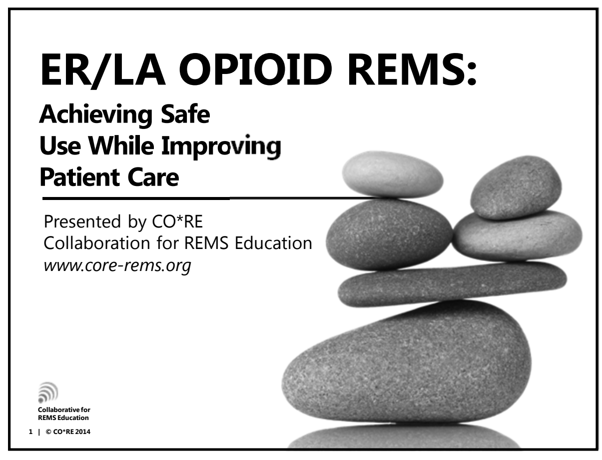

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CORE
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On July 9, 2012, the Food and Drug Administration (FDA) approved a Risk Evaluation and Mitigation Strategy (REMS) for extended-release (ER) and long-acting (LA) opioid medications.

Founded in June, 2010, the Collaborative on REMS Education (CO*RE), a multi disciplinary team of 10 partners and 3 cooperating organizations, has designed a core curriculum based on needs assessment, practice gaps, clinical competencies, and learner self-assessment to meet the requirements of the FDA REMS Blueprint.

www.core-rems.org

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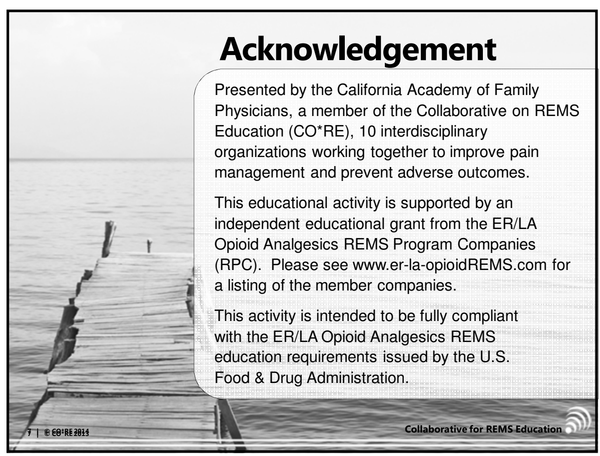
Acknowledgement
Presented by the California Academy of Family Physicians, a member of the Collaborative on REMS Education (CO*RE), 10 interdisciplinary organizations working together to improve pain management and prevent adverse outcomes.
This educational activity is supported by an independent educational grant from the ER/LA Opioid Analgesics REMS Program Companies (RPC). Please see www.er-la-opioidREMS.com for a listing of the member companies.
This activity is intended to be fully compliant with the ER/LA Opioid Analgesics REMS education requirements issued by the U.S. Food & Drug Administration.
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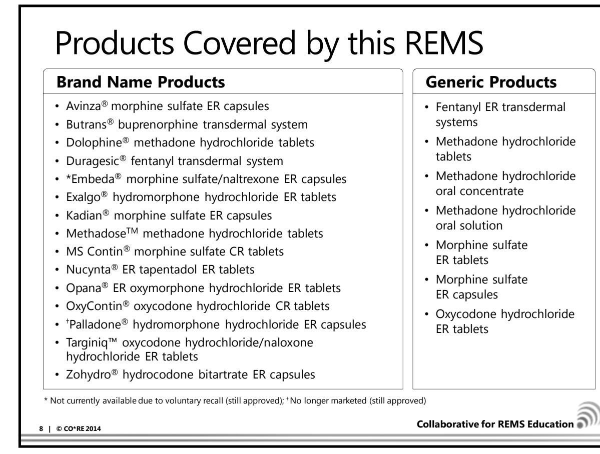
Products Covered by this REMS
Brand Name Products
• Avinza® morphine sulfate ER capsules
• Butrans® buprenorphine transdermal system
• Dolophine® methadone hydrochloride tablets
• Duragesic® fentanyl transdermal system
• *Embeda® morphine sulfate/naltrexone ER capsules
• Exalgo® hydromorphone hydrochloride ER tablets
• Kadian® morphine sulfate ER capsules
• Methadose™ methadone hydrochloride tablets
• MS Contin® morphine sulfate CR tablets
• Nucynta® ER tapentadol ER tablets
• Opana® ER oxymorphone hydrochloride ER tablets
• OxyContin® oxycodone hydrochloride CR tablets
• †Palladone® hydromorphone hydrochloride ER capsules
• Targiniq™ oxycodone hydrochloride/naloxone hydrochloride ER tablets
• 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
* Not currently available due to voluntary recall (still approved); † No longer marketed (still approved)
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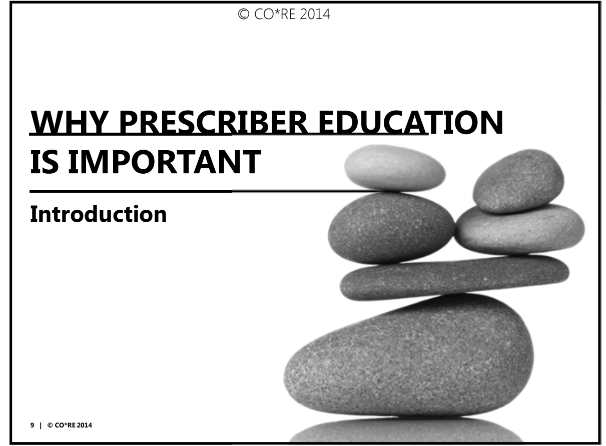
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WHY PRESCRIBER EDUCATION IS IMPORTANT
Introduction
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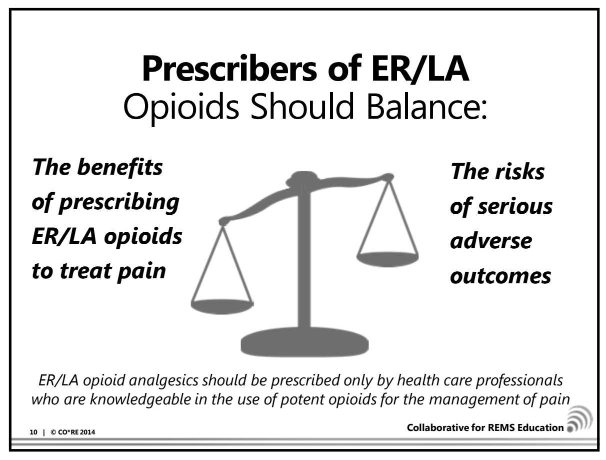
Prescribers of ER/LA Opioids Should Balance:
The benefits of prescribing ER/LA opioids to treat pain
The risks of serious adverse outcomes
ER/LA opioid analgesics should be prescribed only by health care professionals who are knowledgeable in the use of potent opioids for the management of pain
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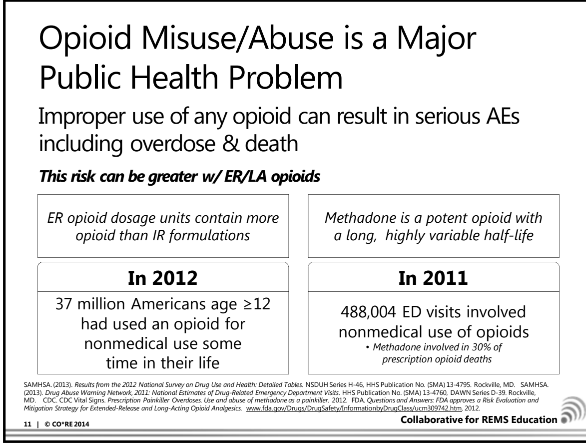
Opioid Misuse/Abuse is a Major Public Health Problem
Improper use of any opioid can result in serious AEs including overdose & death
This risk can be greater w/ ER/LA opioids
ER opioid dosage units contain more opioid than IR formulations
Methadone is a potent opioid with a long, highly variable half-life
In 2012
37 million Americans age ≥12 had used an opioid for nonmedical use some time in their life
In 2011
488,004 ED visits involved nonmedical use of opioids
• Methadone involved in 30% of prescription opioid deaths
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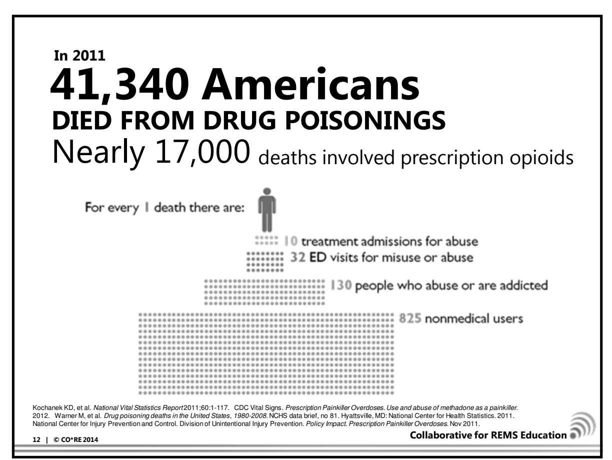
In 2011
41,340 Americans
DIED FROM DRUG POISONINGS
Nearly 17,000 deaths involved prescription opioids
For every 1 death there are:
10 treatment admissions for abuse
32 ED visits for misuse or abuse
130 people who abuse or are addicted
825 nonmedical users
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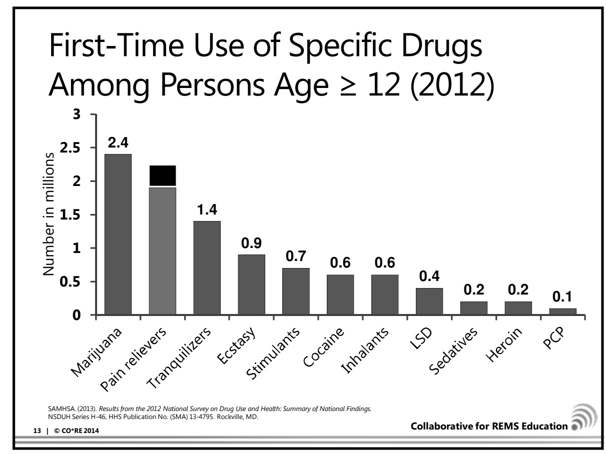

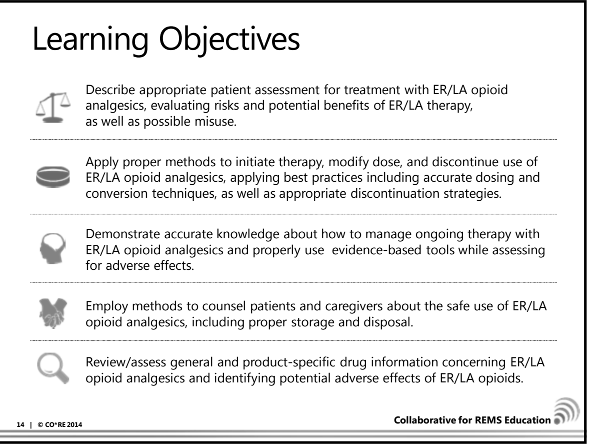

Misuse, abuse, divergence and overdose of ER/LA opioids is a major public health crisis.

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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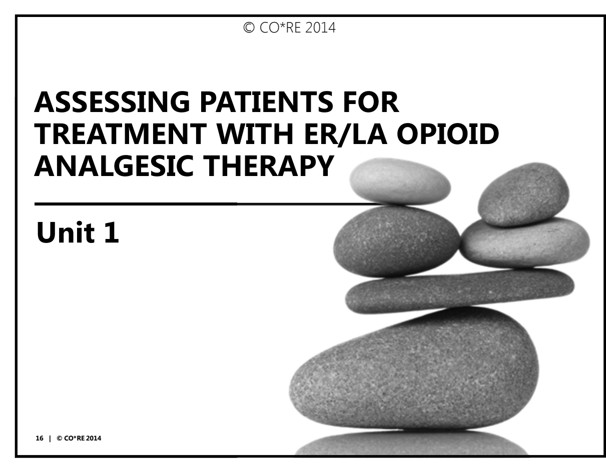

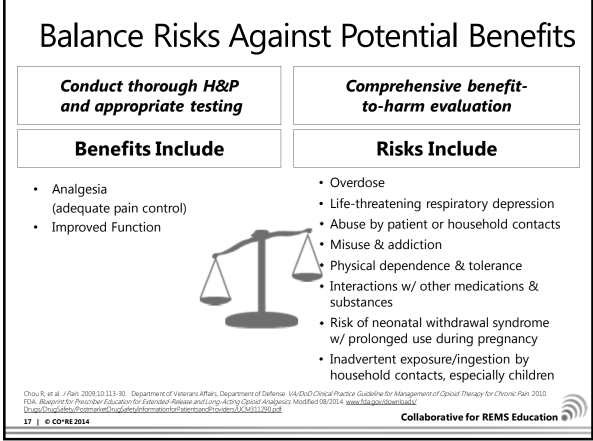

Adequately **DOCUMENT** all patient interactions, assessments, test results, & treatment plans

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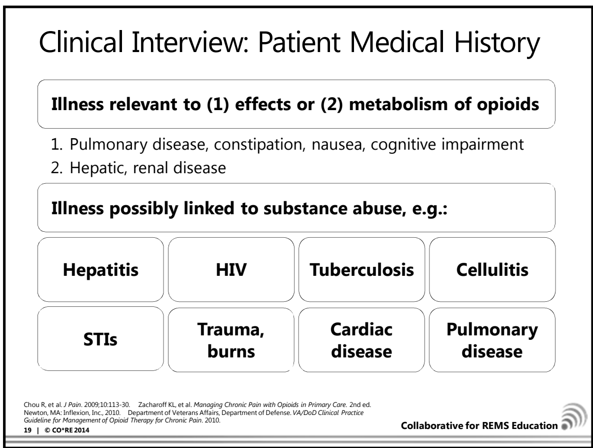

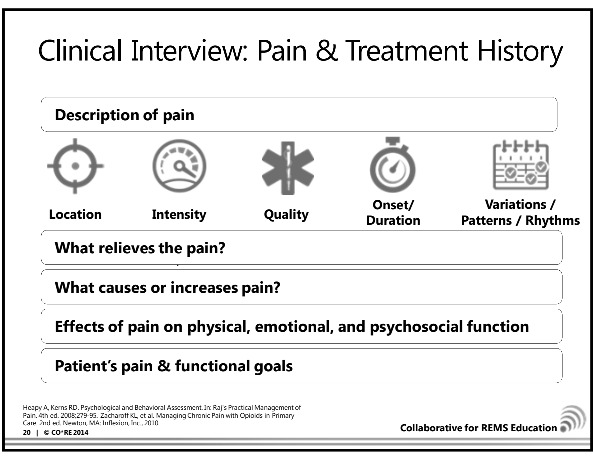

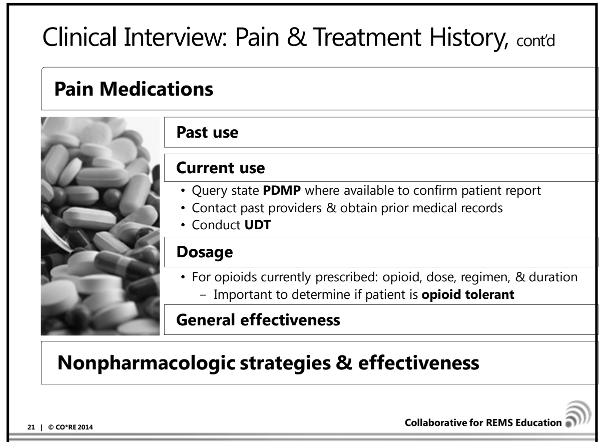

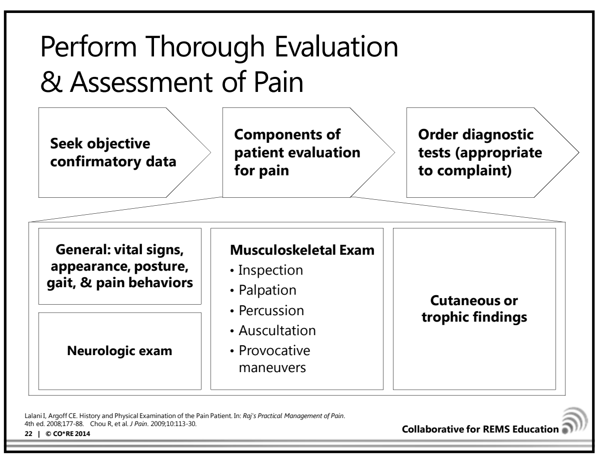

Assess Risk of Abuse, Including Substance Use & Psychiatric Hx

Obtain a complete Hx of current & past substance use

- Prescription drugs
- Illegal substances
- Alcohol & tobacco
  - Substance abuse Hx does not prohibit treatment w/ ER/LA opioids but may require additional monitoring & expert consultation/referral
- Family Hx of substance abuse & psychiatric disorders
- Hx of sexual abuse

Social history also relevant

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

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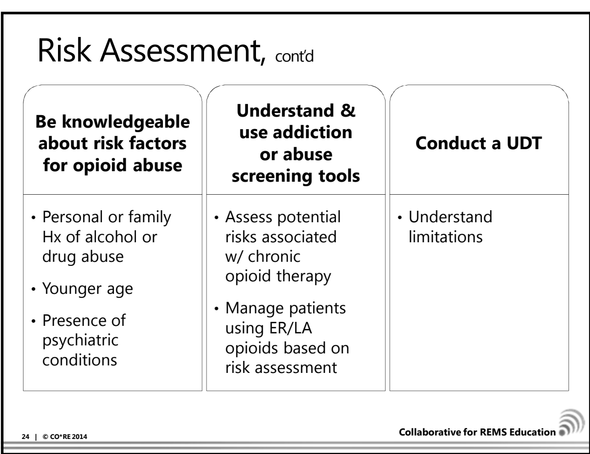

Risk Assessment Tools: Examples

Tool	# of items	Administered By
Patients considered for long-term opioid therapy:		
ORT Opioid Risk Tool	5	patient
SOAPP® Screener & Opioid Assessment for Patients w/ Pain	24, 14, & 5	patient
DIRE Diagnosis, Intractability, Risk, & Efficacy Score	7	clinician
Characterize misuse once opioid treatments 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, Adjusted to Include Drugs	4	clinician
RAFFT Relax, Alone, Friends, Family, Trouble	5	patient
DAST Drug Abuse Screening Test	28	patient
SBIRT Screening, Brief Intervention, & Referral to Treatment	Varies	clinician

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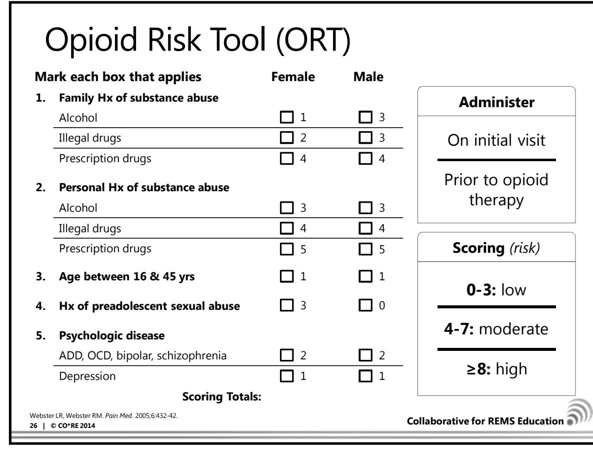

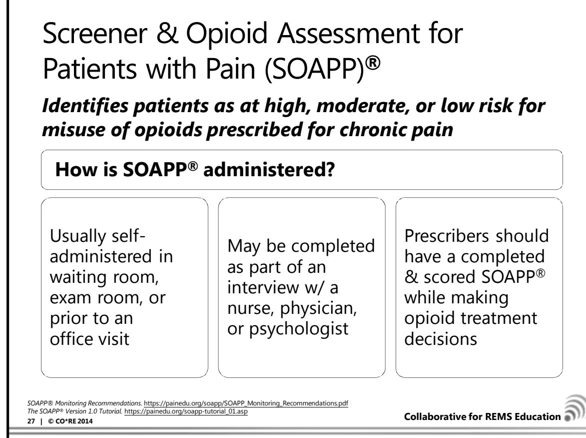

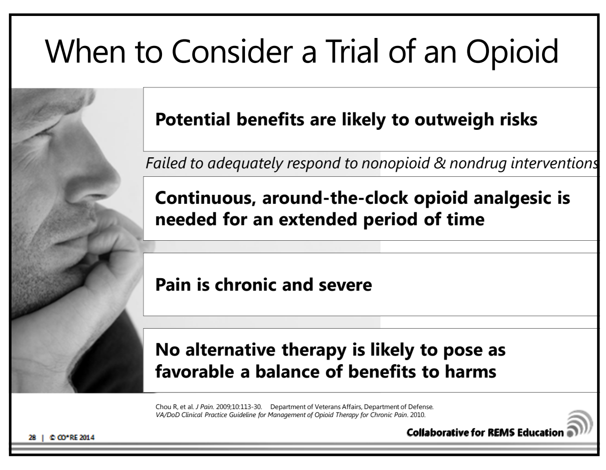

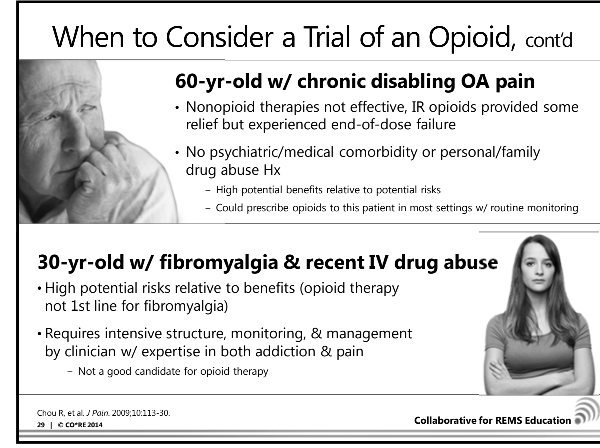

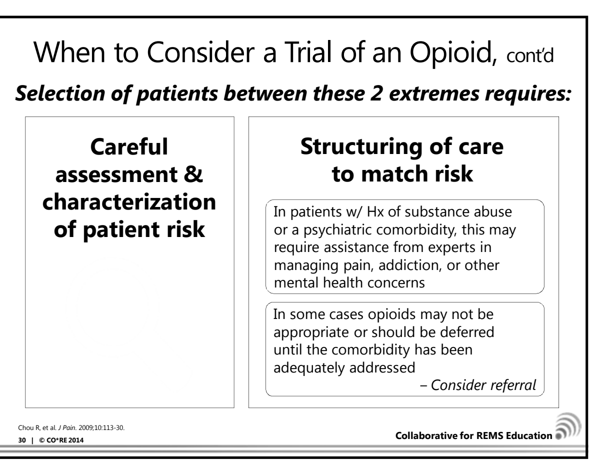

Referring High-Risk Patients
Prescribers should
Understand when to appropriately refer high-risk patients to pain management or addiction specialists
Also check your state regulations for requirements
Chou R, et al. J Pain. 2009;10:113-30.
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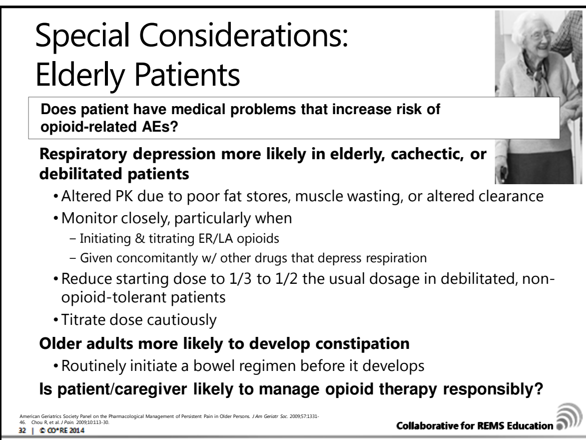
Special Considerations: Elderly Patients
Does patient have medical problems that increase risk of opioid-related AEs?
Respiratory depression more likely in elderly, cachectic, or debilitated patients
• Altered PK due to poor fat stores, muscle wasting, or altered clearance
• Monitor closely, particularly when
– Initiating & titrating ER/LA opioids
– Given concomitantly w/ other drugs that depress respiration
• Reduce starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients
• Titrate dose cautiously
Older adults more likely to develop constipation
• Routinely initiate a bowel regimen before it develops
Is patient/caregiver likely to manage opioid therapy responsibly?
American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. J Am Geriatr Soc. 2009;57:1331-46. Chou R, et al. J Pain. 2009;10:113-30.
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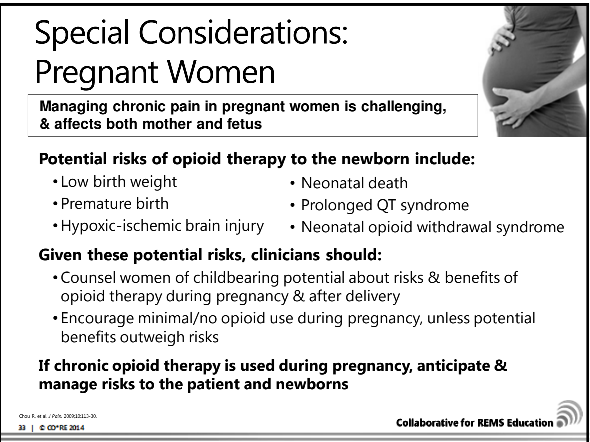
Special Considerations: Pregnant Women
Managing chronic pain in pregnant women is challenging, & affects both mother and fetus
Potential risks of opioid therapy to the newborn include:
• Low birth weight
• Premature birth
• Hypoxic-ischemic brain injury
• Neonatal death
• Prolonged QT syndrome
• Neonatal opioid withdrawal syndrome
Given these potential risks, clinicians should:
• Counsel women of childbearing potential about risks & benefits of opioid therapy during pregnancy & after delivery
• Encourage minimal/no opioid use during pregnancy, unless potential benefits outweigh risks
If chronic opioid therapy is used during pregnancy, anticipate & manage risks to the patient and newborns
Chou R, et al. J Pain. 2009;10:113-30.
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Special Considerations: Children (<18 years)
Safety & effectiveness of most ER/LA opioids unestablished
Pediatric analgesic trials pose challenges
Transdermal fentanyl approved in children aged ≥2 yrs
Most opioid studies focus on inpatient safety
Opioids are common sources of drug error
Opioid indications are primarily life-limiting conditions
Few children with chronic pain due to non-life-limiting conditions should receive opioids
When prescribing opioids to children:
Consult pediatric palliative care team or pediatric pain specialist or refer to a specialized multidisciplinary pain clinic
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.
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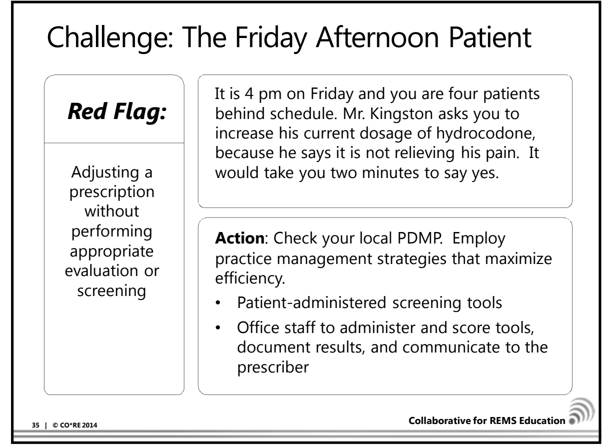
Challenge: The Friday Afternoon Patient
Red Flag:
Adjusting a prescription without performing appropriate evaluation or screening
It is 4 pm on Friday and you are four patients behind schedule. Mr. Kingston asks you to increase his current dosage of hydrocodone, because he says it is not relieving his pain. It would take you two minutes to say yes.
Action: Check your local PDMP. Employ practice management strategies that maximize efficiency.
• Patient-administered screening tools
• Office staff to administer and score tools, document results, and communicate to the prescriber
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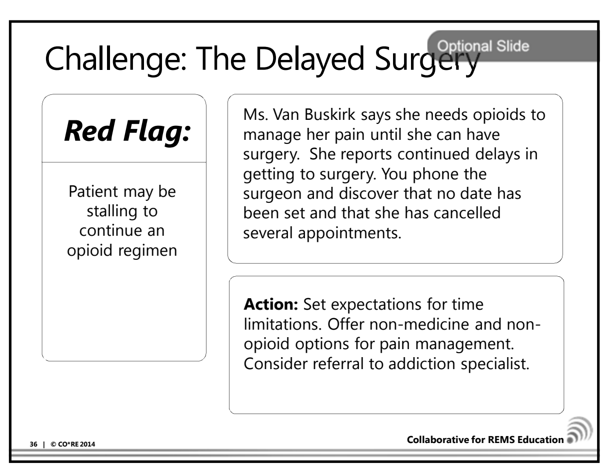
Challenge: The Delayed Surgery
Optional Slide
Red Flag:
Patient may be stalling to continue an opioid regimen
Ms. Van Buskirk says she needs opioids to manage her pain until she can have surgery. She reports continued delays in getting to surgery. You phone the surgeon and discover that no date has been set and that she has cancelled several appointments.
Action: Set expectations for time limitations. Offer non-medicine and non-opioid options for pain management. Consider referral to addiction specialist.
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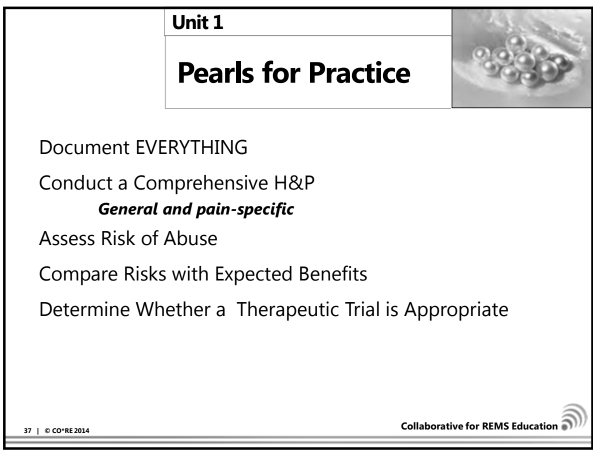
Unit 1
Pearls for Practice
Document EVERYTHING
Conduct a Comprehensive H&P
General and pain-specific
Assess Risk of Abuse
Compare Risks with Expected Benefits
Determine Whether a Therapeutic Trial is Appropriate
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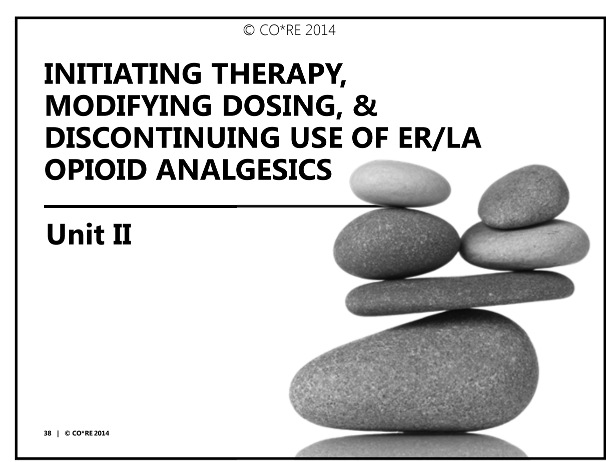
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INITIATING THERAPY, MODIFYING DOSING, & DISCONTINUING USE OF ER/LA OPIOID ANALGESICS
Unit II
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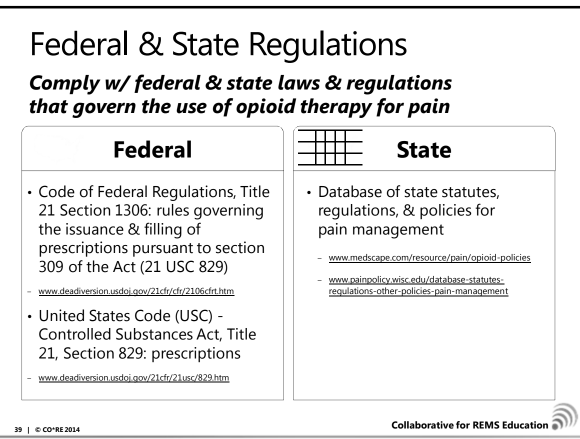
Federal & State Regulations
Comply w/ federal & state laws & regulations that govern the use of opioid therapy for pain
Federal
• Code of Federal Regulations, Title 21 Section 1306: rules governing the issuance & filling of prescriptions pursuant to section 309 of the Act (21 USC 829)
– www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm
• 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, & 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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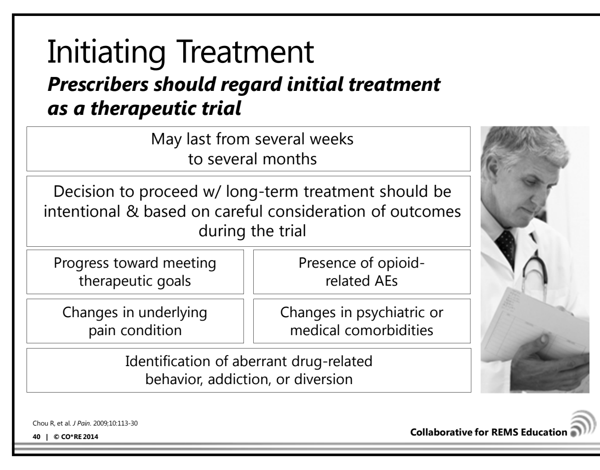
Initiating Treatment
Prescribers should regard initial treatment as a therapeutic trial
May last from several weeks to several months
Decision to proceed w/ long-term treatment should be intentional & based on careful consideration of outcomes during the trial
Progress toward meeting therapeutic goals
Presence of opioid-related AEs
Changes in underlying pain condition
Changes in psychiatric or medical comorbidities
Identification of aberrant drug-related behavior, addiction, or diversion
Chou R, et al. J Pain. 2009;10:113-30
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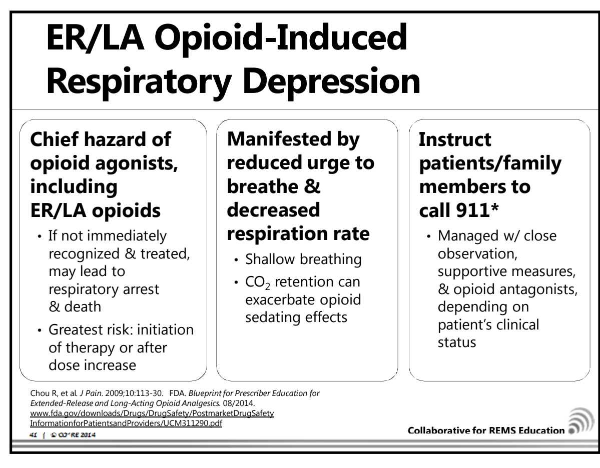
ER/LA Opioid-Induced Respiratory Depression
Chief hazard of opioid agonists, including ER/LA opioids
• If not immediately recognized & treated, may lead to respiratory arrest & death
• Greatest risk: initiation of therapy or after dose increase
Manifested by reduced urge to breathe & decreased respiration rate
• Shallow breathing
• CO2 retention can exacerbate opioid sedating effects
Instruct patients/family members to call 911*
• Managed w/ close observation, supportive measures, & opioid antagonists, depending on patient's clinical status
Chou R, et al. J Pain. 2009;10:113-30. FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 08/2014.
www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf
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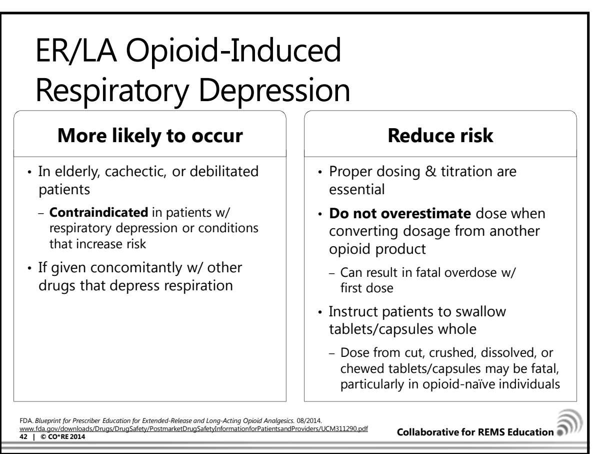
ER/LA Opioid-Induced Respiratory Depression
More likely to occur
• In elderly, cachectic, or debilitated patients
– Contraindicated in patients w/ respiratory depression or conditions that increase risk
• If given concomitantly w/ other drugs that depress respiration
Reduce risk
• Proper dosing & titration are essential
• Do not overestimate dose when converting dosage from another opioid product
– Can result in fatal overdose w/ 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
FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 08/2014.
www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf
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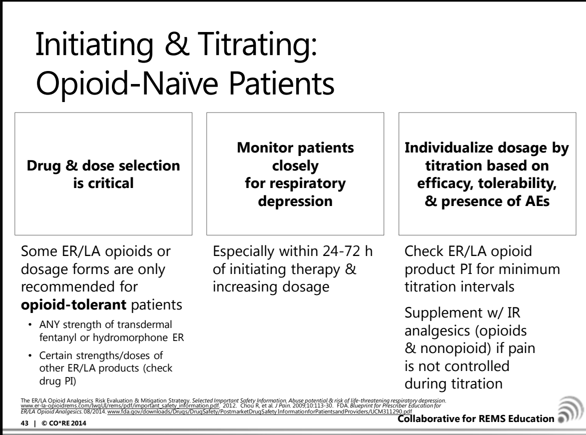

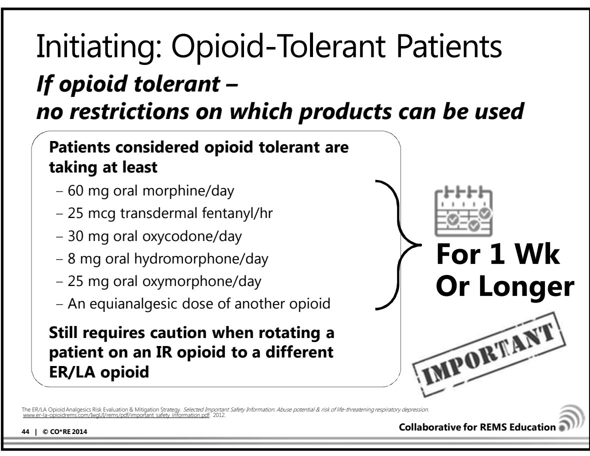

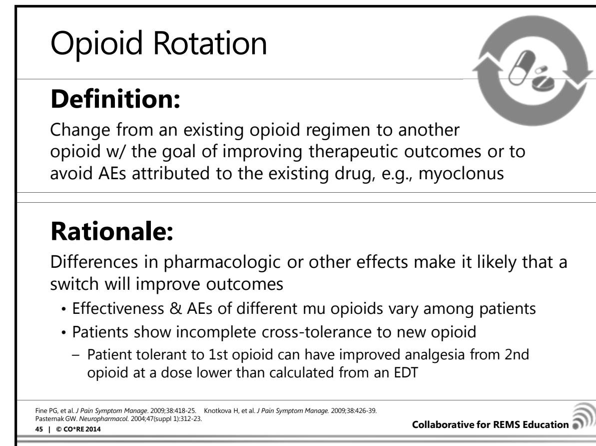

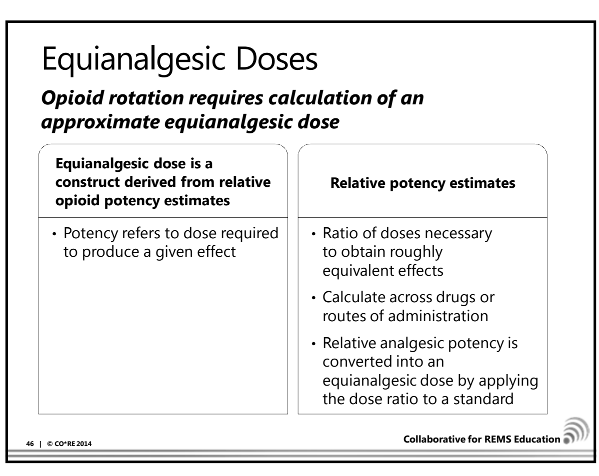

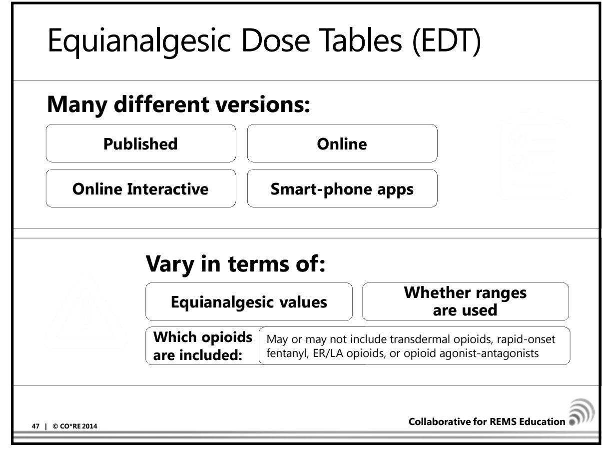

Example of an EDT for Adults

	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 – 2.5mg)	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 (⇔0.2mg)	1-2 mg q3-4hr (⇔0.5-1 mg)

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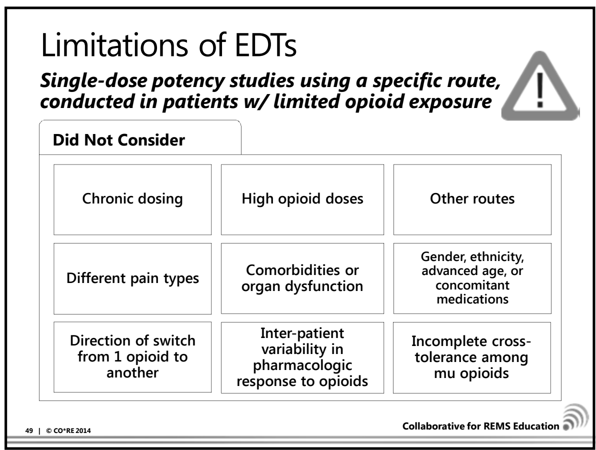
Limitations of EDTs
Single-dose potency studies using a specific route, conducted in patients w/ limited opioid exposure
Did Not Consider
Chronic dosing
High opioid doses
Other routes
Different pain types
Comorbidities or organ dysfunction
Gender, ethnicity, advanced age, or concomitant medications
Direction of switch from 1 opioid to another
Inter-patient variability in pharmacologic response to opioids
Incomplete cross-tolerance among mu opioids
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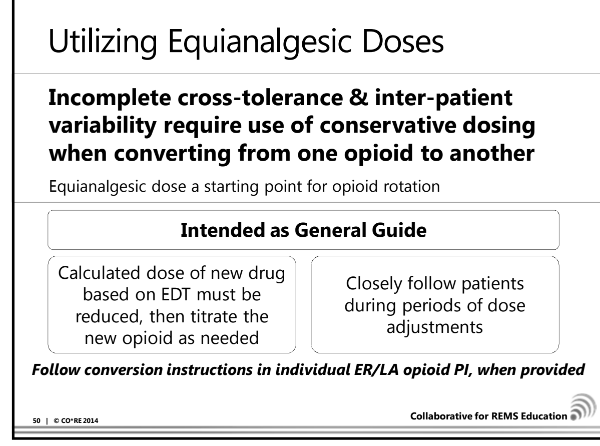
Utilizing Equianalgesic Doses
Incomplete cross-tolerance & inter-patient variability require use of conservative dosing when converting from one opioid to another
Equianalgesic dose a starting point for opioid rotation
Intended as General Guide
Calculated dose of new drug based on EDT must be reduced, then titrate the new opioid as needed
Closely follow patients during periods of dose adjustments
Follow conversion instructions in individual ER/LA opioid PI, when provided
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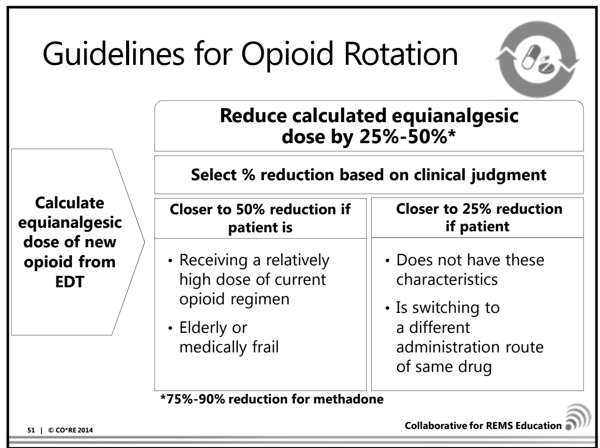
Guidelines for Opioid Rotation
Calculate equianalgesic dose of new opioid from EDT
Reduce calculated equianalgesic dose by 25%-50%*
Select % reduction based on clinical judgment
Closer to 50% reduction if patient is
• Receiving a relatively high dose of current opioid regimen
• Elderly or medically frail
Closer to 25% reduction if patient
• Does not have these characteristics
• Is switching to a different administration route of same drug
*75%-90% reduction for methadone
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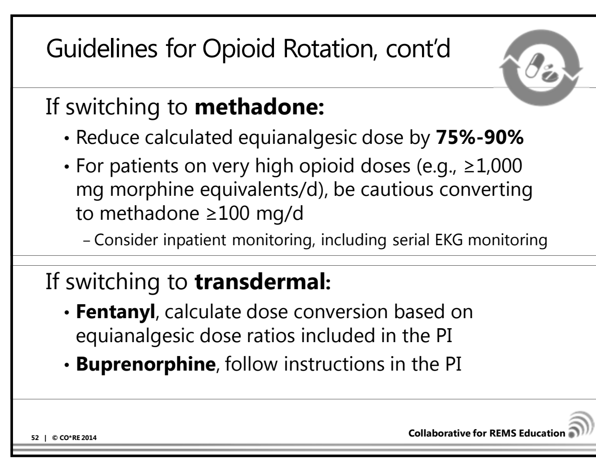
Guidelines for Opioid Rotation, cont'd
If switching to methadone:
• Reduce calculated equianalgesic dose by 75%-90%
• For patients on very high opioid doses (e.g., ≥1,000 mg morphine equivalents/d), be cautious converting to methadone ≥100 mg/d
– Consider inpatient monitoring, including serial EKG monitoring
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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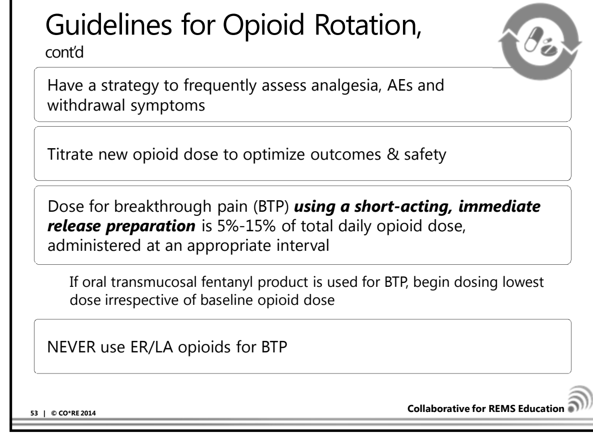
Guidelines for Opioid Rotation, cont'd
Have a strategy to frequently assess analgesia, AEs and withdrawal symptoms
Titrate new opioid dose to optimize outcomes & safety
Dose for breakthrough pain (BTP) using a short-acting, immediate release preparation is 5%-15% of total daily opioid dose, administered at an appropriate interval
If oral transmucosal fentanyl product is used for BTP, begin dosing lowest dose irrespective of baseline opioid dose
NEVER use ER/LA opioids for BTP
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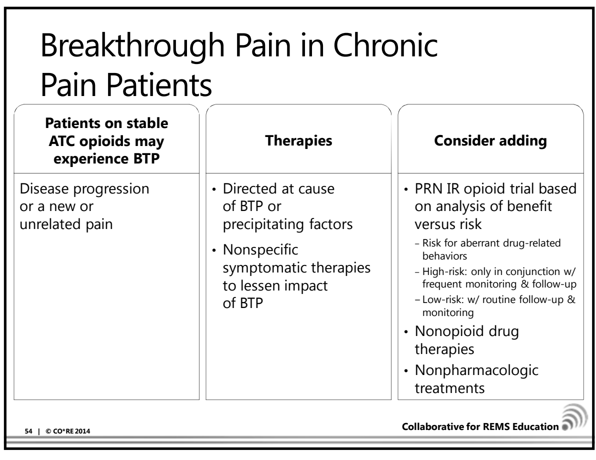
Breakthrough Pain in Chronic Pain Patients
Patients on stable ATC opioids may experience BTP
Therapies
Consider adding
Disease progression or a new or unrelated pain
• Directed at cause of BTP or precipitating factors
• Nonspecific symptomatic therapies to lessen impact of BTP
• PRN IR opioid trial based 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
• Nonopioid drug therapies
• Nonpharmacologic treatments
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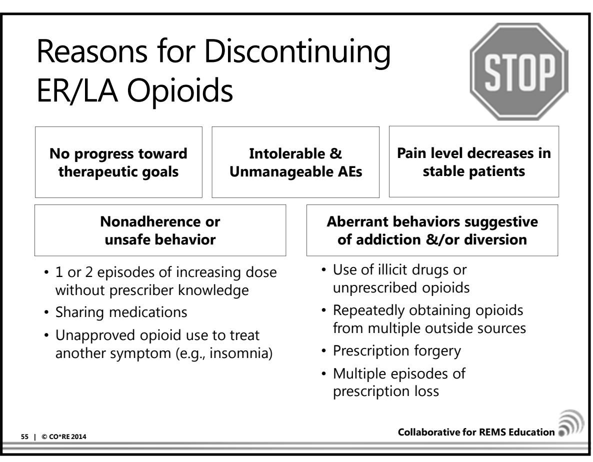
Reasons for Discontinuing ER/LA Opioids
STOP
No progress toward therapeutic goals
Intolerable & Unmanageable AEs
Pain level decreases in stable patients
Nonadherence or unsafe behavior
• 1 or 2 episodes of increasing dose without prescriber knowledge
• Sharing medications
• Unapproved opioid use to treat another symptom (e.g., insomnia)
Aberrant behaviors suggestive of addiction &/or diversion
• Use of illicit drugs or unprescribed opioids
• Repeatedly obtaining opioids from multiple outside sources
• Prescription forgery
• Multiple episodes of prescription loss
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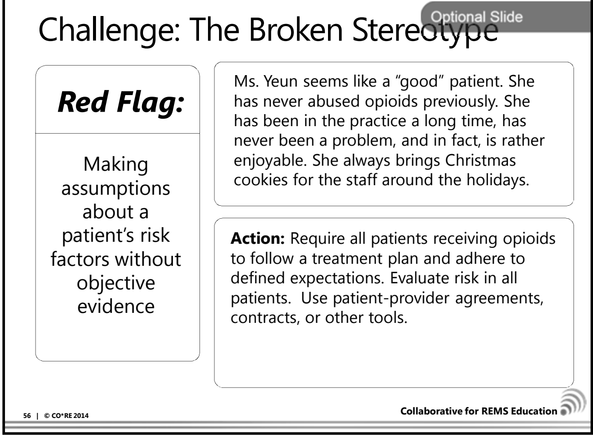
Challenge: The Broken Stereotype
Optional Slide
Red Flag:
Making assumptions about a patient's risk factors without objective evidence
Ms. Yeun seems like a "good" patient. She has never abused opioids previously. She has been in the practice a long time, has never been a problem, and in fact, is rather enjoyable. She always brings Christmas cookies for the staff around the holidays.
Action: Require all patients receiving opioids to follow a treatment plan and adhere to defined expectations. Evaluate risk in all patients. Use patient-provider agreements, contracts, or other tools.
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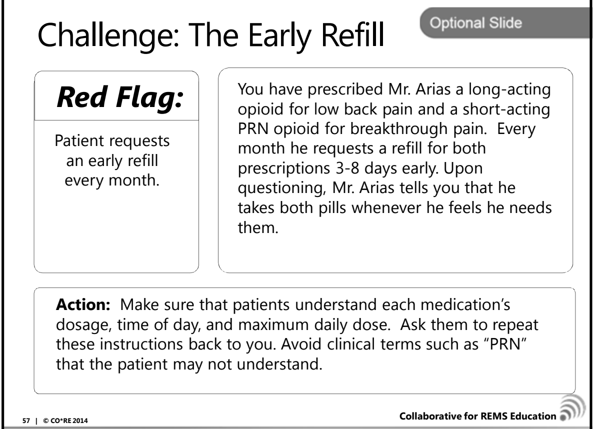
Challenge: The Early Refill
Optional Slide
Red Flag:
Patient requests an early refill every month.
You have prescribed Mr. Arias a long-acting opioid for low back pain and a short-acting PRN opioid for breakthrough pain. Every month he requests a refill for both prescriptions 3-8 days early. Upon questioning, Mr. Arias tells you that he takes both pills whenever he feels he needs them.
Action: Make sure that patients understand each medication's dosage, time of day, and maximum daily dose. Ask them to repeat these instructions back to you. Avoid clinical terms such as "PRN" that the patient may not understand.
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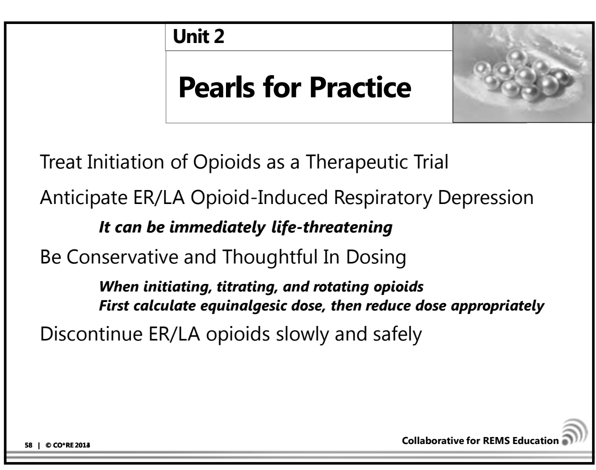
Unit 2
Pearls for Practice
Treat Initiation of Opioids as a Therapeutic Trial
Anticipate ER/LA Opioid-Induced Respiratory Depression
It can be immediately life-threatening
Be Conservative and Thoughtful In Dosing
When initiating, titrating, and rotating opioids
First calculate equinalgesic dose, then reduce dose appropriately
Discontinue ER/LA opioids slowly and safely
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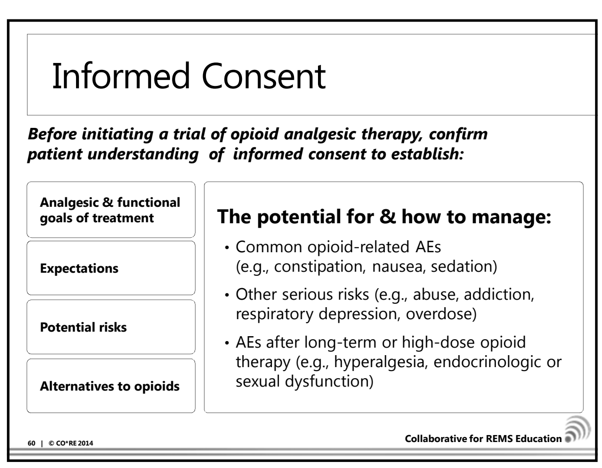
MANAGING THERAPY WITH ER/LA OPIOID ANALGESICS
Unit III


Informed Consent
Before initiating a trial of opioid analgesic therapy, confirm patient understanding of informed consent to establish:
Analgesic & functional goals of treatment
Expectations
Potential risks
Alternatives to opioids
The potential for & how to manage:
• Common opioid-related AEs (e.g., constipation, nausea, sedation)
• Other serious risks (e.g., abuse, addiction, respiratory depression, overdose)
• AEs after long-term or high-dose opioid therapy (e.g., hyperalgesia, endocrinologic or sexual dysfunction)
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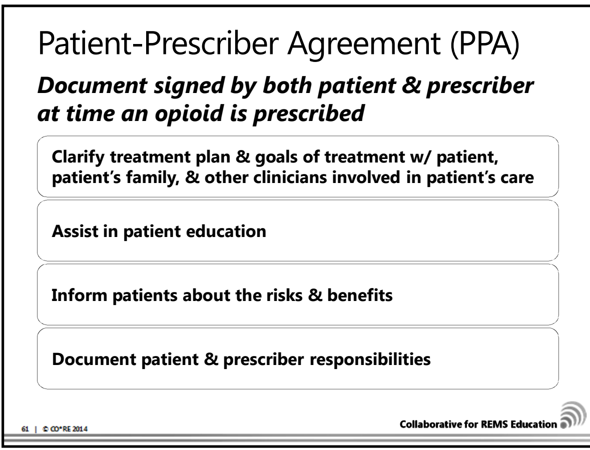
Patient-Prescriber Agreement (PPA)
Document signed by both patient & prescriber at time an opioid is prescribed
Clarify treatment plan & goals of treatment w/ patient, patient's family, & other clinicians involved in patient's care
Assist in patient education
Inform patients about the risks & benefits
Document patient & prescriber responsibilities
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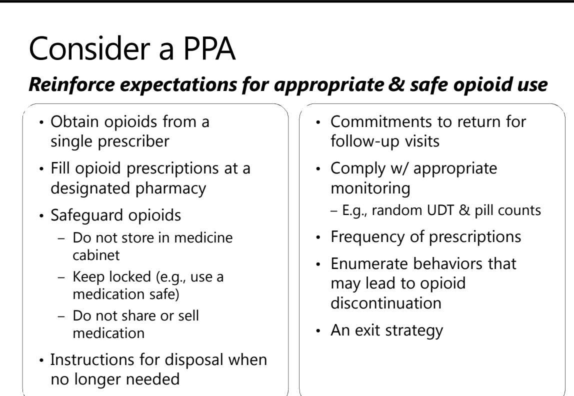
Consider a PPA
Reinforce expectations for appropriate & safe opioid use
Obtain opioids from a single prescriber
Fill opioid prescriptions at a designated pharmacy
Safeguard opioids
Do not store in medicine cabinet
Keep locked (e.g., use a medication safe)
Do not share or sell medication
Instructions for disposal when no longer needed
Commitments to return for follow-up visits
Comply w/ appropriate monitoring
E.g., random UDT & pill counts
Frequency of prescriptions
Enumerate behaviors that may lead to opioid discontinuation
An exit strategy
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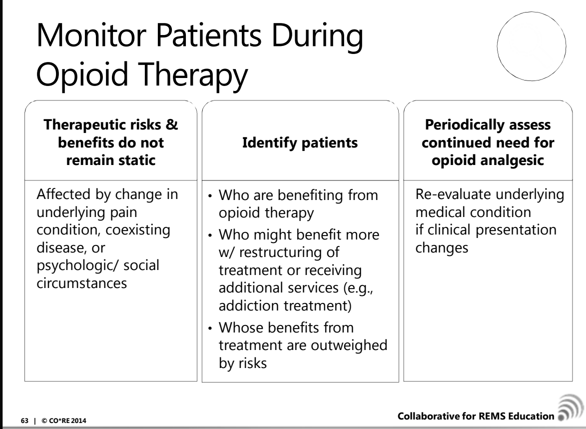
Monitor Patients During Opioid Therapy
Therapeutic risks & benefits do not remain static
Affected by change in underlying pain condition, coexisting disease, or psychologic/ social circumstances
Identify patients
Who are benefiting from opioid therapy
Who might benefit more w/ restructuring of treatment or receiving additional services (e.g., addiction treatment)
Whose benefits from treatment are outweighed by risks
Periodically assess continued need for opioid analgesic
Re-evaluate underlying medical condition if clinical presentation changes
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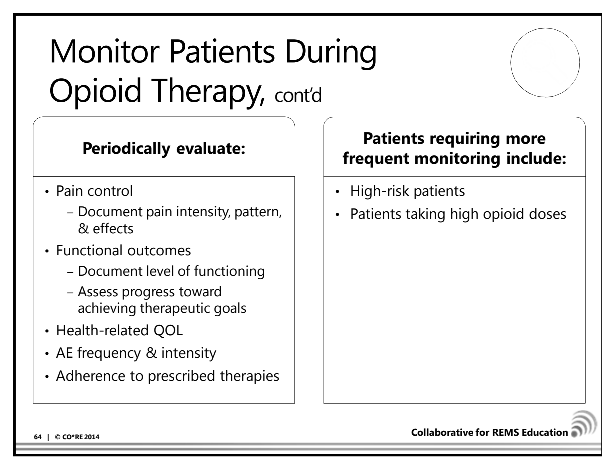
Monitor Patients During Opioid Therapy, cont'd
Periodically evaluate:
Pain control
Document pain intensity, pattern, & effects
Functional outcomes
Document level of functioning
Assess progress toward achieving therapeutic goals
Health-related QOL
AE frequency & intensity
Adherence to prescribed therapies
Patients requiring more frequent monitoring include:
High-risk patients
Patients taking high opioid doses
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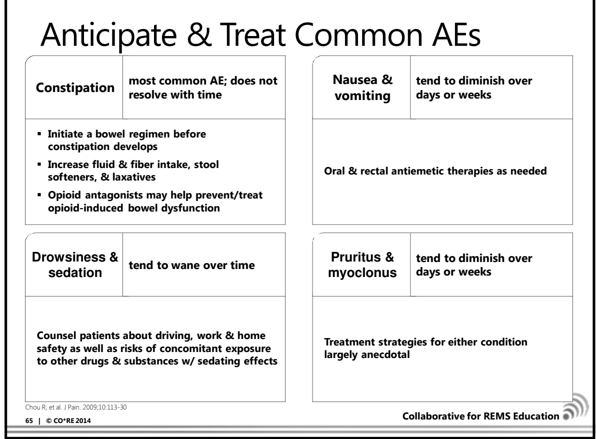
Anticipate & Treat Common AEs
Constipation
most common AE; does not resolve with time
Initiate a bowel regimen before constipation develops
Increase fluid & fiber intake, stool softeners, & laxatives
Opioid antagonists may help prevent/treat opioid-induced bowel dysfunction
Nausea & vomiting
tend to diminish over days or weeks
Oral & rectal antiemetic therapies as needed
Drowsiness & sedation
tend to wane over time
Counsel patients about driving, work & home safety as well as risks of concomitant exposure to other drugs & substances w/ sedating effects
Pruritus & myoclonus
tend to diminish over days or weeks
Treatment strategies for either condition largely anecdotal
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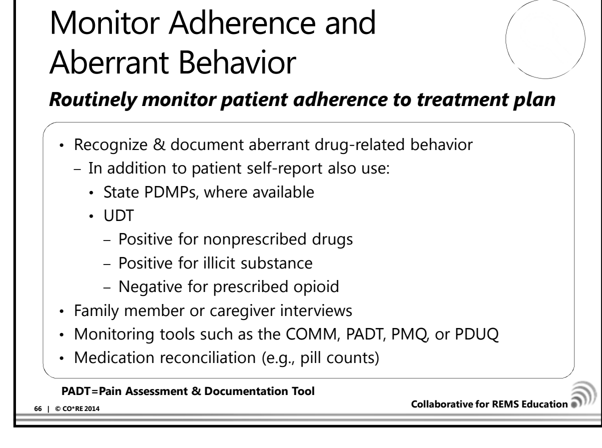
Monitor Adherence and Aberrant Behavior
Routinely monitor patient adherence to treatment plan
Recognize & document aberrant drug-related behavior
In addition to patient self-report also use:
State PDMPs, where available
UDT
Positive for nonprescribed drugs
Positive for illicit substance
Negative for 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 & Documentation Tool
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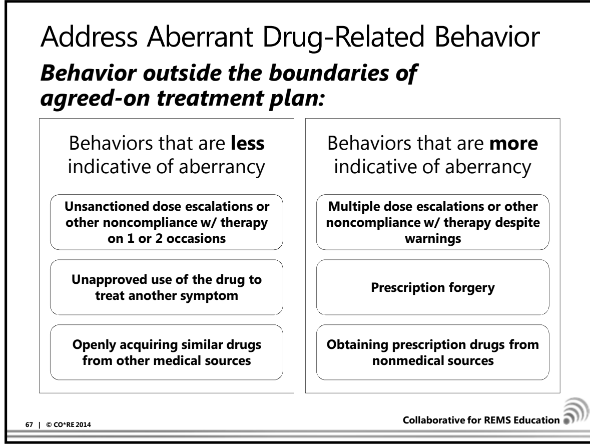
Address Aberrant Drug-Related Behavior
Behavior outside the boundaries of agreed-on treatment plan:
Behaviors that are less indicative of aberrancy
Unsanctioned dose escalations or other noncompliance w/ therapy on 1 or 2 occasions
Unapproved use of the drug to treat another symptom
Openly acquiring similar drugs from other medical sources
Behaviors that are more indicative of aberrancy
Multiple dose escalations or other noncompliance w/ therapy despite warnings
Prescription forgery
Obtaining prescription drugs from nonmedical sources
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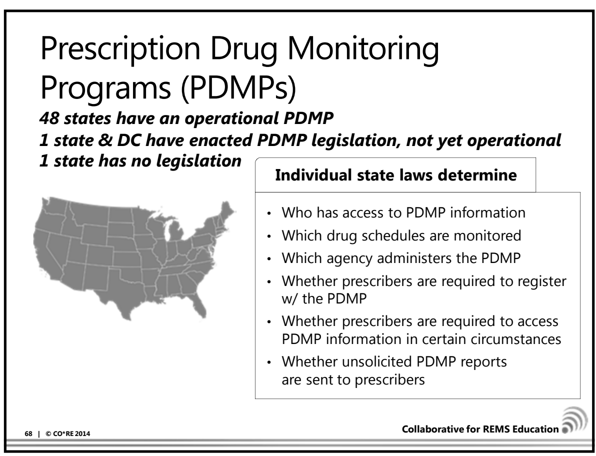
Prescription Drug Monitoring Programs (PDMPs)
48 states have an operational PDMP
1 state & DC have enacted PDMP legislation, not yet operational
1 state has no legislation
Individual state laws determine
Who has access to PDMP information
Which drug schedules are monitored
Which agency administers the PDMP
Whether prescribers are required to register w/ the PDMP
Whether prescribers are required to access PDMP information in certain circumstances
Whether unsolicited PDMP reports are sent to prescribers
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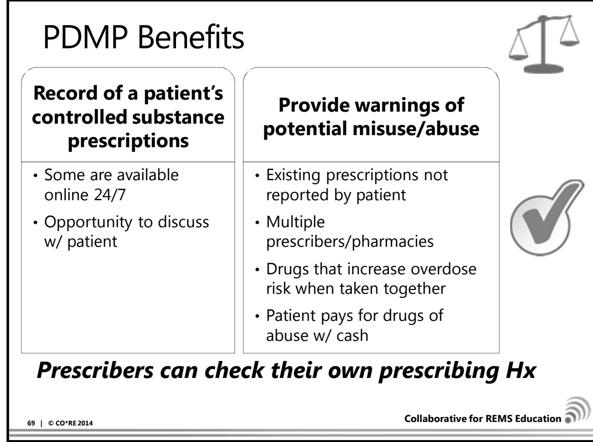
PDMP Benefits
Record of a patient's controlled substance prescriptions
Some are available online 24/7
Opportunity to discuss w/ patient
Provide warnings of potential misuse/abuse
Existing prescriptions not reported by patient
Multiple prescribers/pharmacies
Drugs that increase overdose risk when taken together
Patient pays for drugs of abuse w/ cash
Prescribers can check their own prescribing Hx
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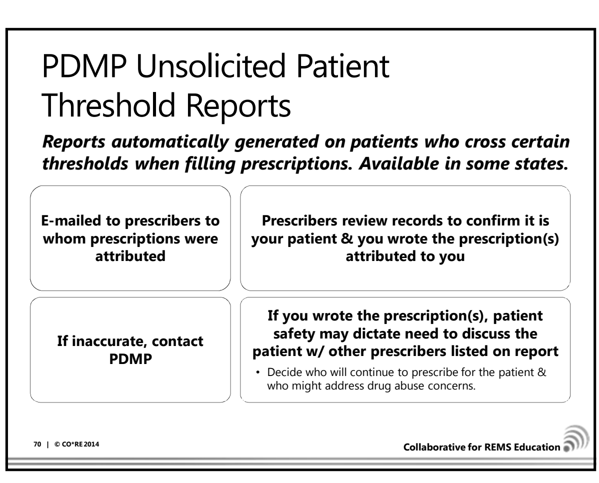
PDMP Unsolicited Patient Threshold Reports
Reports automatically generated on patients who cross certain thresholds when filling prescriptions. Available in some states.
E-mailed to prescribers to whom prescriptions were attributed
Prescribers review records to confirm it is your patient & you wrote the prescription(s) attributed to you
If inaccurate, contact PDMP
If you wrote the prescription(s), patient safety may dictate need to discuss the patient w/ other prescribers listed on report
Decide who will continue to prescribe for the patient & who might address drug abuse concerns.
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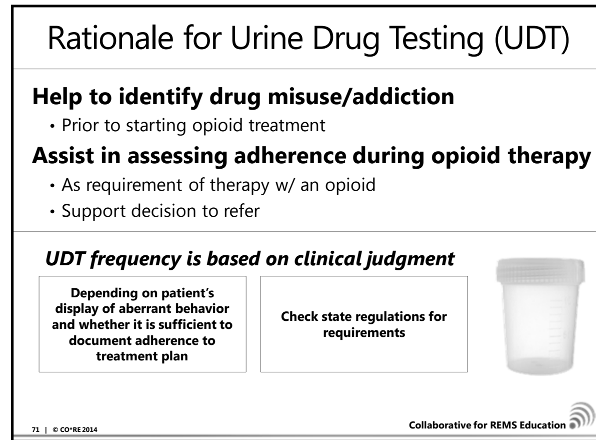
Rationale for Urine Drug Testing (UDT)
Help to identify drug misuse/addiction
Prior to starting opioid treatment
Assist in assessing adherence during opioid therapy
As requirement of therapy w/ an opioid
Support decision to refer
UDT frequency is based on clinical judgment
Depending on patient's display of aberrant behavior and whether it is sufficient to document adherence to treatment plan
Check state regulations for requirements
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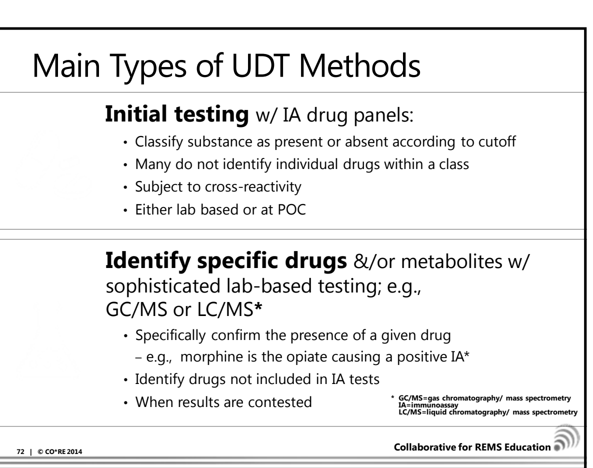
Main Types of UDT Methods
Initial testing w/ IA drug panels:
Classify substance as present or absent according to cutoff
Many do not identify individual drugs within a class
Subject to cross-reactivity
Either lab based or at POC
Identify specific drugs &/or metabolites w/ sophisticated lab-based testing; e.g., GC/MS or LC/MS*
Specifically confirm the presence of a given drug
– e.g., morphine is the opiate causing a positive IA*
Identify drugs not included in IA tests
When results are contested
* GC/MS=gas chromatography/ mass spectrometry
IA=immunoassay
LC/MS=liquid chromatography/ mass spectrometry
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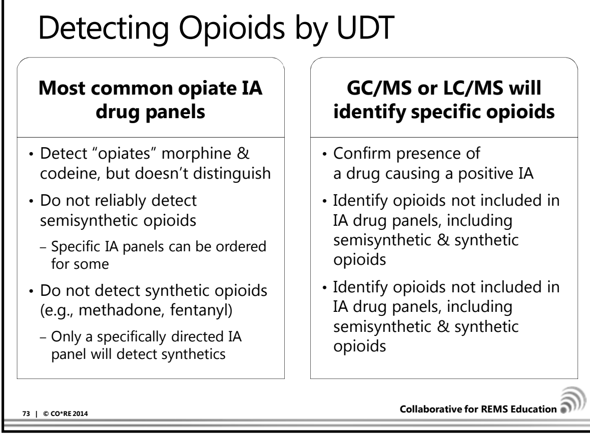
Detecting Opioids by UDT
Most common opiate IA drug panels
• Detect "opiates" morphine & codeine, but doesn't distinguish
• Do not reliably detect semisynthetic opioids
– Specific IA panels can be ordered for some
• Do not detect synthetic opioids (e.g., methadone, fentanyl)
– Only a specifically directed IA panel will detect synthetics
GC/MS or LC/MS will identify specific opioids
• Confirm presence of a drug causing a positive IA
• Identify opioids not included in IA drug panels, including semisynthetic & synthetic opioids
• Identify opioids not included in IA drug panels, including semisynthetic & synthetic opioids
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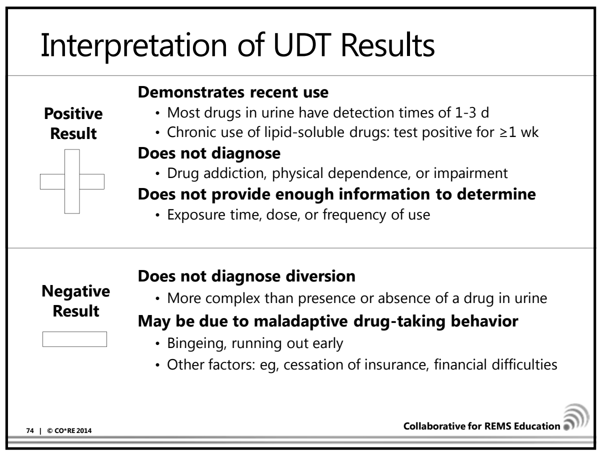
Interpretation of UDT Results
Positive Result
Demonstrates recent use
• Most drugs in urine have detection times of 1-3 d
• Chronic use of lipid-soluble drugs: test positive for ≥1 wk
Does not diagnose
• Drug addiction, physical dependence, or impairment
Does not provide enough information to determine
• 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
• Bingeing, running out early
• Other factors: eg, cessation of insurance, financial difficulties
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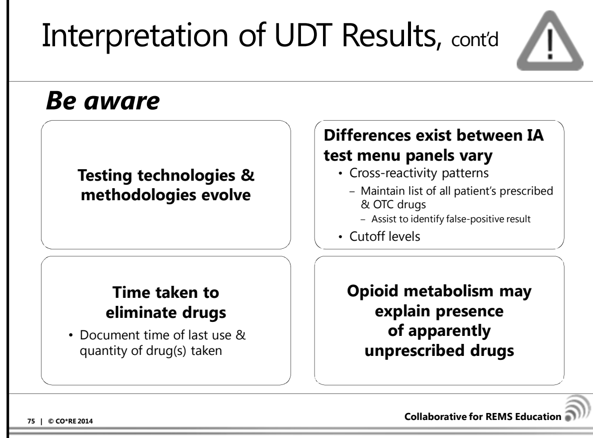
Interpretation of UDT Results, cont'd
Be aware
Testing technologies & methodologies evolve
Differences exist between IA test menu panels vary
• Cross-reactivity patterns
– Maintain list of all patient's prescribed & OTC drugs
– Assist to identify false-positive result
• Cutoff levels
Time taken to eliminate drugs
• Document time of last use & quantity of drug(s) taken
Opioid metabolism may explain presence of apparently unprescribed drugs
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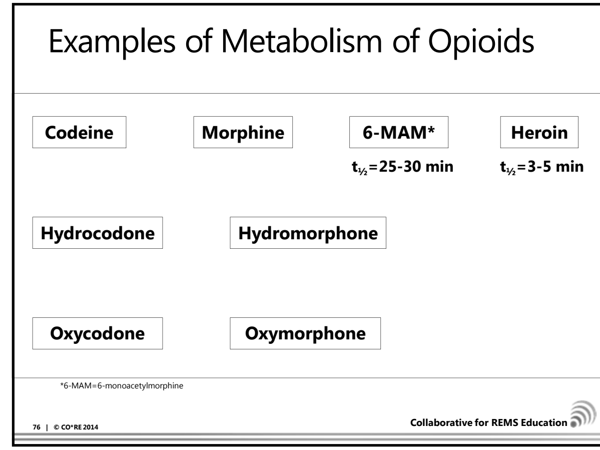
Examples of Metabolism of Opioids
Codeine
Morphine
6-MAM*
$t_{1/2}$=25-30 min
Heroin
$t_{1/2}$=3-5 min
Hydrocodone
Hydromorphone
Oxycodone
Oxymorphone
*6-MAM=6-monoacetylmorphine
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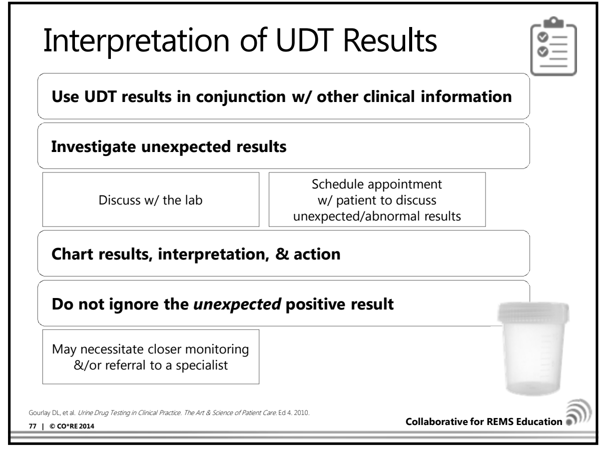
Interpretation of UDT Results
Use UDT results in conjunction w/ other clinical information
Investigate unexpected results
Discuss w/ the lab
Schedule appointment w/ patient to discuss unexpected/abnormal results
Chart results, interpretation, & action
Do not ignore the unexpected positive result
May necessitate closer monitoring &/or referral to a specialist
Gourlay DL, et al. Urine Drug Testing in Clinical Practice. The Art & Science of Patient Care. Ed 4. 2010.
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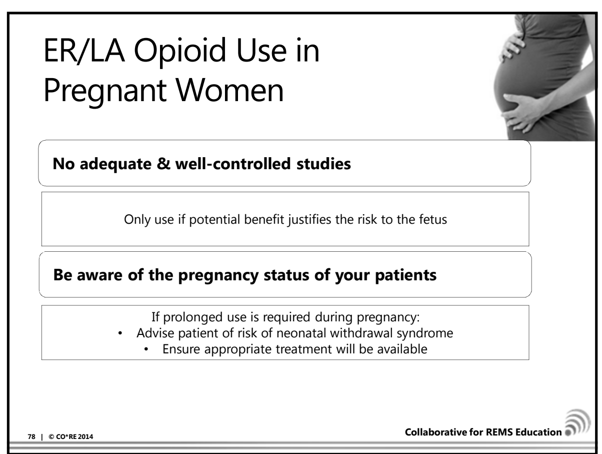
ER/LA Opioid Use in Pregnant Women
No adequate & well-controlled studies
Only use if potential benefit justifies the risk to the fetus
Be aware of the pregnancy status of your patients
If prolonged use is required during pregnancy:
• Advise patient of risk of neonatal withdrawal syndrome
• Ensure appropriate treatment will be available
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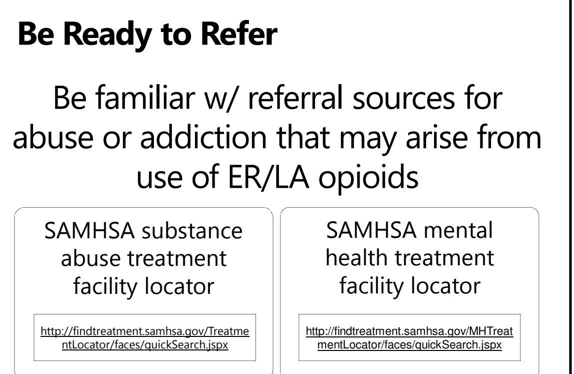
Be Ready to Refer
Be familiar w/ referral sources for abuse or addiction that may arise from use of ER/LA opioids
SAMHSA substance abuse treatment facility locator
http://findtreatment.samhsa.gov/TreatmentLocator/faces/quickSearch.jspx
SAMHSA mental health treatment facility locator
http://findtreatment.samhsa.gov/MHTreatmentLocator/faces/quickSearch.jspx
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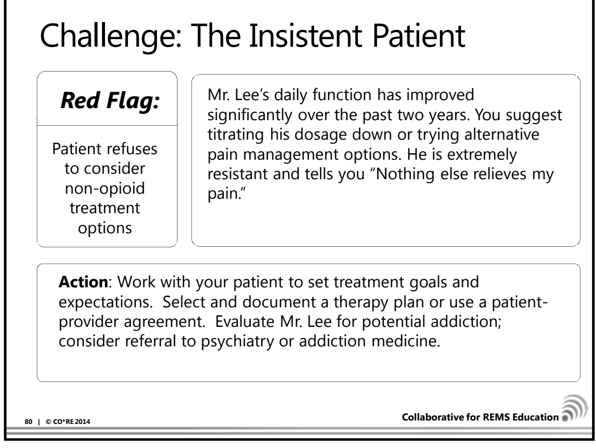
Challenge: The Insistent Patient
Red Flag:
Patient refuses to consider non-opioid treatment options
Mr. Lee's daily function has improved significantly over the past two years. You suggest titrating his dosage down or trying alternative pain management options. He is extremely resistant and tells you "Nothing else relieves my pain."
Action: Work with your patient to set treatment goals and expectations. Select and document a therapy plan or use a patient-provider agreement. Evaluate Mr. Lee for potential addiction; consider referral to psychiatry or addiction medicine.
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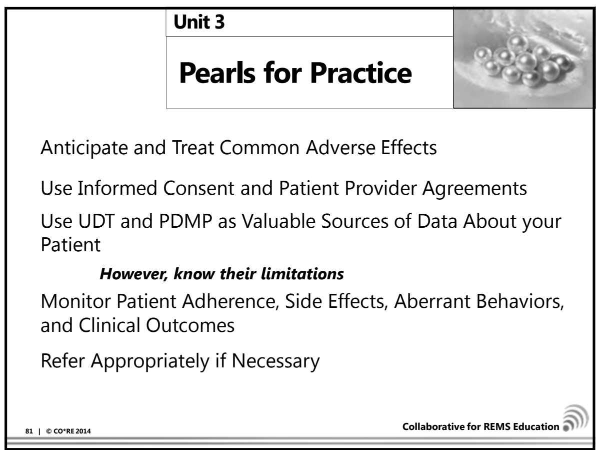
Unit 3
Pearls for Practice
Anticipate and Treat Common Adverse Effects
Use Informed Consent and Patient Provider Agreements
Use UDT and PDMP as Valuable Sources of Data About your Patient
However, know their limitations
Monitor Patient Adherence, Side Effects, Aberrant Behaviors, and Clinical Outcomes
Refer Appropriately if Necessary
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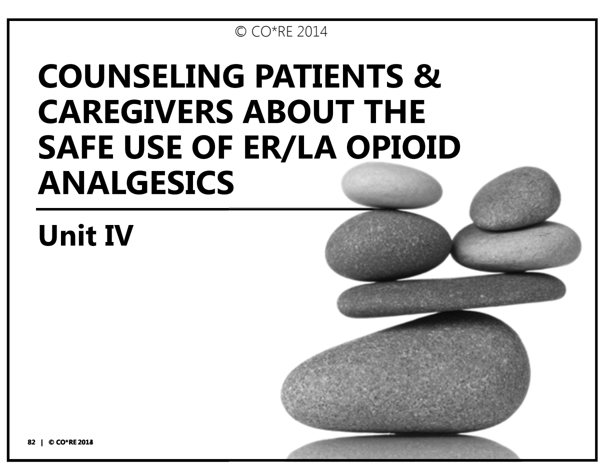
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COUNSELING PATIENTS & CAREGIVERS ABOUT THE SAFE USE OF ER/LA OPIOID ANALGESICS
Unit IV
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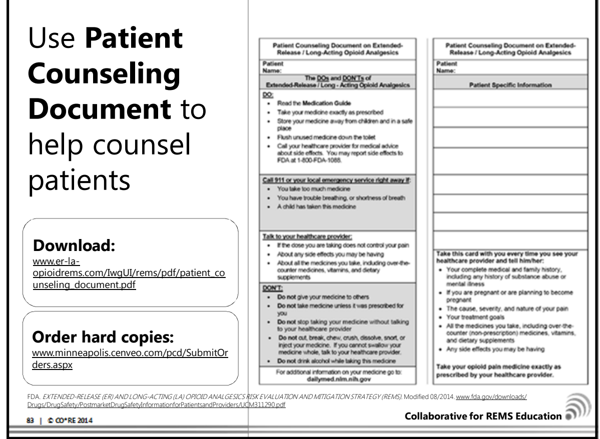
Use Patient Counseling Document to help counsel patients
Download:
www.er-la-opioidrems.com/IwgUI/rems/pdf/patient_counseling_document.pdf
Order hard copies:
www.minneapolis.cenveo.com/pcd/SubmitOrders.aspx
Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics
The DOs and DON'Ts of Extended-Release / Long-Acting Opioid Analgesics
Patient Specific Information
FDA. EXTENDED-RELEASE (ER) AND LONG-ACTING (LA) OPIOID ANALGESICS RISK EVALUATION AND MITIGATION STRATEGY (REMS). Modified 08/2014.
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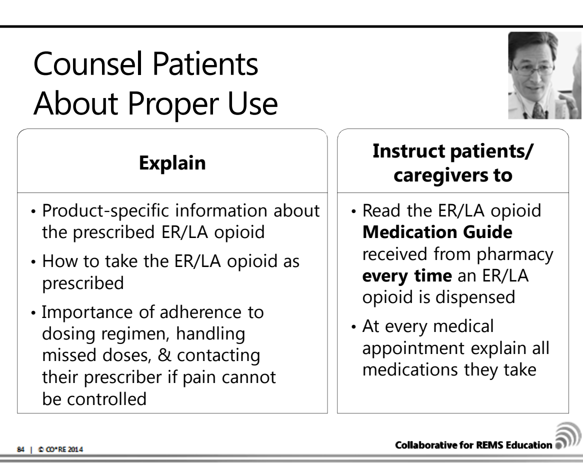
Counsel Patients About Proper Use
Explain
• Product-specific information about the prescribed ER/LA opioid
• How to take the ER/LA opioid as prescribed
• Importance of adherence to dosing regimen, handling missed doses, & contacting their prescriber if pain cannot be controlled
Instruct patients/ caregivers to
• Read the ER/LA opioid Medication Guide received from pharmacy every time an ER/LA opioid is dispensed
• At every medical appointment explain all medications they take
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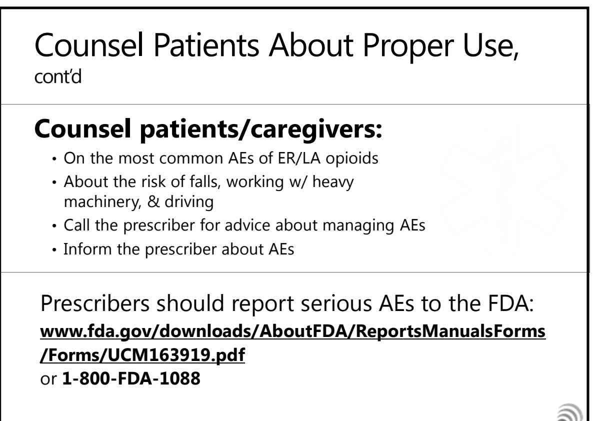
Counsel Patients About Proper Use, cont'd
Counsel patients/caregivers:
• On the most common AEs of ER/LA opioids
• About the risk of falls, working w/ heavy machinery, & driving
• Call the prescriber for advice about managing AEs
• Inform the prescriber about AEs
Prescribers should report serious AEs to the FDA:
www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf
or 1-800-FDA-1088
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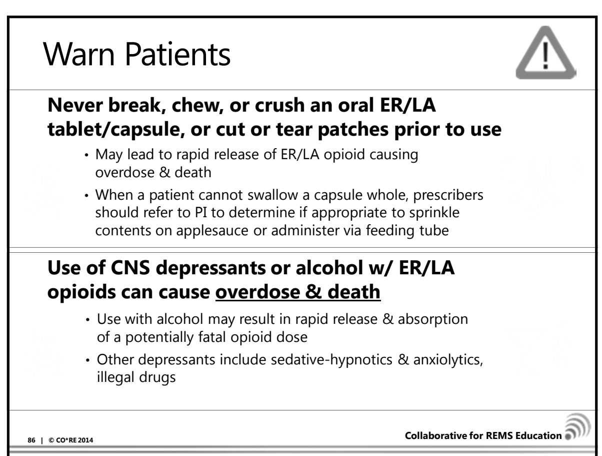
Warn Patients
Never break, chew, or crush an oral ER/LA tablet/capsule, or cut or tear patches prior to use
• May lead to rapid release of ER/LA opioid causing overdose & death
• When a patient cannot swallow a capsule whole, prescribers should refer to PI to determine if appropriate to sprinkle contents on applesauce or administer via feeding tube
Use of CNS depressants or alcohol w/ ER/LA opioids can cause overdose & death
• Use with alcohol may result in rapid release & absorption of a potentially fatal opioid dose
• Other depressants include sedative-hypnotics & anxiolytics, illegal drugs
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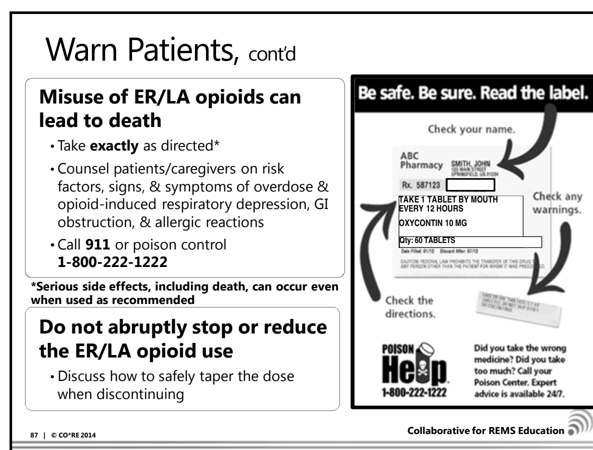
Warn Patients, cont'd
Misuse of ER/LA opioids can lead to death
• Take exactly as directed*
• Counsel patients/caregivers on risk factors, signs, & symptoms of overdose & opioid-induced respiratory depression, GI obstruction, & allergic reactions
• Call 911 or poison control 1-800-222-1222
*Serious side effects, including death, can occur even when used as recommended
Do not abruptly stop or reduce the ER/LA opioid use
• Discuss how to safely taper the dose when discontinuing
Be safe. Be sure. Read the label.
Check your name.
ABC Pharmacy
SMITH, JOHN
Rx. 587123
TAKE 1 TABLET BY MOUTH EVERY 12 HOURS
OXYCONTIN 10 MG
Qty: 60 TABLETS
Check any warnings.
Check the directions.
POISON Help
1-800-222-1222
Did you take the wrong medicine? Did you take too much? Call your Poison Center. Expert advice is available 24/7.
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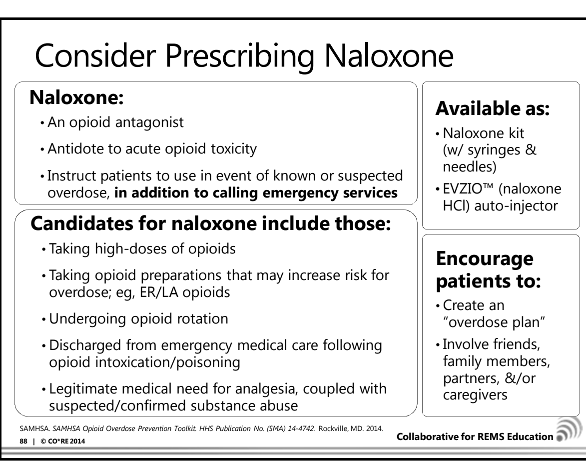
Consider Prescribing Naloxone
Naloxone:
• An opioid antagonist
• Antidote to acute opioid toxicity
• Instruct patients to use in event of known or suspected overdose, in addition to calling emergency services
Candidates for naloxone include those:
• Taking high-doses of opioids
• Taking opioid preparations that may increase risk for overdose; eg, ER/LA opioids
• Undergoing opioid rotation
• Discharged from emergency medical care following opioid intoxication/poisoning
• Legitimate medical need for analgesia, coupled with suspected/confirmed substance abuse
Available as:
• Naloxone kit (w/ syringes & needles)
• EVZIO™ (naloxone HCl) auto-injector
Encourage patients to:
• Create an "overdose plan"
• Involve friends, family members, partners, &/or caregivers
SAMHSA. SAMHSA Opioid Overdose Prevention Toolkit. HHS Publication No. (SMA) 14-4742. Rockville, MD. 2014.
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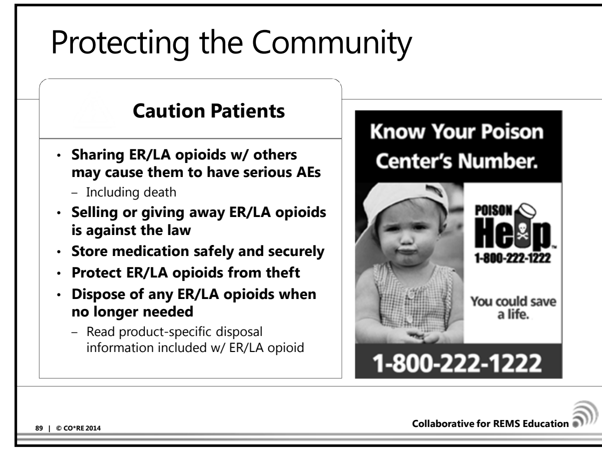
Protecting the Community
Caution Patients
• Sharing ER/LA opioids w/ others may cause them to have serious AEs
– Including death
• Selling or giving away ER/LA opioids is against the law
• Store medication safely and securely
• Protect ER/LA opioids from theft
• Dispose of any ER/LA opioids when no longer needed
– Read product-specific disposal information included w/ ER/LA opioid
Know Your Poison Center's Number.
POISON Help
1-800-222-1222
You could save a life.
1-800-222-1222
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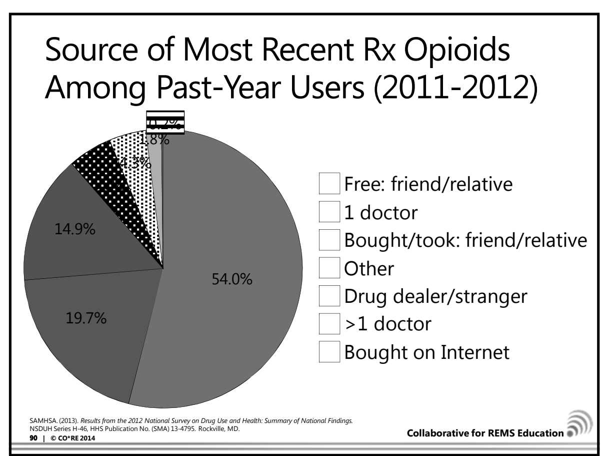
Source of Most Recent Rx Opioids Among Past-Year Users (2011-2012)
54.0%
19.7%
14.9%
Free: friend/relative
1 doctor
Bought/took: friend/relative
Other
Drug dealer/stranger
>1 doctor
Bought on Internet
SAMHSA. (2013). Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings. NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD.
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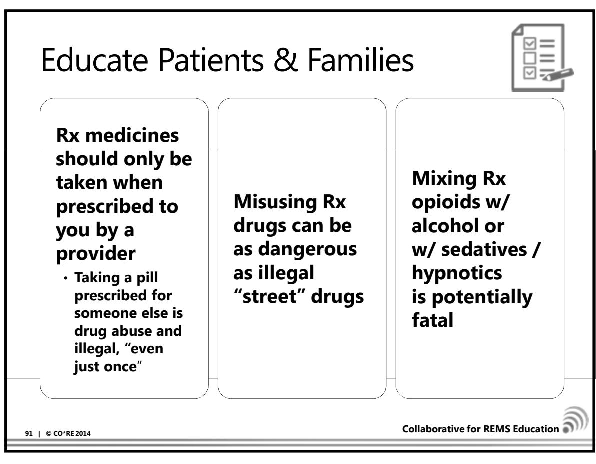
Educate Patients & Families
Rx medicines should only be taken when prescribed to you by a provider
• Taking a pill prescribed for someone else is drug abuse and illegal, "even just once"
Misusing Rx drugs can be as dangerous as illegal "street" drugs
Mixing Rx opioids w/ alcohol or w/ sedatives / hypnotics is potentially fatal
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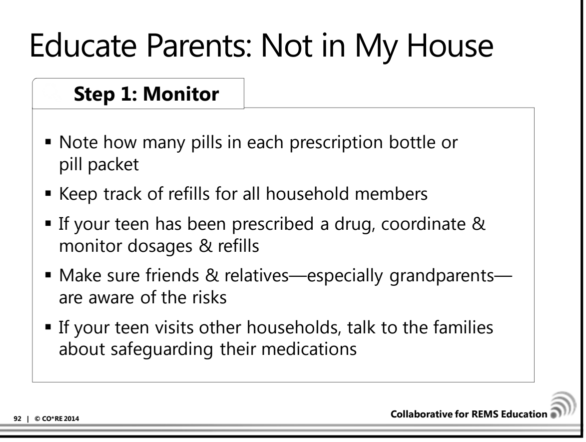
Educate Parents: Not in My House
Step 1: Monitor
▪ Note how many pills in each prescription bottle or pill packet
▪ Keep track of refills for all household members
▪ If your teen has been prescribed a drug, coordinate & monitor dosages & refills
▪ Make sure friends & relatives—especially grandparents—are aware of the risks
▪ If your teen visits other households, talk to the families about safeguarding their medications
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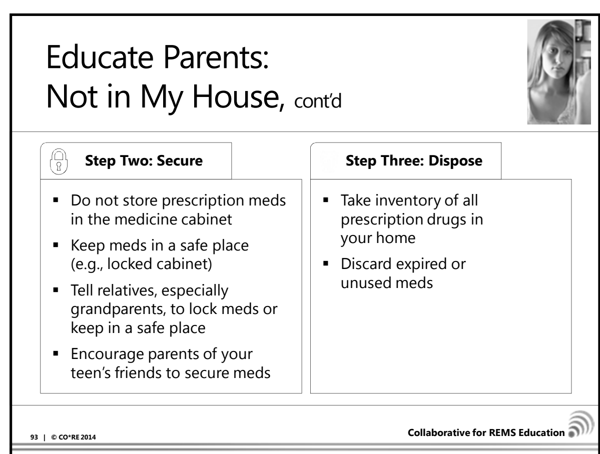
Educate Parents: Not in My House, cont'd
Step Two: Secure
▪ Do not store prescription meds in the medicine cabinet
▪ Keep meds in a safe place (e.g., locked cabinet)
▪ Tell relatives, especially grandparents, to lock meds or keep in a safe place
▪ Encourage parents of your teen's friends to secure meds
Step Three: Dispose
▪ Take inventory of all prescription drugs in your home
▪ Discard expired or unused meds
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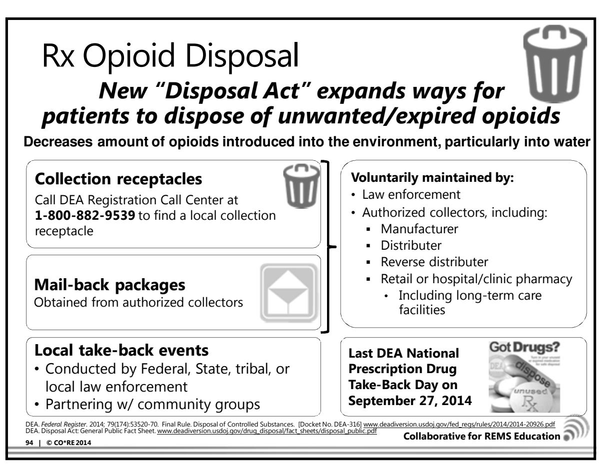
Rx Opioid Disposal
New "Disposal Act" expands ways for patients to dispose of unwanted/expired opioids
Decreases amount of opioids introduced into the environment, particularly into water
Collection receptacles
Call DEA Registration Call Center at 1-800-882-9539 to find a local collection receptacle
Mail-back packages
Obtained from authorized collectors
Voluntarily maintained by:
• Law enforcement
• Authorized collectors, including:
▪ Manufacturer
▪ Distributer
▪ Reverse distributer
▪ Retail or hospital/clinic pharmacy
• Including long-term care facilities
Local take-back events
• Conducted by Federal, State, tribal, or local law enforcement
• Partnering w/ community groups
Last DEA National Prescription Drug Take-Back Day on September 27, 2014
Got Drugs?
dispose
unused
Rx
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
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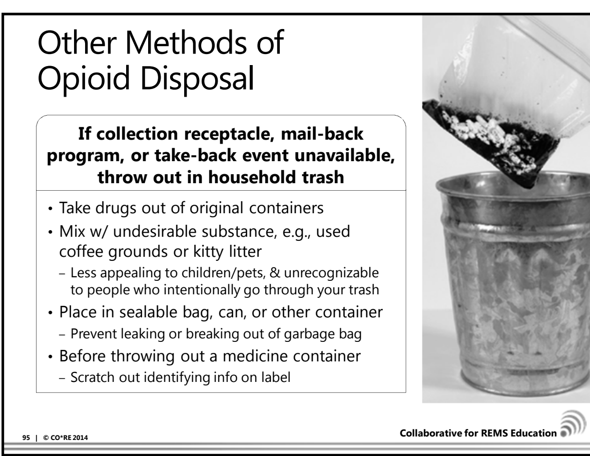
Other Methods of Opioid Disposal
If collection receptacle, mail-back program, or take-back event unavailable, throw out in household trash
• Take drugs out of original containers
• Mix w/ undesirable substance, e.g., used coffee grounds or kitty litter
– Less appealing to children/pets, & unrecognizable to people who intentionally go through your trash
• Place in sealable bag, can, or other container
– Prevent leaking or breaking out of garbage bag
• Before throwing out a medicine container
– Scratch out identifying info on label
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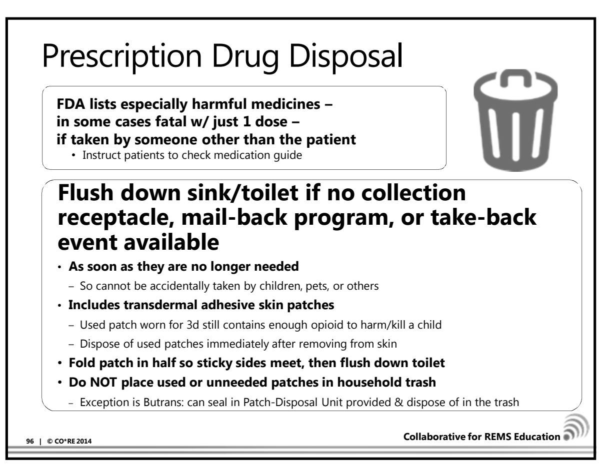
Prescription Drug Disposal
FDA lists especially harmful medicines – in some cases fatal w/ just 1 dose – if taken by someone other than the patient
• Instruct patients to check medication guide
Flush down sink/toilet if no collection receptacle, mail-back program, or take-back event available
• As soon as they are no longer needed
– So cannot be accidentally taken by children, pets, or others
• Includes transdermal adhesive skin patches
– Used patch worn for 3d 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
– Exception is Butrans: can seal in Patch-Disposal Unit provided & dispose of in the trash
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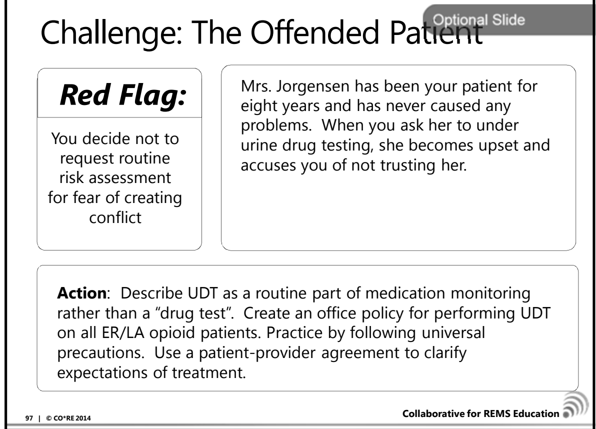

Challenge: The Offended Patient
Optional Slide
Red Flag:
You decide not to request routine risk assessment for fear of creating conflict
Mrs. Jorgensen has been your patient for eight years and has never caused any problems. When you ask her to under urine drug testing, she becomes upset and accuses you of not trusting her.
Action: Describe UDT as a routine part of medication monitoring rather than a "drug test". Create an office policy for performing UDT on all ER/LA opioid patients. Practice by following universal precautions. Use a patient-provider agreement to clarify expectations of treatment.
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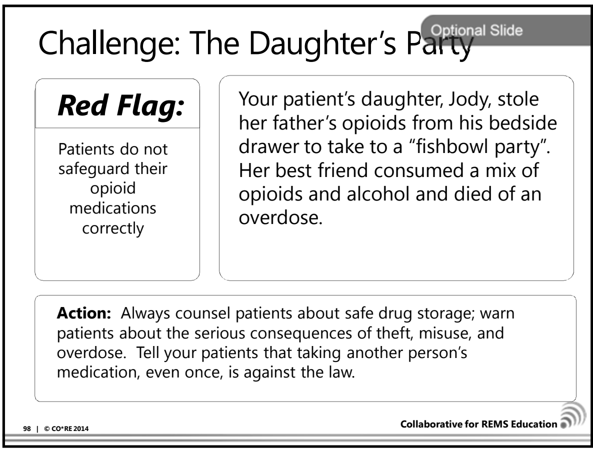

Challenge: The Daughter's Party
Optional Slide
Red Flag:
Patients do not safeguard their opioid medications correctly
Your patient's daughter, Jody, stole her father's opioids from his bedside drawer to take to a "fishbowl party". Her best friend consumed a mix of opioids and alcohol and died of an overdose.
Action: Always counsel patients about safe drug storage; warn patients about the serious consequences of theft, misuse, and overdose. Tell your patients that taking another person's medication, even once, is against the law.
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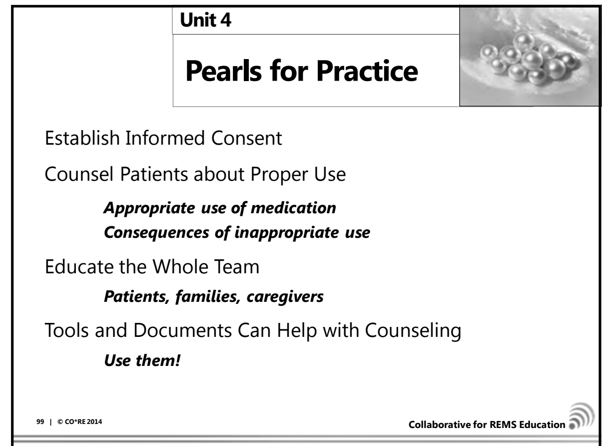

Unit 4
Pearls for Practice
Establish Informed Consent
Counsel Patients about Proper Use
Appropriate use of medication
Consequences of inappropriate use
Educate the Whole Team
Patients, families, caregivers
Tools and Documents Can Help with Counseling
Use them!
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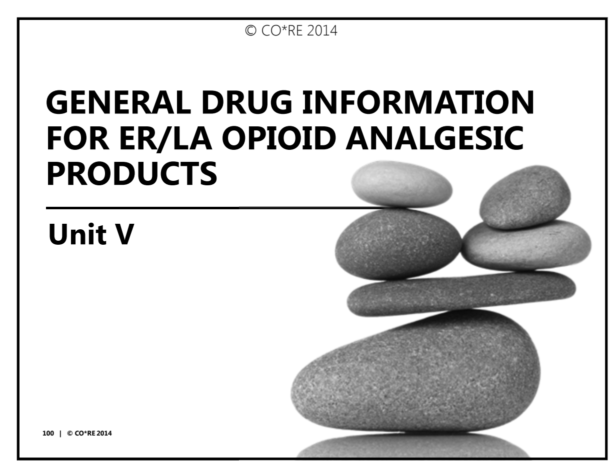

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GENERAL DRUG INFORMATION FOR ER/LA OPIOID ANALGESIC PRODUCTS
Unit V
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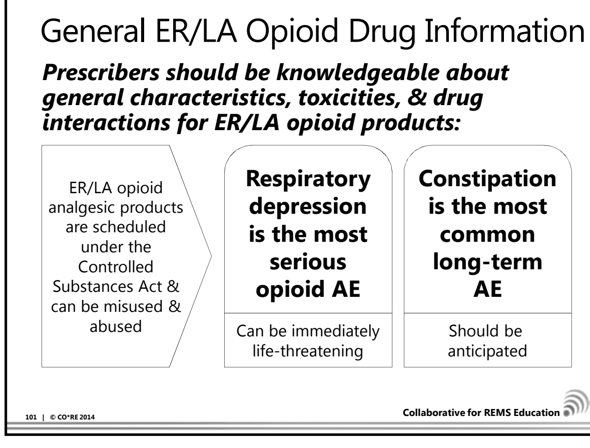

General ER/LA Opioid Drug Information
Prescribers should be knowledgeable about general characteristics, toxicities, & drug interactions for ER/LA opioid products:
ER/LA opioid analgesic products are scheduled under the Controlled Substances Act & can be misused & abused
Respiratory depression is the most serious opioid AE
Can be immediately life-threatening
Constipation is the most common long-term AE
Should be anticipated
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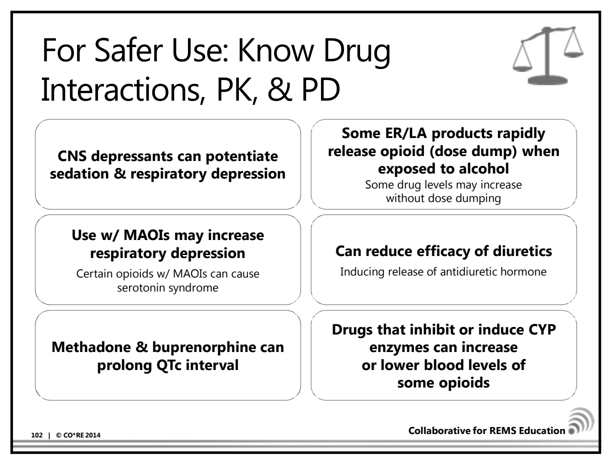

For Safer Use: Know Drug Interactions, PK, & PD
CNS depressants can potentiate sedation & respiratory depression
Some ER/LA products rapidly release opioid (dose dump) when exposed to alcohol
Some drug levels may increase without dose dumping
Use w/ MAOIs may increase respiratory depression
Certain opioids w/ MAOIs can cause serotonin syndrome
Can reduce efficacy of diuretics
Inducing release of antidiuretic hormone
Methadone & 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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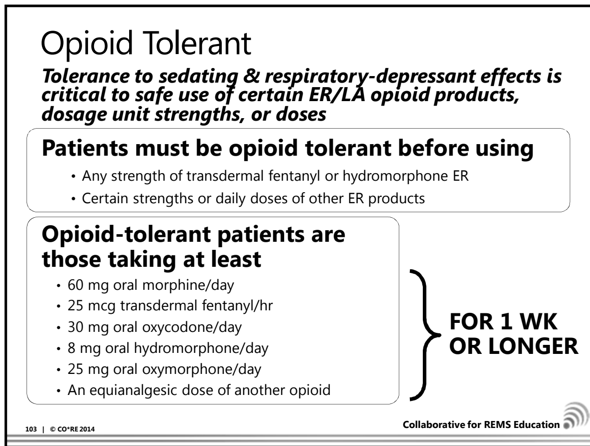

Opioid Tolerant
Tolerance to sedating & respiratory-depressant effects is critical to safe use of certain ER/LA opioid products, dosage unit strengths, or doses
Patients must be opioid tolerant before using
• Any strength of transdermal fentanyl or hydromorphone ER
• Certain strengths or daily doses of other ER products
Opioid-tolerant patients are those taking at least
• 60 mg oral morphine/day
• 25 mcg transdermal fentanyl/hr
• 30 mg oral oxycodone/day
• 8 mg oral hydromorphone/day
• 25 mg oral oxymorphone/day
• An equianalgesic dose of another opioid
FOR 1 WK OR LONGER
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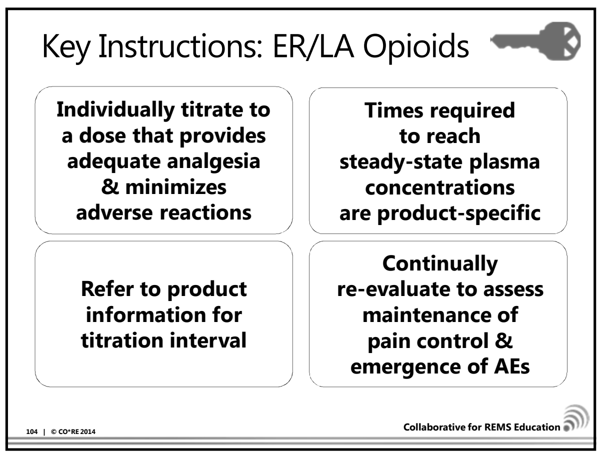

Key Instructions: ER/LA Opioids
Individually titrate to a dose that provides adequate analgesia & minimizes adverse reactions
Times required to reach steady-state plasma concentrations are product-specific
Refer to product information for titration interval
Continually re-evaluate to assess maintenance of pain control & emergence of AEs
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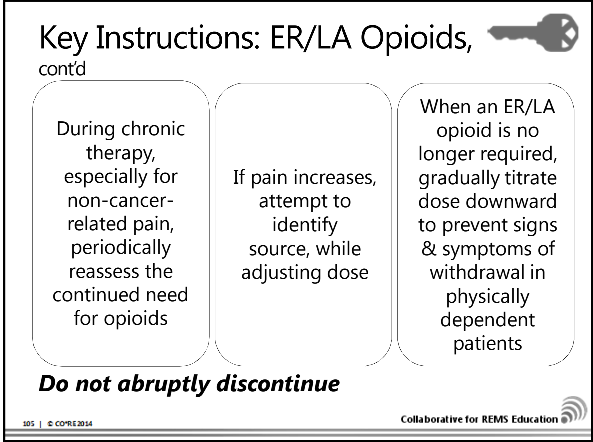

Key Instructions: ER/LA Opioids, cont'd
During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids
If pain increases, attempt to identify source, while adjusting dose
When an ER/LA opioid is no longer required, gradually titrate dose downward to prevent signs & symptoms of withdrawal in physically dependent patients
Do not abruptly discontinue
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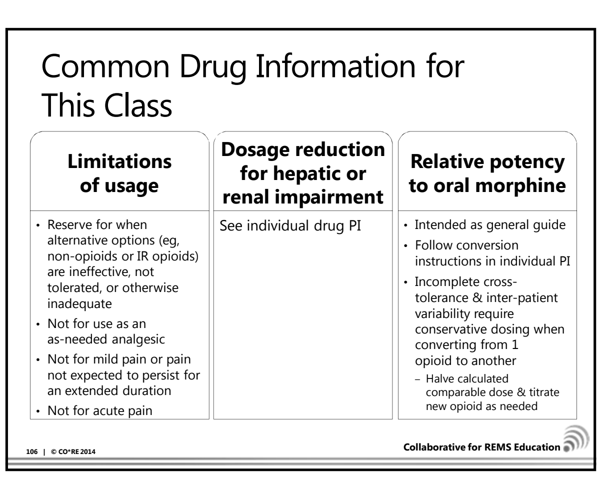

Common Drug Information for This Class
Limitations of usage
• Reserve for when alternative options (eg, non-opioids or IR opioids) are ineffective, not tolerated, or otherwise inadequate
• Not for use as an as-needed analgesic
• Not for mild pain or pain not expected to persist for an extended duration
• Not for acute pain
Dosage reduction for hepatic or renal impairment
See individual drug PI
Relative potency to oral morphine
• Intended as general guide
• Follow conversion instructions in individual PI
• Incomplete cross-tolerance & inter-patient variability require conservative dosing when converting from 1 opioid to another
– Halve calculated comparable dose & titrate new opioid as needed
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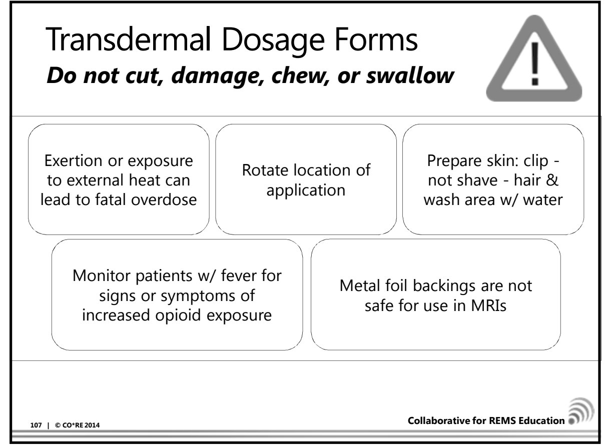

Transdermal Dosage Forms
Do not cut, damage, chew, or swallow
Exertion or exposure to external heat can lead to fatal overdose
Rotate location of application
Prepare skin: clip - not shave - hair & wash area w/ water
Monitor patients w/ fever for signs or symptoms of increased opioid exposure
Metal foil backings are not safe for use in MRIs
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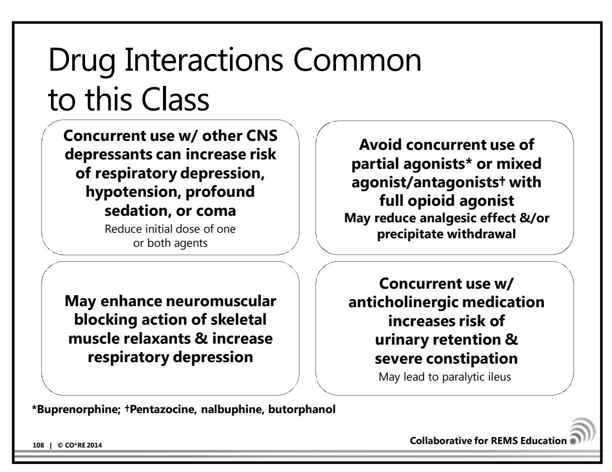

Drug Interactions Common to this Class
Concurrent use w/ other CNS depressants can increase risk of respiratory depression, hypotension, profound sedation, or coma
Reduce initial dose of one or both agents
Avoid concurrent use of partial agonists* or mixed agonist/antagonists† with full opioid agonist
May reduce analgesic effect &/or precipitate withdrawal
May enhance neuromuscular blocking action of skeletal muscle relaxants & increase respiratory depression
Concurrent use w/ anticholinergic medication increases risk of urinary retention & severe constipation
May lead to paralytic ileus
*Buprenorphine; †Pentazocine, nalbuphine, butorphanol
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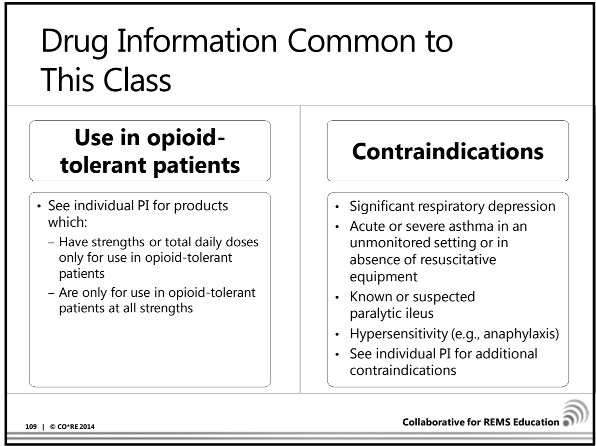
Drug Information Common to This Class
Use in opioid-tolerant patients
• See individual PI for products which:
– Have strengths or total daily doses only for use in opioid-tolerant patients
– Are only for use in opioid-tolerant patients at all strengths
Contraindications
• Significant respiratory depression
• 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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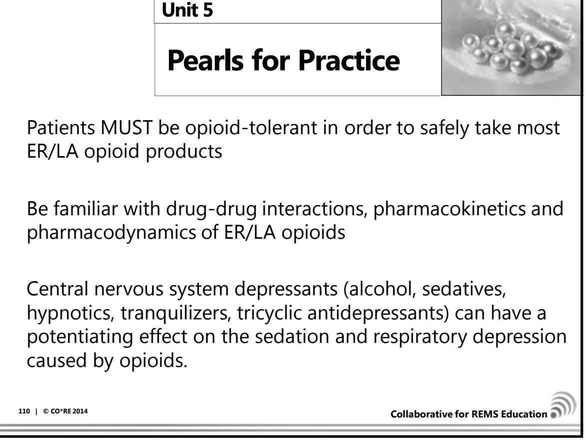
Unit 5
Pearls for Practice
Patients MUST be opioid-tolerant in order to safely take most ER/LA opioid products
Be familiar with drug-drug interactions, pharmacokinetics and pharmacodynamics of ER/LA opioids
Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
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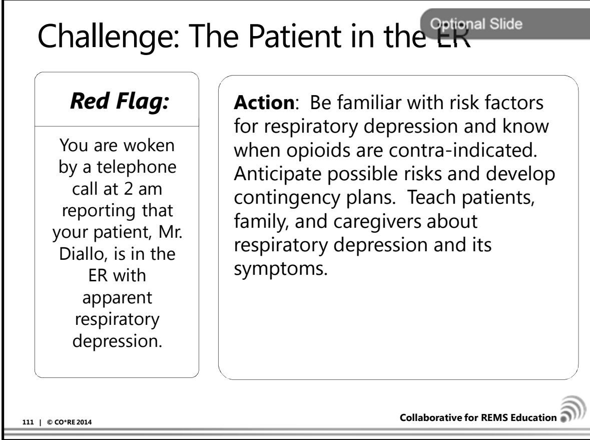
Challenge: The Patient in the ER
Optional Slide
Red Flag:
You are woken by a telephone call at 2 am reporting that your patient, Mr. Diallo, is in the ER with apparent respiratory depression.
Action: Be familiar with risk factors for respiratory depression and know when opioids are contra-indicated. Anticipate possible risks and develop contingency plans. Teach patients, family, and caregivers about respiratory depression and its symptoms.
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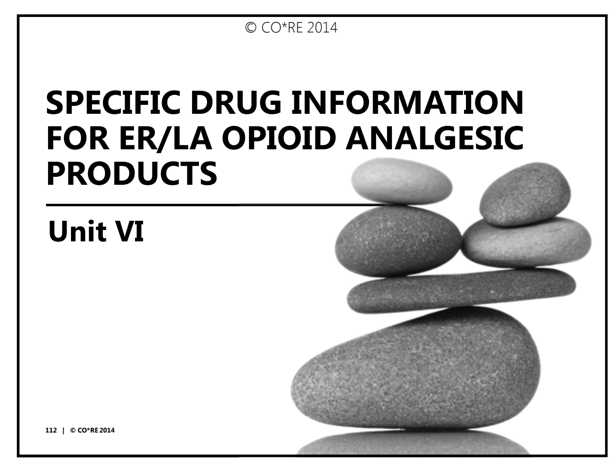
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SPECIFIC DRUG INFORMATION FOR ER/LA OPIOID ANALGESIC PRODUCTS
Unit VI
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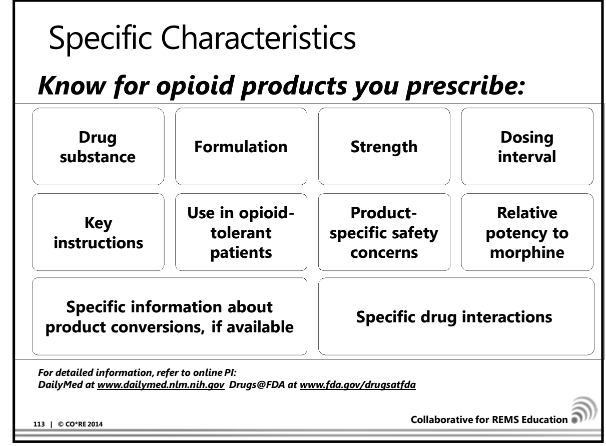
Specific Characteristics
Know for opioid products you prescribe:
Drug substance
Formulation
Strength
Dosing interval
Key instructions
Use in opioid-tolerant patients
Product-specific safety concerns
Relative potency to morphine
Specific information about product conversions, if available
Specific drug 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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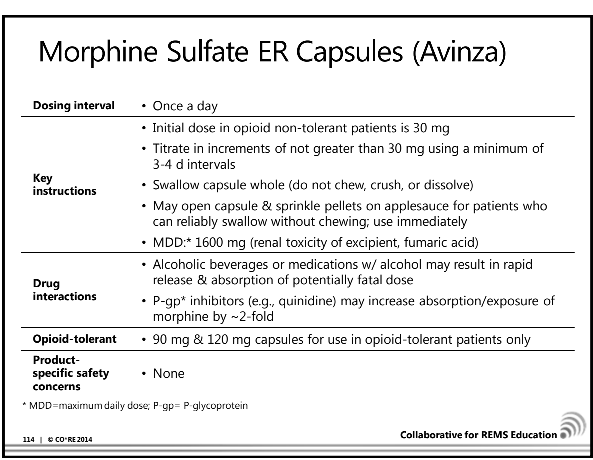
Morphine Sulfate ER Capsules (Avinza)
Dosing interval
• Once a day
Key instructions
• Initial dose in opioid non-tolerant patients is 30 mg
• Titrate in increments of not greater than 30 mg using a minimum of 3-4 d intervals
• Swallow capsule whole (do not chew, crush, or dissolve)
• May open capsule & 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 Transdermal System (Butrans)

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) cont'd

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
Drug-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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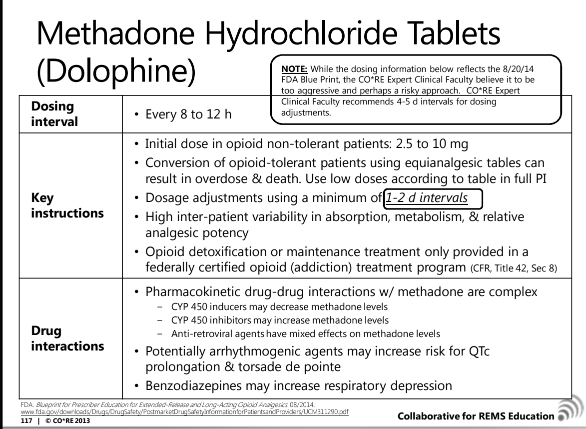

Methadone Hydrochloride Tablets (Dolophine)

NOTE: While the dosing information below reflects the 8/20/14 FDA Blue Print, the CO*RE Expert Clinical Faculty believe it to be too aggressive and perhaps a risky approach. CO*RE Expert Clinical Faculty recommends 4-5 d intervals for dosing adjustments.

Dosing interval	• Every 8 to 12 h
Key instructions	• Initial dose in opioid non-tolerant patients: 2.5 to 10 mg • Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose & death. Use low doses according to table in full PI • Dosage adjustments using a minimum of *1-2 d intervals* • 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

FDA. *Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*. 08/2014. www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf

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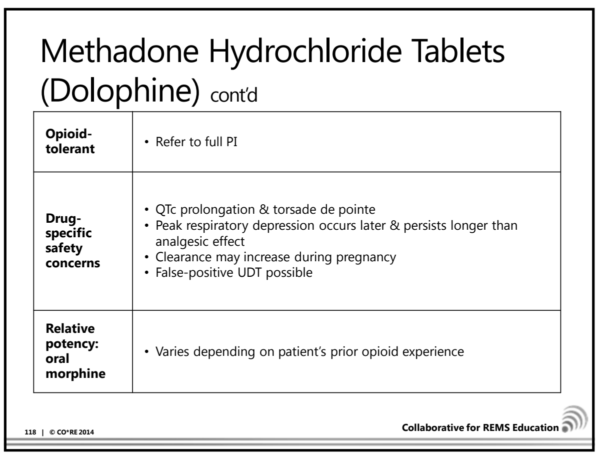

Methadone Hydrochloride Tablets (Dolophine) cont'd

Opioid-tolerant	• Refer to full PI
Drug-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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Fentanyl Transdermal System (Duragesic)

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), cont'd

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
Drug-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 Tablets (Embeda)

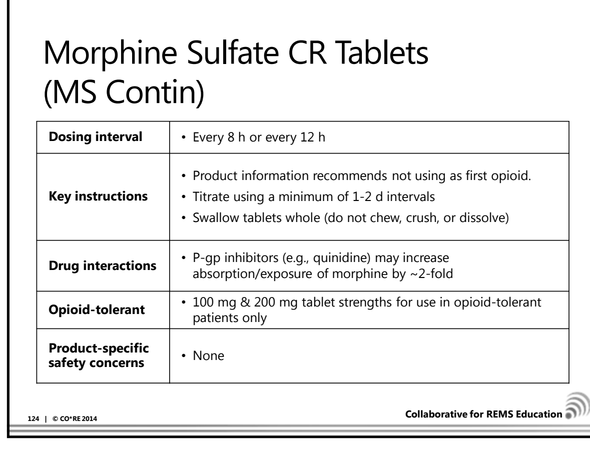
Dosing interval	• Once a day or every 12 h
Key instructions	• Initial dose as first opioid: 20 mg/0.8 mg • Titrate using a minimum of 1-2 d intervals • Swallow capsules whole (do not chew, crush, or dissolve) • Crushing or chewing will release morphine, possibly resulting in fatal overdose, & naltrexone, 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

Hydromorphone Hydrochloride ER Tablets (Exalgo)

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

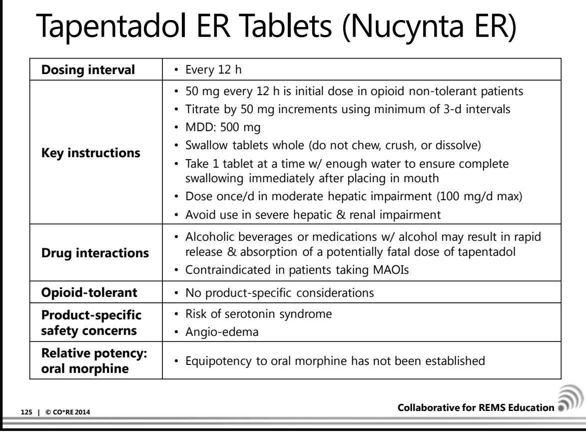
Morphine Sulfate ER Capsules (Kadian)

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 & 200 mg capsules for use in opioid-tolerant patients only
Product-specific safety concerns	• None



Morphine Sulfate CR Tablets (MS Contin)

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



Tapentadol ER Tablets (Nucynta ER)

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

Oxymorphone Hydrochloride ER Tablets (Opana ER)

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

Oxycodone Hydrochloride CR Tablets (OxyContin)

Dosing interval	• Every 12 h
Key instructions	• Initial dose in opioid 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	• 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/Naloxone Hydrochloride ER Tablets (Targiniq ER)

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/ ⅓-½ 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

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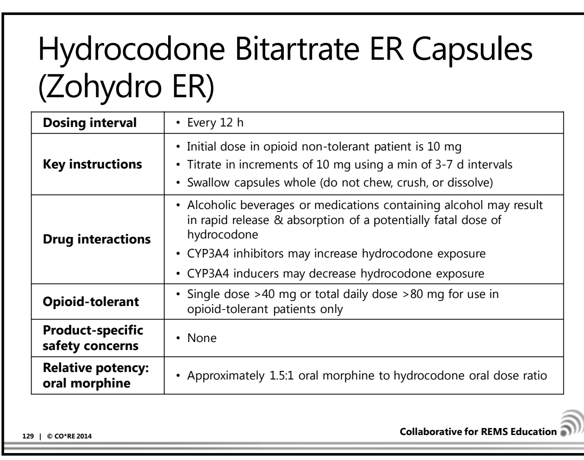

Hydrocodone Bitartrate ER Capsules (Zohydro ER)

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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