can increase or lower blood levels of some opioids

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TRANSDERMAL/TRANSMUCOSAL DOSAGE FORMS

CO•RE

Do not cut, damage, chew, or swallow ⚠

- Exertion or exposure to external heat can lead to fatal overdose
- Rotate location of application
- Prepare skin: clip (not shave) hair & wash area with water
- Monitor patients with fever for signs or symptoms of increased opioid exposure
- Metal foil backings are not safe for use in MRIs
- For buccal film products the film should not be applied if it is cut, damaged, or changed in anyway -- use entire film

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DRUG INTERACTIONS COMMON TO OPIOIDS

CO•RE

- Concurrent use with other CNS depressants can increase risk of respiratory depression, hypotension, profound sedation, or coma
- Reduce initial dose of one or both agents
- Avoid concurrent use of partial agonists* or mixed agonist/antagonists† with full opioid agonist
- May reduce analgesic effect and/or precipitate withdrawal
- May enhance neuromuscular blocking action of skeletal muscle relaxants and increase respiratory depression
- Concurrent use with anticholinergic medication increases risk of urinary retention and severe constipation
- May lead to paralytic ileus

*Buprenorphine; †Pentazocine, nalbuphine, butorphanol

Optional Slide

DRUG INFORMATION COMMON TO OPIOIDS

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USE IN OPIOID-TOLERANT PATIENTS

- See individual PI for products which:
  - Have strengths or total daily doses only for use in opioid-tolerant patients
  - Are only for use in opioid-tolerant patients at all strengths

CONTRAINDICATIONS

- Significant respiratory depression
- Acute or severe asthma in an unmonitored setting or in absence of resuscitative equipment
- Known or suspected paralytic ileus
- Hypersensitivity (e.g., anaphylaxis)
- See individual PI for additional contraindications

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SPECIFIC CHARACTERISTICS

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Know for opioid products you prescribe:

Drug substance	Formulation	Strength	Dosing interval
Key instructions	Use in opioid-tolerant patients	Product-specific safety concerns	Relative potency to morphine
Specific information about product conversions, if available		Specific drug interactions	

For detailed information, refer to online PI:
DailyMed at www.dailymed.nlm.nih.gov Drugs@FDA at www.fda.gov/drugsatfda

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Optional Slide

SUMMARY

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Prescription opioid abuse and overdose is a national epidemic.
Clinicians must play a role in prevention.

- Assess patients for treatment with IR and ER/LA opioids
- Initiate therapy, modify dose, and discontinue use of opioids
- Monitor ongoing therapy with IR and ER/LA opioids
- Counsel patients and caregivers about the safe use of opioids, including proper storage and disposal
- Be familiar with general and product-specific drug information concerning opioids

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Our session stops here, but your review continues…

Refer to Appendix 1
for specific drug information on ER/LA opioid analgesic products

For detailed information, prescribers can refer to prescribing information available online via DailyMed at
www.dailymed.nlm.nih.gov
or Drugs@FDA at www.fda.gov/drugsatfda

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YOUR PARTICIPATION IS IMPORTANT

CO*RE

Thank you for completing the post-activity assessment for this CO*RE session

Your participation in this assessment allows CO*RE to report de-identified numbers to the FDA

A strong show of engagement will demonstrate that clinicians have voluntarily taken this important education and are committed to patient safety and improved outcomes

THANK YOU!

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CO*RE

THANK YOU!
WWW.CORE-REMS.ORG

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Appendix 1. Drug Specific Slides

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Morphine Sulfate ER Tablets (Arymo ER)

Capsules 15 mg, 30 mg, 60 mg

Dosing interval	• Every 8 or 12 hours
Key instructions	• Initial dose in opioid-naïve and opioid non-tolerant patients is 15 mg every 8 or 12 hours • Dosage adjustment may be done every 1 to 2 days. • Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth
Drug interactions	• P-gp inhibitors (e.g. quinidine) can increase the exposure of morphine by about two-fold and increase risk of respiratory depression
Opioid-tolerant	• A single dose of ARYMO ER greater than 60 mg, or total daily dose greater than 120 mg, is for use in opioid-tolerant patients only.
Product-specific safety concerns	• Do not attempt to chew, crush, or dissolve. Swallow whole. • Use with caution in patients who have difficulty in swallowing or have underlying GI disorders that may predispose them to obstruction, such as a small gastrointestinal lumen.

Morphine Sulfate ER Capsules (Avinza)

Capsules 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg

Dosing interval	• Once a day
Key instructions	• Initial dose in opioid non-tolerant patients is 30 mg • Titrate in increments of not greater than 30 mg using a minimum of 3-4 d intervals • Swallow capsule whole (do not chew, crush, or dissolve) • May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately • MDD:* 1600 mg (renal toxicity of excipient, fumaric acid)
Drug interactions	• Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of potentially fatal dose • P-gp* inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold
Opioid-tolerant	• 90 mg & 120 mg capsules for use in opioid-tolerant patients only
Product-specific safety concerns	• None

* MDD=maximum daily dose; P-gp= P-glycoprotein

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Buprenorphine Buccal Film (Belbuca)

75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg

Dosing interval	• Every 12 h (or once every 24 h for initiation in opioid naïve patients & patients taking less than 30 mg oral morphine sulfate eq
Key instructions	• Opioid-naïve pts or pts taking <30 mg oral morphine sulfate eq: Initiate treatment with a 75 mcg buccal film, once daily, or if tolerated, every 12 h - Titrate to 150 mcg every 12 h no earlier than 4 d after initiation - Individual titration to a dose that provides adequate analgesia and minimizes adverse reaction should proceed in increments of 150 mcg every 12 h, no more frequently than every 4 d • When converting from another opioid, first taper the current opioid to no more than 30 mg oral morphine sulfate eq/day prior to initiating Belbuca - If prior daily dose before taper was 30 mg to 89 mg oral morphine sulfate eq, initiate with 150 mcg dose every 12 h - If prior daily dose before taper was 90 mg to 160 mg oral morphine sulfate eq, initiate with 300 mcg dose every 12 h - Titration of the dose should proceed in increments of 150 mcg every 12 h, no more frequently than every 4 d

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Buprenorphine Buccal Film (Belbuca) *continued*

Key instructions	• Maximum dose: 900 mcg every 12 h due to the potential for QTc prolongation • Severe Hepatic Impairment: Reduce the starting and incremental dose by half that of patients with normal liver function • Oral Mucositis: Reduce the starting and incremental dose by half that of patients without mucositis • Do not use if the package seal is broken or the film is cut, damaged, or changed in any way
Specific Drug Interactions	• CYP3A4 inhibitors may increase buprenorphine levels • CYP3A4 inducers may decrease buprenorphine levels • Benzodiazepines may increase respiratory depression • Class IA and III antiarrhythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointes
Use in Opioid-Tolerant Patients	• Belbuca 600 mcg, 750 mcg, and 900 mcg are for use following titration from lower doses of Belbuca
Product-Specific Safety Concerns	• QTc prolongation and torsade de pointes • Hepatotoxicity
Relative Potency: Oral	• Equipotency to oral morphine has not been established.

Buprenorphine Transdermal System (Butrans)

Transdermal System 5 mcg/hr, 7.5 mcg/hr, 10 mcg/hr, 15 mcg/hr, 20 mcg/hr

Dosing interval	• One transdermal system every 7 d

Key instructions	• Initial dose in opioid non-tolerant patients on <30 mg morphine equivalents & in mild-moderate hepatic impairment: 5 mcg/h
	• When converting from 30 mg-80 mg morphine equivalents, first taper to 30 mg morphine equivalent, then initiate w/ 10 mcg/h
	• Titrate in 5 or 10 mcg/h increments by using no more than 2 patches of the 5 or 10 mcg/h system(s) w/ minimum of 72 h prior between dose adjustments. Total dose from all patches should be ≤20 mcg/h
	• Maximum dose: 20 mcg/h due to risk of QTc prolongation
	• Application
	  • Apply only to sites indicated in PI
	  • Apply to intact/non-irritated skin
	  • Prep skin by clipping hair; wash site w/ water only
	  • Rotate application site (min 3 wks before reapply to same site)
	  • Do not cut
	• Avoid exposure to heat
	• Dispose of patches: fold adhesive side together & flush down toilet

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Buprenorphine Transdermal System (Butrans)
continued

Drug interactions	• CYP3A4 inhibitors may increase buprenorphine levels • CYP3A4 inducers may decrease buprenorphine levels • Benzodiazepines may increase respiratory depression • Class IA & III antiarrythmics, other potentially arrhythmogenic agents, may increase risk of QTc prolongation & torsade de pointe
Opioid-tolerant	• 7.5 mcg/h, 10 mcg/h, 15 mcg/h, & 20 mcg/h for use in opioid-tolerant patients only
Product-specific safety concerns	• QTc prolongation & torsade de pointe • Hepatotoxicity • Application site skin reactions
Relative potency: oral morphine	• Equipotency to oral morphine not established

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Methadone Hydrochloride Tablets (Dolophine)
continued

Opioid-tolerant	• Refer to full PI
Product-specific safety concerns	• QTc prolongation & torsade de pointe • Peak respiratory depression occurs later & persists longer than analgesic effect • Clearance may increase during pregnancy • False-positive UDT possible
Relative potency: oral morphine	• Varies depending on patient's prior opioid experience

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Methadone Hydrochloride Tablets (Dolophine)

Dosing interval	• Every 8 to 12 h
Key instructions	• Initial dose in opioid non-tolerant patients: 2.5 – 10 mg • Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose & death. Use low doses according to table in full PI • Titrate slowly with dose increases no more frequent than every 3-5 d. Because of high variability in methadone metabolism, some patients may require substantially longer periods between dose increases (up to 12 d). • High inter-patient variability in absorption, metabolism, & relative analgesic potency • Opioid detoxification or maintenance treatment only provided in a federally certified opioid (addiction) treatment program (CFR, Title 42, Sec 8)
Drug interactions	• Pharmacokinetic drug-drug interactions w/ methadone are complex – CYP 450 inducers may decrease methadone levels – CYP 450 inhibitors may increase methadone levels – Anti-retroviral agents have mixed effects on methadone levels • Potentially arrhythmogenic agents may increase risk for QTc prolongation & torsade de pointe • Benzodiazepines may increase respiratory depression

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Fentanyl Transdermal System (Duragesic)

12, 25, 37.5*, 50, 62.5*, 75, 87.5*, and 100 mcg/hr
(*These strengths are available only in generic form)

Dosing interval	• Every 72 h (3 d)
Key instructions	• Use product-specific information for dose conversion from prior opioid • Hepatic or renal impairment: use 50% of dose if mild/moderate, avoid use if severe • Application – Apply to intact/non-irritated/non-irradiated skin on a flat surface – Prep skin by clipping hair, washing site w/ water only – Rotate site of application – Titrate using a minimum of 72 h intervals between dose adjustments – Do not cut • Avoid exposure to heat • Avoid accidental contact when holding or caring for children • Dispose of used/unused patches: fold adhesive side together & flush down toilet

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Fentanyl Transdermal System (Duragesic), *continued*

Key instructions	**Specific contraindications:** • Patients who are not opioid-tolerant • Management of – Acute or intermittent pain, or patients who require opioid analgesia for a short time – Post-operative pain, out-patient, or day surgery – Mild pain
Drug interactions	• CYP3A4 inhibitors may increase fentanyl exposure • CYP3A4 inducers may decrease fentanyl exposure • Discontinuation of concomitant CYP P450 3A4 inducer may increase fentanyl plasma concentration
Opioid-tolerant	• All doses indicated for opioid-tolerant patients only
Product-specific safety concerns	• Accidental exposure due to secondary exposure to unwashed/unclothed application site • Increased drug exposure w/ increased core body temp or fever • Bradycardia • Application site skin reactions
Relative potency: oral morphine	• See individual PI for conversion recommendations from prior opioid

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Morphine Sulfate ER-Naltrexone (Embeda)

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, 100 mg/4 mg

Dosing interval	• Once a day or every 12 h
Key instructions	• Initial dose as first opioid: 20 mg/0.8 mg • Titrate using a minimum of 1-2 d intervals • Swallow capsules whole (do not chew, crush, or dissolve) • Crushing or chewing will release morphine, possibly resulting in fatal overdose, & naltrexone, possibly resulting in withdrawal symptoms • May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately
Drug interactions	• Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of potentially fatal dose • P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold
Opioid-tolerant	• 100 mg/4 mg capsule for use in opioid-tolerant patients only
Product-specific safety concerns	• None

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Hydromorphone Hydrochloride (Exalgo)

ER Tablets 8 mg, 12 mg, 16 mg, 32 mg

Dosing interval	• Once a day
Key instructions	• Use conversion ratios in individual PI • Start patients w/ moderate hepatic impairment on 25% dose prescribed for patient w/ normal function • Renal impairment: start patients w/ moderate on 50% & patients w/ severe on 25% dose prescribed for patient w/ normal function • Titrate in increments of 4-8 mg using a minimum of 3-4 d intervals • Swallow tablets whole (do not chew, crush, or dissolve) • Do not use in patients w/ sulfite allergy (contains sodium metabisulfite)
Drug interactions	• None
Opioid-tolerant	• All doses are indicated for opioid-tolerant patients only
Product-specific adverse reactions	• Allergic manifestations to sulfite component
Relative potency: oral morphine	• ~5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in individual product information

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Hydrocodone Bitartrate (Hysingla ER)

ER Tablets, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120mg

Dosing interval	• Once a day
Key instructions	• Opioid-naïve patients: initiate treatment with 20 mg orally once daily. • During titration, adjust the dose in increments of 10 mg to 20 mg every 3 to 5 days until adequate analgesia is achieved. • Swallow tablets whole (do not chew, crush, or dissolve). • Consider use of an alternative analgesic in patients who have difficulty swallowing or have underlying gastrointestinal disorders that may predispose them to obstruction. • Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. • Use 1/2 of the initial dose and monitor closely for adverse events, such as respiratory depression and sedation, when administering Hysingla ER to patients with severe hepatic impairment or patients with moderate to severe renal impairment.

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Hydrocodone Bitartrate (Hysingla ER)

continued

Drug interactions	• CYP3A4 inhibitors may increase hydrocodone exposure. • CYP3A4 inducers may decrease hydrocodone exposure. • Concomitant use of Hysingla ER with strong laxatives (e.g., Lactulose) that rapidly increase GI motility may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. • The use of MAO inhibitors or tricyclic antidepressants with Hysingla ER may increase the effect of either the antidepressant or Hysingla ER.
Opioid-tolerant	• A single dose ≥ 80 mg is only for use in opioid tolerant patients.
Product-specific safety concerns	• Use with caution in patients with difficulty swallowing the tablet or underlying gastrointestinal disorders that may predispose patients to obstruction. • Esophageal obstruction, dysphagia, and choking have been reported with Hysingla ER. • In nursing mothers, discontinue nursing or discontinue drug. QTc prolongation has been observed with Hysingla ER following daily doses of 160 mg. • Avoid use in patients with congenital long QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. • In patients who develop QTc prolongation, consider reducing the dose.
Relative potency:	• See individual PI for conversion recommendations from prior opioid

Morphine Sulfate (Kadian)

ER Capsules 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 100 mg, 130mg, 150 mg, 200 mg

Dosing interval	• Once a day or every 12 h
Key instructions	• PI recommends not using as first opioid • Titrate using minimum of 2-d intervals • Swallow capsules whole (do not chew, crush, or dissolve) • May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately
Drug interactions	• Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of potentially fatal dose of morphine • P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold
Opioid-tolerant	• 100 mg, 130 mg, 150 mg, 200 mg capsules for use in opioid-tolerant patients only
Product-specific safety concerns	• None

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Morphine Sulfate (MorphaBond)

ER Tablets 15 mg, 30 mg, 60 mg, 100 mg

Dosing interval	• Every 8 h or every 12h
Key instructions	• Product information recommends not using as first opioid • Titrate using a minimum of 1 – 2 d intervals • Swallow tablets whole (do not chew, crush, or dissolve)
Specific Drug interactions	• P-gp inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold
Opioid-tolerant	• MorphaBond 100 mg tablets are for use in opioid-tolerant patients only
Product-specific safety concerns	• None

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Morphine Sulfate (MS Contin)

ER Tablets 15 mg, 30 mg, 60 mg, 100 mg, 200mg

Dosing interval	• Every 8 h or every 12 h
Key instructions	• Product information recommends not using as first opioid. • Titrate using a minimum of 1-2 d intervals • Swallow tablets whole (do not chew, crush, or dissolve)
Drug interactions	• P-gp inhibitors (e.g., quinidine) may increase absorption/exposure of morphine by ~2-fold
Opioid-tolerant	• 100 mg & 200 mg tablet strengths for use in opioid-tolerant patients only
Product-specific safety concerns	• None

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Tapentadol (Nucynta ER)

ER Tablets 50 mg, 100 mg, 150 mg, 200 mg, 250 mg

Dosing interval	• Every 12 h
Key instructions	• 50 mg every 12 h is initial dose in opioid non-tolerant patients • Titrate by 50 mg increments using minimum of 3-d intervals • MDD: 500 mg • Swallow tablets whole (do not chew, crush, or dissolve) • Take 1 tablet at a time w/ enough water to ensure complete swallowing immediately after placing in mouth • Dose once/d in moderate hepatic impairment (100 mg/d max) • Avoid use in severe hepatic & renal impairment
Drug interactions	• Alcoholic beverages or medications w/ alcohol may result in rapid release & absorption of a potentially fatal dose of tapentadol • Contraindicated in patients taking MAOIs
Opioid-tolerant	• No product-specific considerations
Product-specific safety concerns	• Risk of serotonin syndrome • Angio-edema
Relative potency: oral morphine	• Equipotency to oral morphine has not been established

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Oxymorphone Hydrochloride (Opana ER)

ER Tablets 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg

Dosing interval	• Every 12 h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing
Key instructions	• Use 5 mg every 12 h as initial dose in opioid non-tolerant patients & patients w/ mild hepatic impairment & renal impairment (creatinine clearance <50 mL/min) & patients >65 yrs • Swallow tablets whole (do not chew, crush, or dissolve) • Take 1 tablet at a time, w/ enough water to ensure complete swallowing immediately after placing in mouth • Titrate in increments of 5-10 mg using a minimum of 3-7 d intervals • Contraindicated in moderate & severe hepatic impairment
Drug interactions	• Alcoholic beverages or medications w/ alcohol may result in absorption of a potentially fatal dose of oxymorphone
Opioid-tolerant	• No product-specific considerations
Product-specific safety concerns	• Use with caution in patients who have difficulty swallowing or underlying GI disorders that may predispose to obstruction (e.g. small gastrointestinal lumen)
Relative potency: oral morphine	• Approximately 3:1 oral morphine to oxymorphone oral dose ratio

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Oxycodone Hydrochloride (OxyContin)

NEW DOSING INFO

ER Tablets 10mg, 15mg, 20,mg, 30mg, 40mg, 60mg and 80 mg

Dosing interval	• Every 12 h
Key instructions	• Initial dose in opioid-naïve and non-tolerant patients: 10 mg every 12 h • Titrate using a minimum of 1-2 d intervals • Hepatic impairment: start w/ ⅓-½ usual dosage • Renal impairment (creatinine clearance <60 mL/min): start w/ ½ usual dosage • Consider other analgesics in patients w/ difficulty swallowing or underlying GI disorders that predispose to obstruction. Swallow tablets whole (do not chew, crush, or dissolve) • Take 1 tablet at a time, w/ enough water to ensure complete swallowing immediately after placing in mouth
Drug interactions	• CYP3A4 inhibitors may increase oxycodone exposure • CYP3A4 inducers may decrease oxycodone exposure
Opioid-tolerant	• For Adults: Single dose >40 mg or total daily dose >80 mg for use in opioid-tolerant patients only
Product-specific safety concerns	• Choking, gagging, regurgitation, tablets stuck in throat, difficulty swallowing tablet • Contraindicated in patients w/ GI obstruction
Relative potency: oral morphine	• Approximately 2:1 oral morphine to oxycodone oral dose ratio

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Oxycodone Hydrochloride (OxyContin) *continued*

IMPORTANT

ER Tablets 10mg, 15mg, 20,mg, 30mg, 40mg, 60mg and 80 mg

Key instructions	**For Adults**: • Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in adult patients in whom tolerance to an opioid of comparable tolerance has been established. • When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose. **For Pediatric Patients (11 years and older):** • For use only in opioid tolerant pediatric patients already receiving and tolerating opioids for at least five (5) consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least 2 days immediately preceding dosing with Oxycodon ER. Renal impairment (creatinine clearance <60 mL/min): start w/ ½ usual dosage • If needed, pediatric dose may be adjusted in 1 to 2 day intervals. • When a dose increase is clinically indicated, the total daily oxycodone dose usually can be increased by 25% of the current daily dose.
IMPORTANT:	• Opioids are rarely indicated or used to treat pediatric patients with chronic pain. • The recent FDA approval for this oxycodone formulation was NOT intended to increase prescribing or use of this drug in pediatric pain treatment. Review the product information and adhere to best practices in the literature.

Oxycodone Hydrochloride/Naloxone Hydrochloride (Targiniq ER)

ER Tablets 10 mg/5mg, 20 mg/10mg, 40 mg/20mg

Dosing interval	• Every 12 h
Key instructions	• Opioid-naïve patients: initiate treatment w/ 10mg/5mg every 12 h • Titrate using min of 1-2 d intervals • Do not exceed 80 mg/40 mg total daily dose (40 mg/20 mg q12h) • May be taken w/ or without food • Swallow whole. Do not chew, crush, split, or dissolve: this will release oxycodone (possible fatal overdose) & naloxone (possible withdrawal) • Hepatic impairment: contraindicated in moderate-severe impairment. In patients w/ mild impairment, start w/ ½-½ usual dosage • Renal impairment (creatinine clearance <60 mL/min): start w/ ½ usual dosage
Drug interactions	• CYP3A4 inhibitors may increase oxycodone exposure • CYP3A4 inducers may decrease oxycodone exposure
Opioid-tolerant	• Single dose >40 mg/20 mg or total daily dose of 80 mg/40 mg for opioid-tolerant patients only
Product-specific safety concerns	• Contraindicated in patients w/ moderate-severe hepatic impairment
Relative potency: oral morphine	• See individual PI for conversion recommendations from prior opioids

Oxycodone Hydrochloride/Naltrexone Hydrochloride (Troxyca ER)

ER Capsules 10/1.2mg, 20/2.4mg, 30/3.6mg, 40/4.8mg, 60/7.2mg, 80/9.6mg

Dosing interval	• Every 12 h
Key instructions	• Opioid-naïve & non-tolerant patient is 10/1.2mg, every 12h • Total daily dose may be adjusted by 20/2.4 mg every 2-3 d • Swallow capsules whole (do not chew, crush, or dissolve); possible fatal overdose, and naltrexone (possible withdrawal) • May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately • Do not administer through NG or G tube
Drug interactions	• CYP3A4 inhibitors may increase hydrocodone exposure • CYP3A4 inducers may decrease hydrocodone exposure
Opioid-tolerant	• Single dose >40/4.8mg or total daily dose >80/9.6mg for use in opioid-tolerant patients only
Product-specific safety concerns	• None
Relative potency: oral morphine	• See individual product information for conversion recommendations from prior opioid

Hydrocodone Bitartrate (Vantrela ER)

ER Tablets 15 mg, 30 mg, 45 mg, 60 mg, 90 mg

Dosing interval	• Every 12 h
Key instructions	• Initial dose in opioid naïve and non-tolerant patient is 15 mg every 12 h. Dose can be increased to next higher dose every 3-7 d • Swallow capsules whole (do not chew, crush, or dissolve) • Mild or moderate hepatic and moderate to severe renal impairment: initiate therapy with ½ recommended initial dose. If a dose <15 mg needed, use alternative options
Drug interactions	• CYP3A4 inhibitors may increase hydrocodone exposure • CYP3A4 inducers may decrease hydrocodone exposure
Opioid-tolerant	• A 90 mg tablet, a single dose greater than 60 mg, or a total daily dose >120 mg are for use in opioid-tolerant patients only
Product-specific safety concerns	• None
Relative potency: oral morphine	• See individual product information for conversion recommendations from prior opioid

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Oxycodone (Xtampza ER)

ER Capsules 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg

Dosing interval	• Every 12 h
Key instructions	• Opioid naïve and non-tolerant, initiate with 9 mg every 12 h • Titrate using a minimum of 1-2 d intervals • Take with same amt of food in order to ensure consistent plasma levels • Maximum daily dose: 288 mg (8 x 36 mg), safety of excipients not established for higher doses • May open capsule & sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately • May also be administered through a NG or G feeding tube • Hepatic impairment: initiate therapy at 1/3 to ½ usual dose • Renal impairment: creatinine clearance <60 mL/min, follow conservative approach
Drug interactions	• CYP3A4 inhibitors may increase hydrocodone exposure • CYP3A4 inducers may decrease hydrocodone exposure
Opioid-tolerant	• A single dose >36 mg or a total daily dose >72 mg for opioid-tolerant patients only
Product-specific safety concerns	• None
Relative potency: oral morphine	• There are no established conversion ratios for Xtampza ER, defined by clinical trials

Naloxone (Narcan)

Dosing interval	• IM or SQ: onset 2-5 minutes, duration >45 min • IV: onset 1-2 min, duration 45 minutes • IN: onset 2-3 min, duration ~ 2 hours
Key instructions	• Monitor respiratory rate • Monitor level of consciousness for 3-4 hours after expected peak of blood concentrations • Note that reversal of analgesia will occur
Drug interactions	• Larger doses required to reverse effects of buprenorphine, butorphanol, nalbuphine, or pentazocine
Opioid-tolerant	• Assess signs and symptoms of opioid withdrawal, may occur w-i 2 min – 2 hrs • Vomiting, restlessness, abdominal cramps, increased BP, temperature • Severity depends on naloxone dose, opioid involved & degree of dependence
Product-specific safety concerns	• Ventricular arrhythmias, hypertension, hypotension, nausea & vomiting • As naloxone plasma levels decrease, sedation from opioid overdose may increase

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Hydrocodone Bitartrate (Zohydro ER)

ER Capsules 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg

Dosing interval	• Every 12 h
Key instructions	• Initial dose in opioid non-tolerant patient is 10 mg • Titrate in increments of 10 mg using a min of 3-7 d intervals • Swallow capsules whole (do not chew, crush, or dissolve)
Drug interactions	• Alcoholic beverages or medications containing alcohol may result in rapid release & absorption of a potentially fatal dose of hydrocodone • CYP3A4 inhibitors may increase hydrocodone exposure • CYP3A4 inducers may decrease hydrocodone exposure
Opioid-tolerant	• Single dose >40 mg or total daily dose >80 mg for use in opioid-tolerant patients only
Product-specific safety concerns	• None
Relative potency: oral morphine	• Approximately 1.5:1 oral morphine to hydrocodone oral dose ratio

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Appendix 2. Detailed Disclosure Information for CO*RE Staff and Faculty

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The following individuals disclose no relevant financial relationships:

Faculty Advisory Panel & Reviewer COI

Faculty Advisory Panel	Affiliation
David Bazzo, MD	Clinical Professor of Family Medicine, University of California San Diego, School of Medicine
Ron Crossno, MD	Vice President, Medical Affairs and Chief Medical Officer at Kindred at Home
Katherine Galluzzi, DO	Professor and Chair, Department of Geriatrics, Philadelphia College of Osteopathic Medicine
Carol Havens, MD	Director of Physician Education and Development, Kaiser Permanente, Northern California
Randall Steven Hudspeth PhD, MBA, MS, APRN-CNP, FRE, FAANP	Practice and Regulation Consultant in Advanced Practice Pain Management and Palliative Care
Dennis Rivenburgh, MS, ATC, PA-C, DFAAPA	Physician Assistant, LifeBridge Health Sports Medicine Institute
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Edwin A. Salsitz, MD, DFASAM	Mount Sinai Beth Israel Medical Center, Division of Chemical Dependency; Assistant Professor, Icahn School of Medicine at Mount Sinai
Seddon R. Savage, MD	Associate Professor, Geisel School of Medicine, Dartmouth College, Director Dartmouth Center on Addiction Recovery and Education

External / Consulting Reviewers	Affiliation
Roberto Cardarelli, DO, MPH	Professor, Department of Family and Community Medicine, University of Kentucky College of Medicine
Marcia Jackson, PhD	CME by Design

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The following individuals disclose no relevant financial relationships:

CO*RE Partner Staff COI

Staff Person	Partner Affiliation
Julie Bruno	American Academy of Hospice and Palliative Medicine
Michele McKay Anne Norman	American Association of Nurse Practitioners
Marie-Michèle Léger Eric Peterson	American Academy of Physician Assistants
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Pam Jenkins Phyllis Zimmer	Nurse Practitioner Healthcare Foundation
Tom McKeithen Chris Larrison	Healthcare Performance Consulting

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The following individuals disclose no relevant financial relationships:

CO*RE Operations Organizations

Staff Person	Affiliation
Cynthia Kear	Cynthia Kear, LLC
Katie Detzler	Forefront Collaborative
Sheila Robertson	
Robin Heyden Neil Heyden	Heyden Ty, LLC

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