Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS)

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Faculty Disclosure

Dr. Beth B. Murinson has no financial disclosures.

She is a board member of the American Academy of Pain Medicine.
She is a salaried neurologist at the DCVAMC, her opinions expressed here to not represent the VAMC.
She is a faculty member at the Johns Hopkins School of Medicine.

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OUTLINE

The topics to be covered in this first section are:

1) Assessing patients for LA/ER opioids

2) Initiating, modifying, and discontinuing therapy

3) Managing therapy: goals, balancing analgesia, mitigating risk

In the next session, we will address:

4) Counseling patients and families for safe use

5) General information about ER/LA opioids

6) Drug specific information about ER/LA opioids

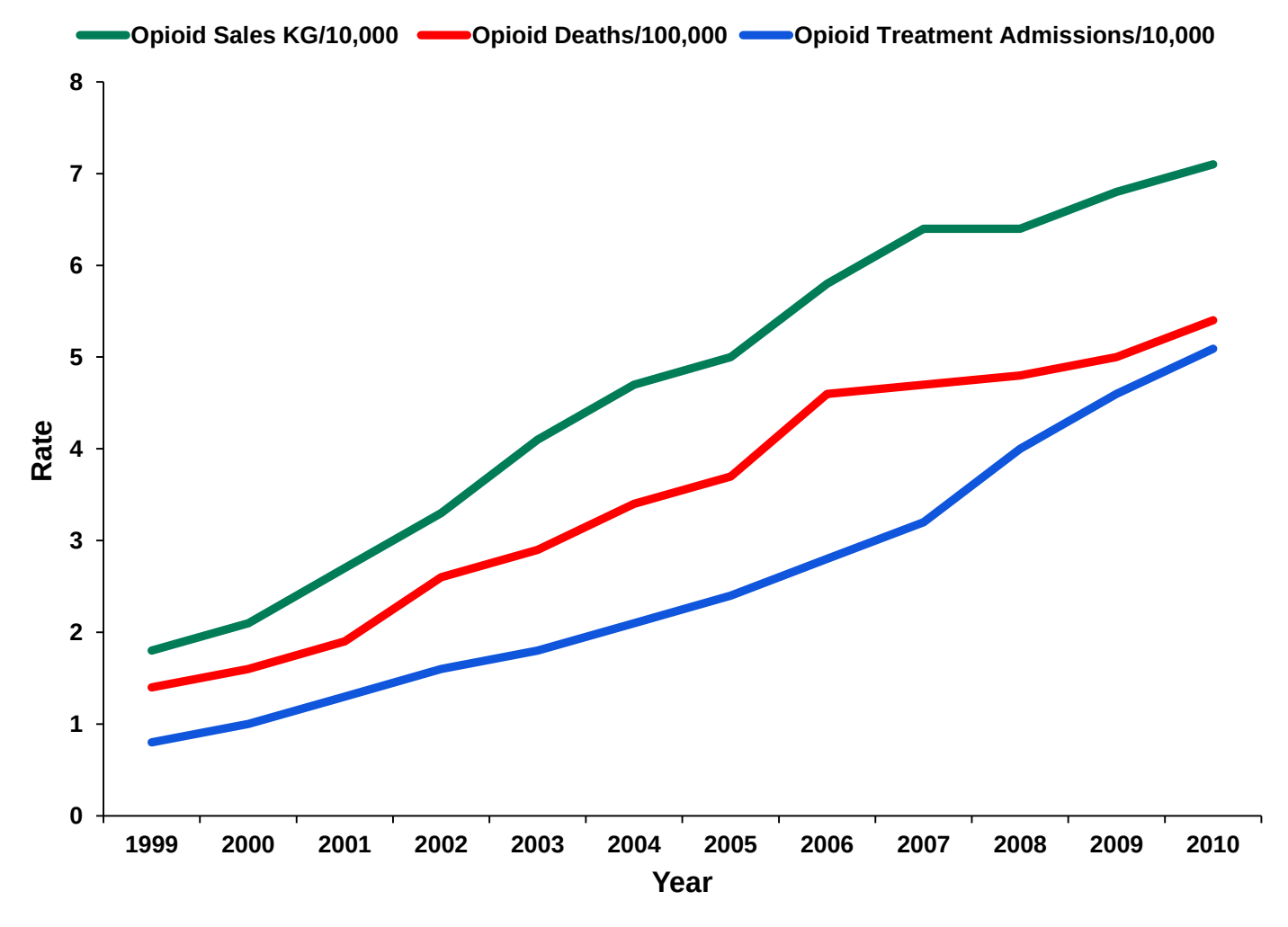
Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

Module 1

Learning Objectives

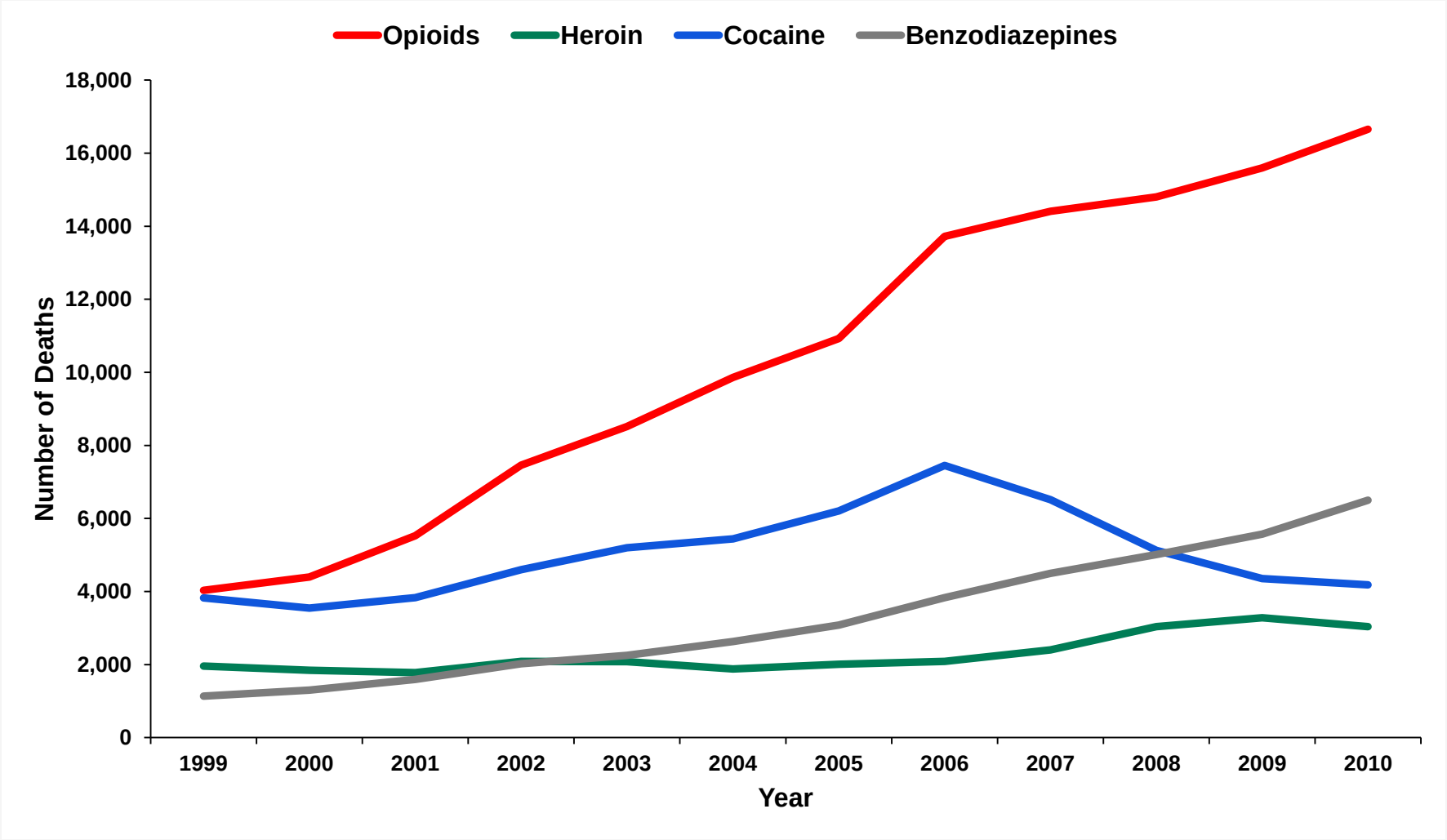
- Appropriately assess patients for the treatment of pain with ER/LA opioid analgesics, including analyzing risks versus potential benefits
- Assess patient's risk of abuse, including substance use and psychiatric history
- Identify state and federal regulations on opioid prescribing
- Incorporate strategies to effectively initiate therapy, modify dosing or discontinue use of ER/LA opioid analgesics in patients with pain
- Manage ongoing therapy with ER/LA opioid analgesics
- Incorporate effective counseling for patients and caregivers about the safe use of ER/LA opioid analgesics
- Discuss general and product-specific drug information related to ER/LA opioid analgesics

Rates of Opioid Overdose Deaths, Sales, and Treatment Admissions, United States, 1999–2010



CDC. *MMWR* 2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm60e1101a1.htm?s_cid=mm60e1101a1_w. Updated with 2009 mortality and 2010 treatment admission data.

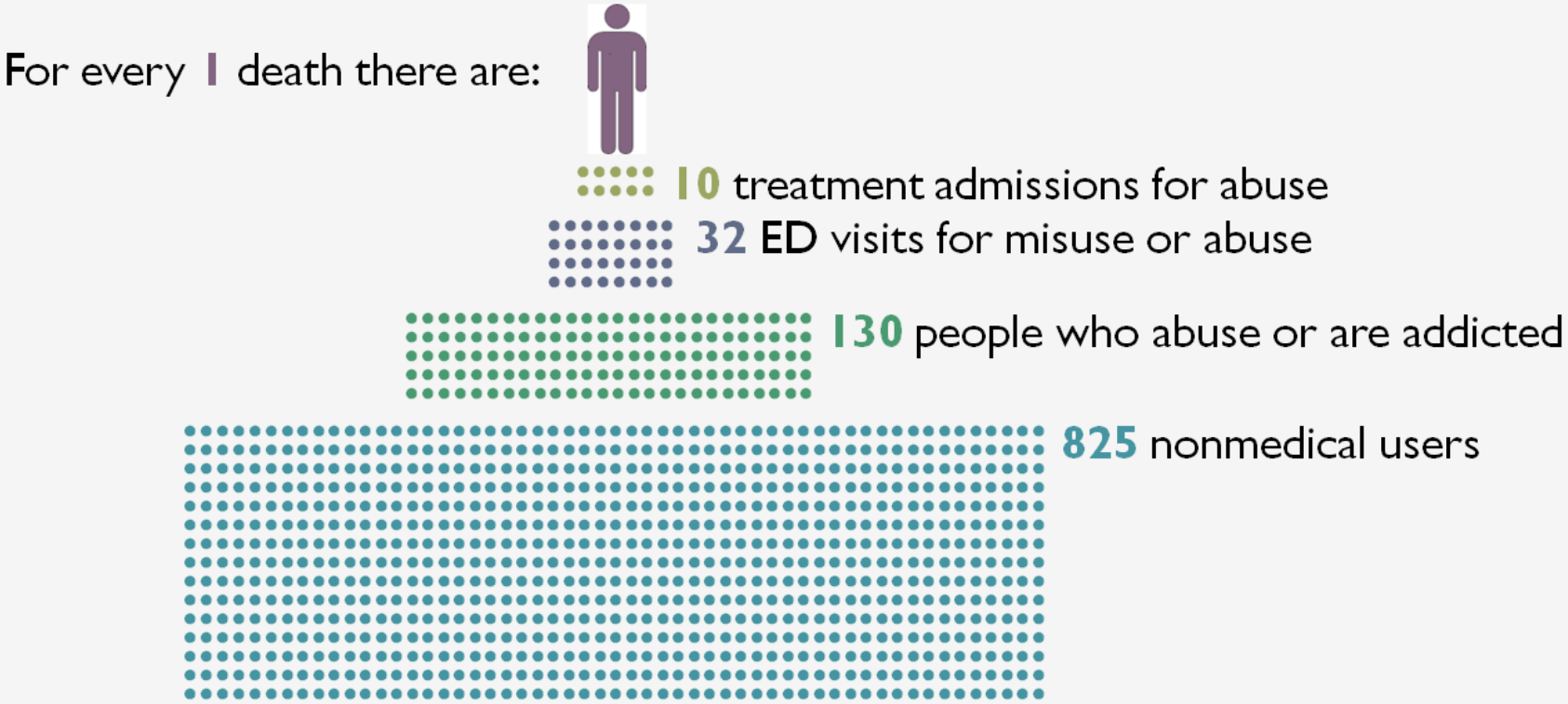
Drug Overdose Deaths by Major Drug Type, United States, 1999–2010



CDC, National Center for Health Statistics, National Vital Statistics System, CDC Wonder. Updated with 2010 mortality data.

Widespread Abuse and Misuse of Opioids

In 2008, there were 14,800 prescription painkiller deaths



http://www.cdc.gov/homeandrecreationalsafety/rxbrief/. Accessed Jan 2014.

PAIN

OPIOIDS

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Critical Vocabulary

- **Aberrant drug-related behavior:** Conduct outside the boundaries of the agreed upon treatment plan
- **Abuse:** Any use of an illegal drug, or a medication for a nonmedical purpose
- **Addiction:** Impaired control over drug use, compulsive use, continued use despite harm, and/or craving
- **Diversion:** The intentional transfer of a controlled substance from legitimate distribution and dispensing channels
- **Misuse:** Use of a medication other than as directed or as indicated
- **Physical dependence:** A state of biologic adaptation manifested by a withdrawal syndrome produced by decreasing blood levels of the drug
- **Tolerance:** A state of physiologic adaptation in which exposure to a drug induces a diminution of one or more opioid effects over time

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

REMS Education

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

http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm. Accessed Jan 2014.

What Drugs Are 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†
- Zohydro™ ER hydrocodone bitartrate ER capsules

Generics

- 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)

ER/LA Opioid Analgesics REMS. http://www.er-la-opioidrems.com/IwgUI/rems/products.action. Accessed Dec 2013.

Risks of ER/LA Opioid Analgesics

- Overdose with ER/LA formulations
- Abuse by patient or household contacts
  - Especially adolescent children
- Inadvertent exposure by household contacts
- Misuse and addiction
- Physical dependence and tolerance
- Interactions with other medications and substances
  - Medication reconciliation
- Financial (diverting drugs for illegal sale)

Your Patient Complains of Pain: Where to Start

- Consider source or etiology of pain
- In most circumstances, use a non-opioid pain medication first

FSMB Model Policy. http://www.fsmb.org/grpol_policydocs.html#2013. Accessed Dec 2013.

Clinical Interview: Getting Started

- **Complete history**
  - Family history of substance abuse (does not preclude treatment with ER/LA opioid)
  - Family history of psychiatric disorders
  - Social history, including criminal record
- **Complete physical examination**
- **Use a screening tool**
  - ORT, SOAPP, DIRE

Chou R, et al. *J Pain*. 2009;10(2):113-130.
http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm. Accessed Jan 2014.

Clinical Interview: Description and Impact of Pain

Description of current pain complaint

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

What causes or increases pain?

Effects of pain on physical, emotional, and psychosocial function

Patient's pain and functional goals

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

Brief Pain Inventory

General activity

Mood

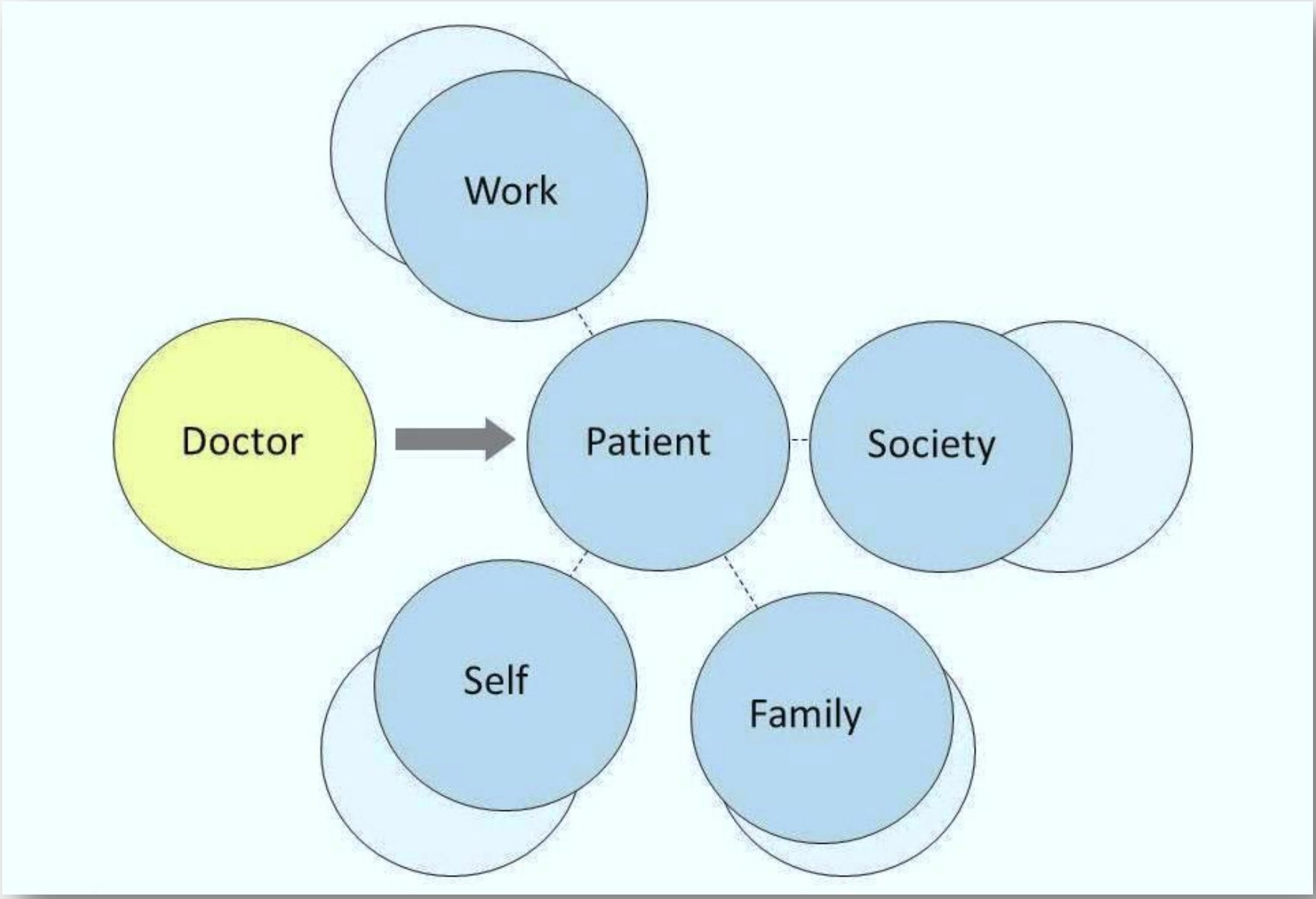
Walking ability

Normal work

Relations with other people

Sleep

Enjoyment of life


Work
Doctor
Patient
Society
Self
Family

Clinical Interview: Pain Coping Strategies

Pain Medications

Past use

Current use

- Query state **PDMP** where available to confirm patient report
- Contact past providers and obtain prior medical records
- Conduct Urine Drug Test **(UDT)**

Dosage

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

General Effectiveness

Nonpharmacologic strategies and effectiveness

Heapy A, Kerns RD. Psychological and Behavioral Assessment. In: *Raj's Practical Management of Pain*. 4th ed. 2008; 279-295. Department of Veterans Affairs, Department of Defense. *VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain*. 2010.

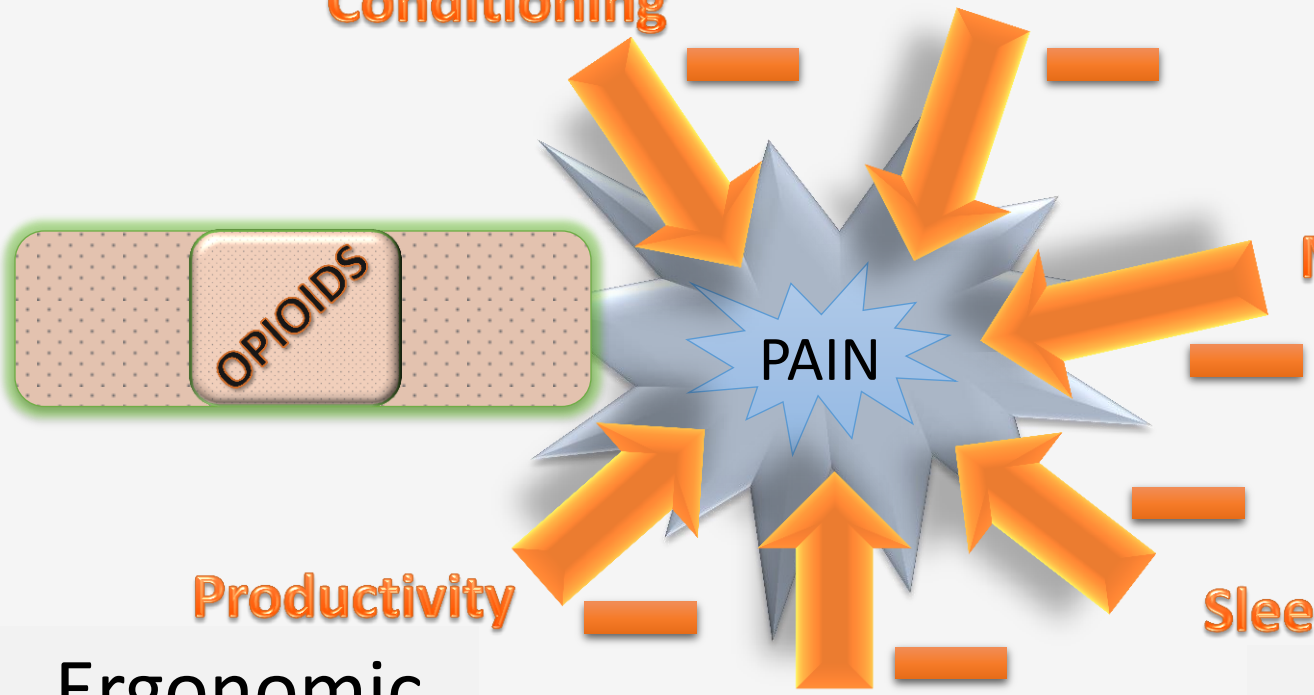
Types of pain treatments

Physical therapy

Psychological support

Skillful living

Conditioning



Acupuncture, Massage

Natural defenses

Productivity

Sleep

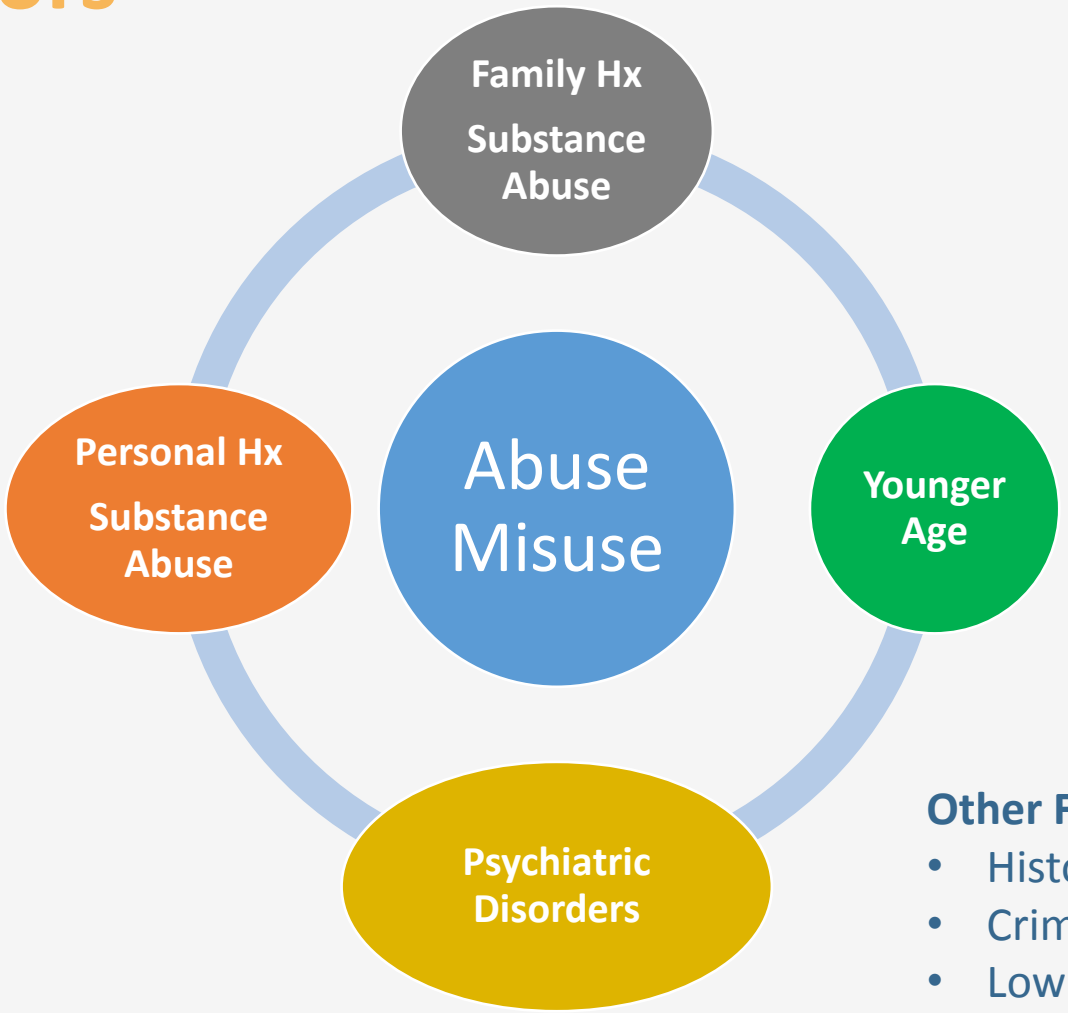
Ergonomic adaptation

Pain Resistance

‘Neuro-active’ medications

Sleep ‘tune-up’

Risk Factors for Aberrant Drug-related Behaviors



Other Factors:

- History of sexual abuse
- Criminal record
- Low reliability
- Lack of social support
- Smoking

Edlund MJ, et al. *Pain*. 2007;129(3):355-362.
Chou R, et al. *J Pain*. 2009;10(2):113-130.
Fishbain DA, et al. *Pain Med*. 2012;13(9):1212-1226.

What Were They Thinking?

- Is this patient really in pain?
- Is he/she seeking opioids?
- Is he/she an abuser?
- Is he/she addicted?

- Is the doctor taking my pain seriously?
- Should I reveal my history?
- Should I reveal my home life?

Validated Questionnaires

ORT	Opioid Risk Tool
SOAPP	Screener & Opioid Assessment for Patients with Pain
DIRE	Diagnosis, Intractability, Risk, and Efficacy inventory
STAR	Screening Tool for Addiction Risk
SISAP	Screening Instrument for Substance Abuse Potential
PDUQ	Prescription Drug Use Questionnaire

- No “gold standard”
- Lack of rigorous testing

Moore TM, et al. *Pain Medicine.* 2009;10(8):1426-1433.

Opioid Risk Tool (ORT)

Mark each box that applies		Female	Male
1.	**Family Hx 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 & 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)*

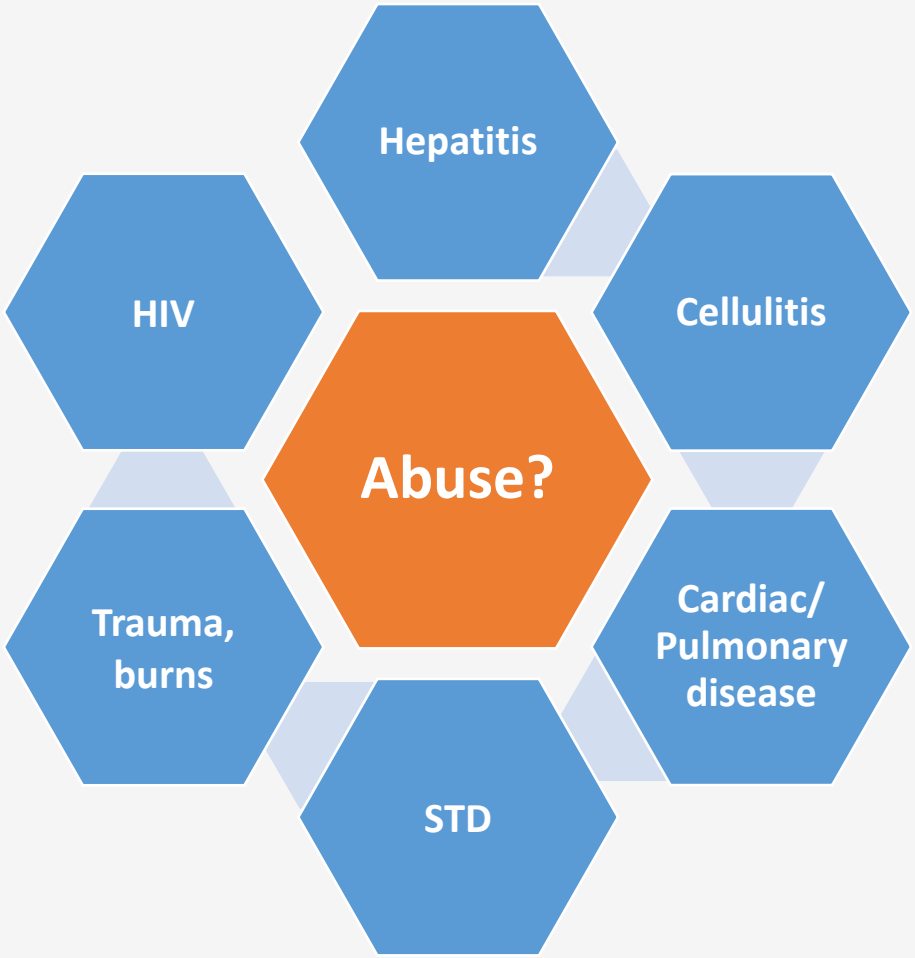
0-3: low

4-7: moderate

≥ 8: high

http://www.opioidrisk.com/node/2424. Accessed Jan 2014.
Webster LR, et al. *Pain Med.* 2005;6:432-442.

Clinical Interview: Conditions Suggestive of Abuse



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

Rationale for Urine Drug Testing (UDT)

Prior to Therapy

- Prior drug use
- Other drug use

During Therapy

- Adherence
- Legal requirement
- Grounds for referral
- Frequency per provider

Patient Presentation

- A 38-year-old divorced mother of three teenagers presents with complaints of lower back pain since an MVA 4 years ago
- She describes the pain as constant, intense, and encompassing her whole lower back area. She relates that it is exacerbated by walking, bending, and lifting. The pain makes activities of daily life difficult
- She would like to have her pain reduced to a tolerable level

Patient Work-Up

- Medical Hx
  - Prior physical therapy and medication have failed
- Social Hx
  - Remote history of marijuana use
  - Once convicted of writing bad checks
- Family Hx
  - Father abused alcohol
  - Recent break-up with an abusive boyfriend with a drug problem
- Exam
  - While describing the severity of her pain and her limitations, she does not appear to be in pain
  - Lower back demonstrates tenderness with some wincing
  - Gait is normal

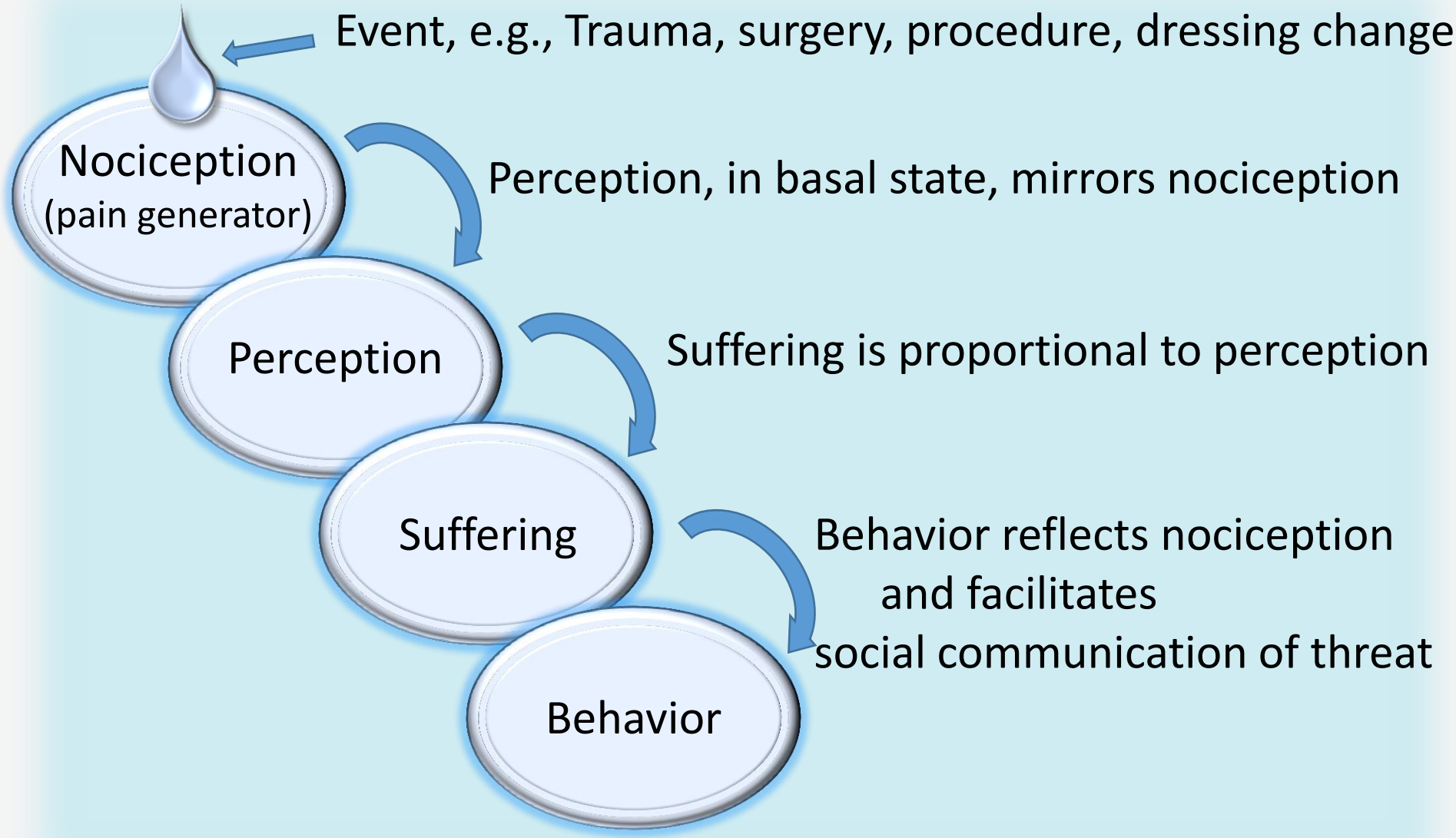
Patient Case

What is this patient's risk of abuse, misuse, or other aberrant behavior?

Low			Medium			High
1	2	3	4	5	6	7
◯	◯	◯	◯	◯	◯	◯

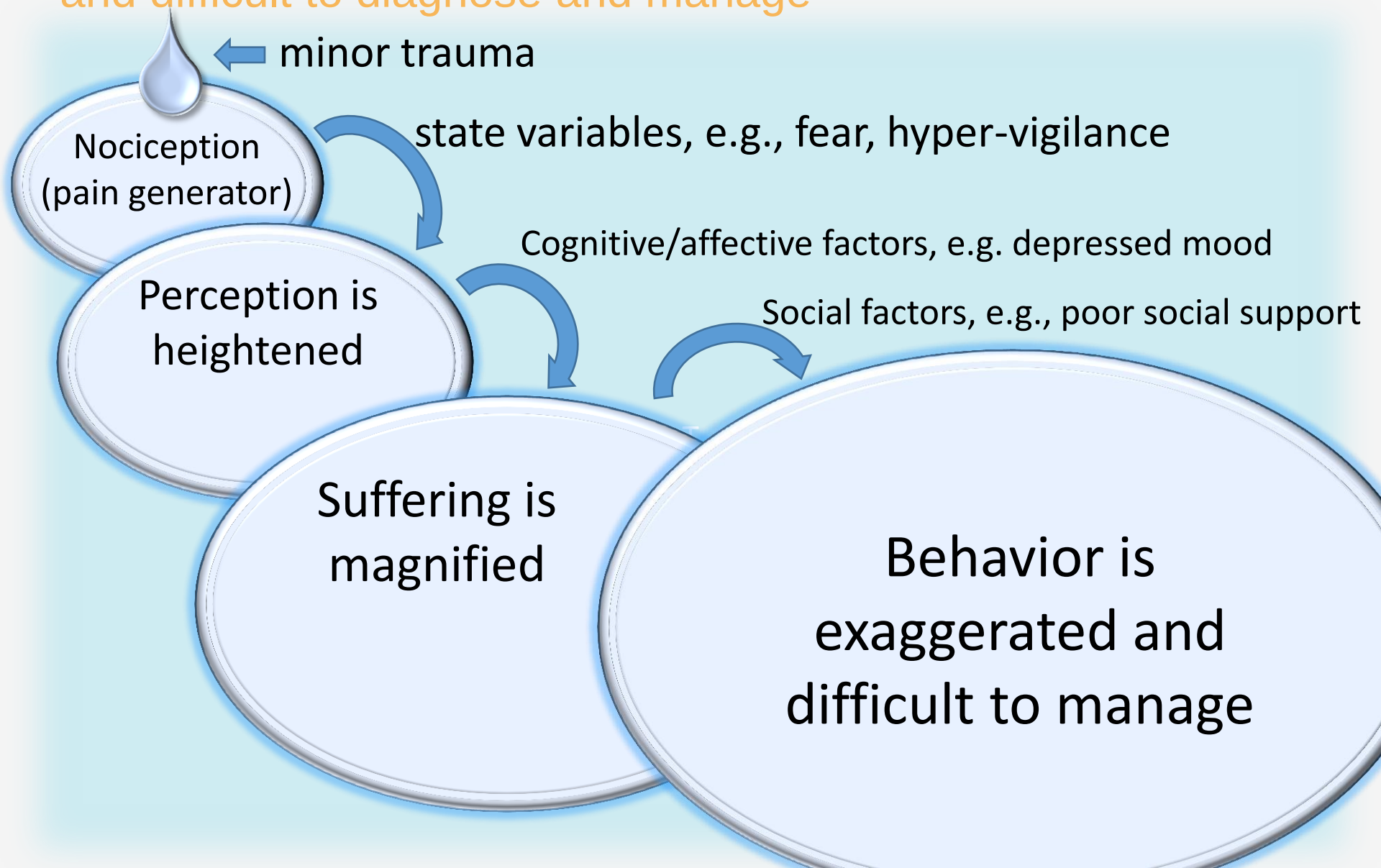
Biopsychosocial model of pain - modified

Modified to show normative function of the pain system



Biopsychosocial model of pain

How psychosocial factors can make pain amplified, chronic, and difficult to diagnose and manage



Referring High-Risk Patients

Prescribers should

Understand when to appropriately refer high-risk patients to pain management or addiction specialists

Regularly check your state's regulations for requirements

http://www.painpolicy.wisc.edu/database-statutes-regulations-other-policies-pain-management. Accessed February 2014.

Documentation

- A risk/benefit evaluation
  - History
  - Physical exam
  - Diagnostic testing
- Patient interactions
- Previous health records, including prescriptions, MRI, CT
- Patient permission to obtain records from other providers
- Provider communication with other providers
- Treatment plan, patient/provider agreement, informed consent (module 3)
- Aberrant drug-related behavior

Chou R, et al. *J Pain*. 2009;10(2):113-130.
http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm. Accessed Jan 2014.

Module 1 Key Messages

- ER/LA opioids can be effective for pain management
- Benefit must be weighed against risk
- Medical and behavioral factors influence risk of abuse or misuse
- Patients should be regularly assessed
- Documentation of assessments, patient interactions, treatment plans, aberrant drug-related behavior, and involvement of other providers is critical

Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics

Module 2

Learning Objectives

- Appropriately assess patients for the treatment of pain with ER/LA opioid analgesics, including analyzing risks versus potential benefits
- Assess patient's risk of abuse, including substance use and psychiatric history
- Identify state and federal regulations on opioid prescribing
- Incorporate strategies to effectively initiate therapy, modify dosing or discontinue use of ER/LA opioid analgesics in patients with pain
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Analgesic and Functional Goals

- **Decrease pain**
  - Treat underlying cause where possible
  - Minimize medication use
- **Restore function**
  - Physical, emotional, social
- **Correct secondary consequences of pain**
  - Postural deficits, weakness, overuse
  - Maladaptive behavior, poor coping

Patient Prescriber Agreements

Informed Consent

Communication process between patient and provider, including:

- Potential risks and benefits
  - Side effects (both short- and long-term)
  - Tolerance and physical dependence
  - Drug interactions and over-sedation
  - Impaired motor skills
  - Misuse, dependence, addiction, and overdose
  - Evidence of benefit
- Physician's prescribing policies and expectations
  - Number and frequency of refills
  - Policy on early refills and replacement of lost or stolen medications
- Specific reasons for changing or discontinuing opioid therapy, including violation of the treatment agreement

www.fsmb.org. Accessed Jan 2014.

Analgesic Selection

Non-opioid approaches should be considered first

- Address underlying condition
- Non-opioid analgesia

Short-acting opioids are probably safer than ER/LA for initial therapy

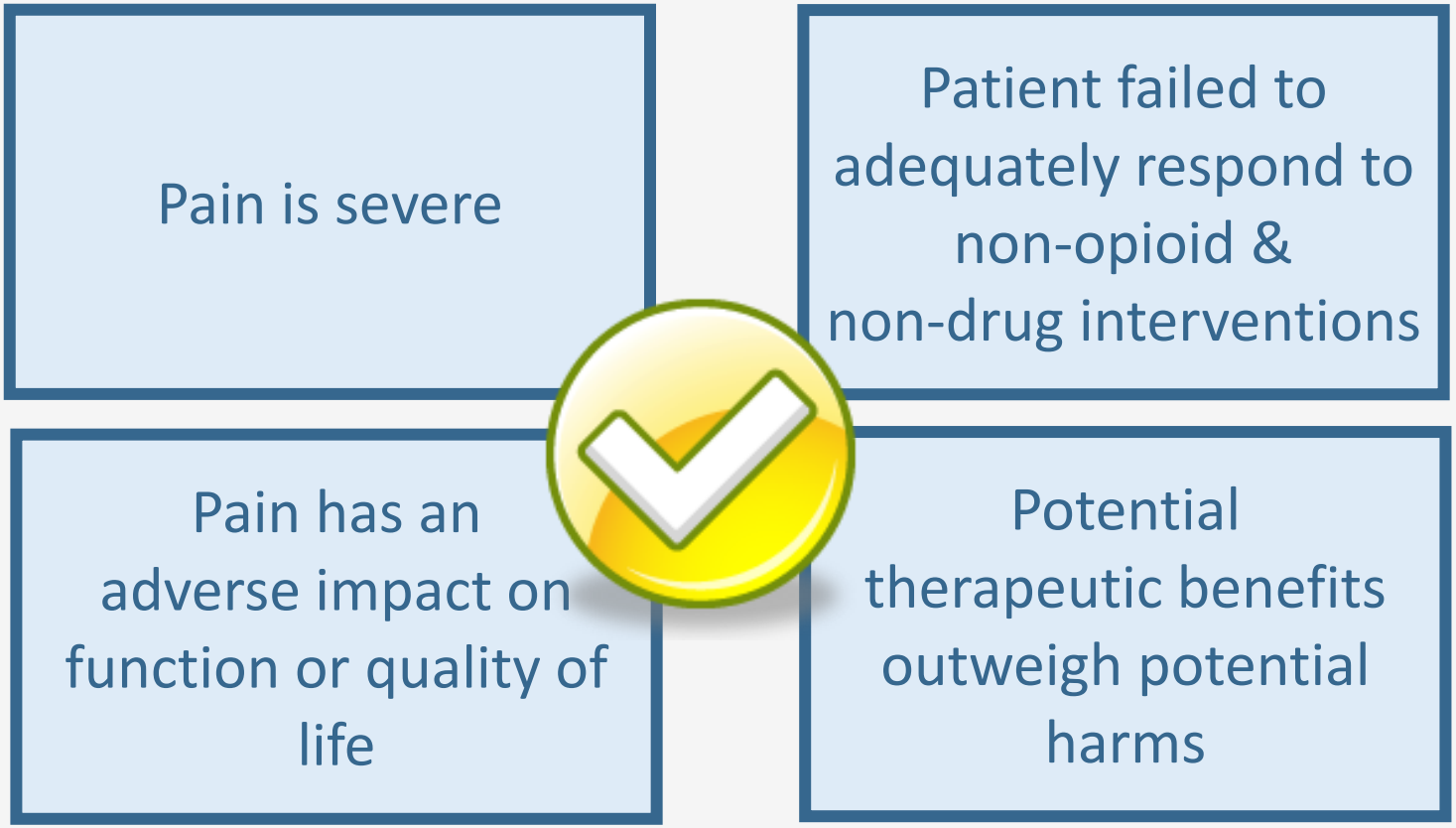
- Shorter half-life
- May have a lower risk of inadvertent overdose
- Better for break-through pain

Proposed benefits of long-acting opioids

- More consistent control of pain
- Improved adherence
- Lower risk of addiction or abuse

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

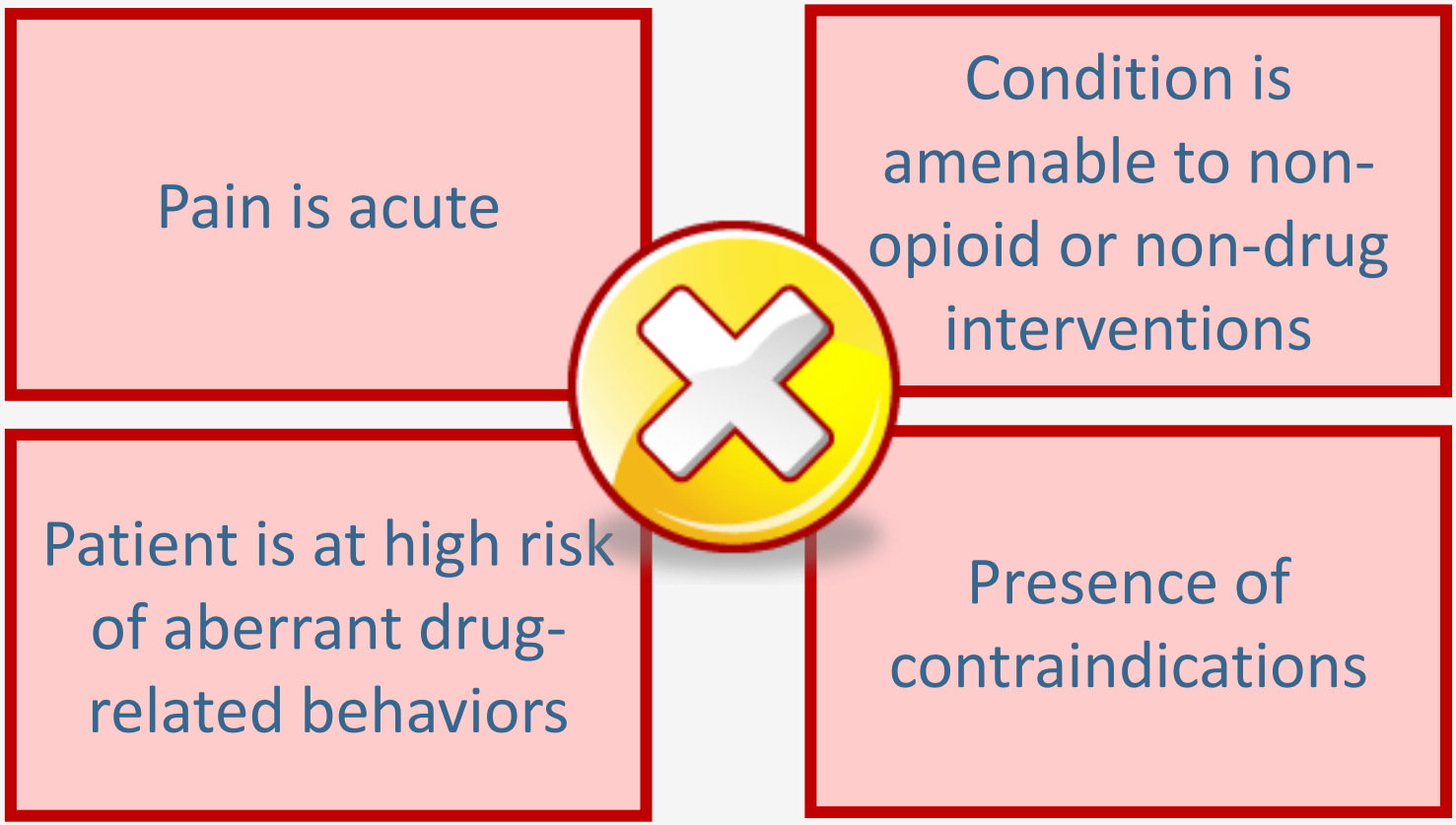
When to Consider a Trial of an ER/LA Opioid



Consider referral to pain or addiction specialist when risks outweigh benefits

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM367726.htm. Accessed April 2014.
Chou R, et al. *J Pain.* 2009;10:113-130.

When to Not Consider a Trial of an ER/LA Opioid



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

Initiating & Titrating ER/LA Opioid Analgesics: Opioid-Naïve Patients

Drug/Dose

- For naïve?
- Drug PI

Monitor

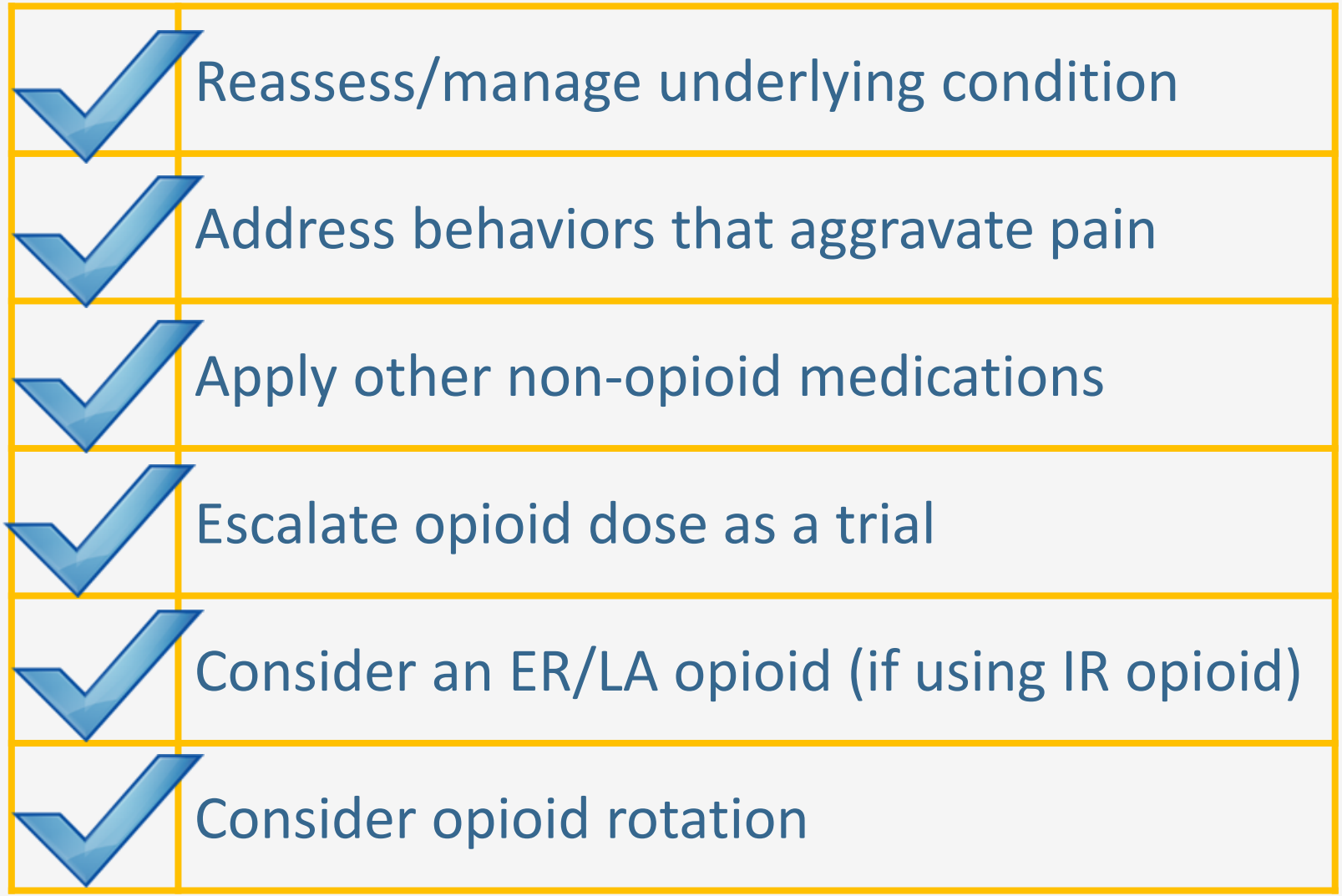
- Respiratory Depression
- 24-72 hours

Titrate

- Efficacy
- Tolerability
- Adverse Effects
- Minimum interval→ Drug PI

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

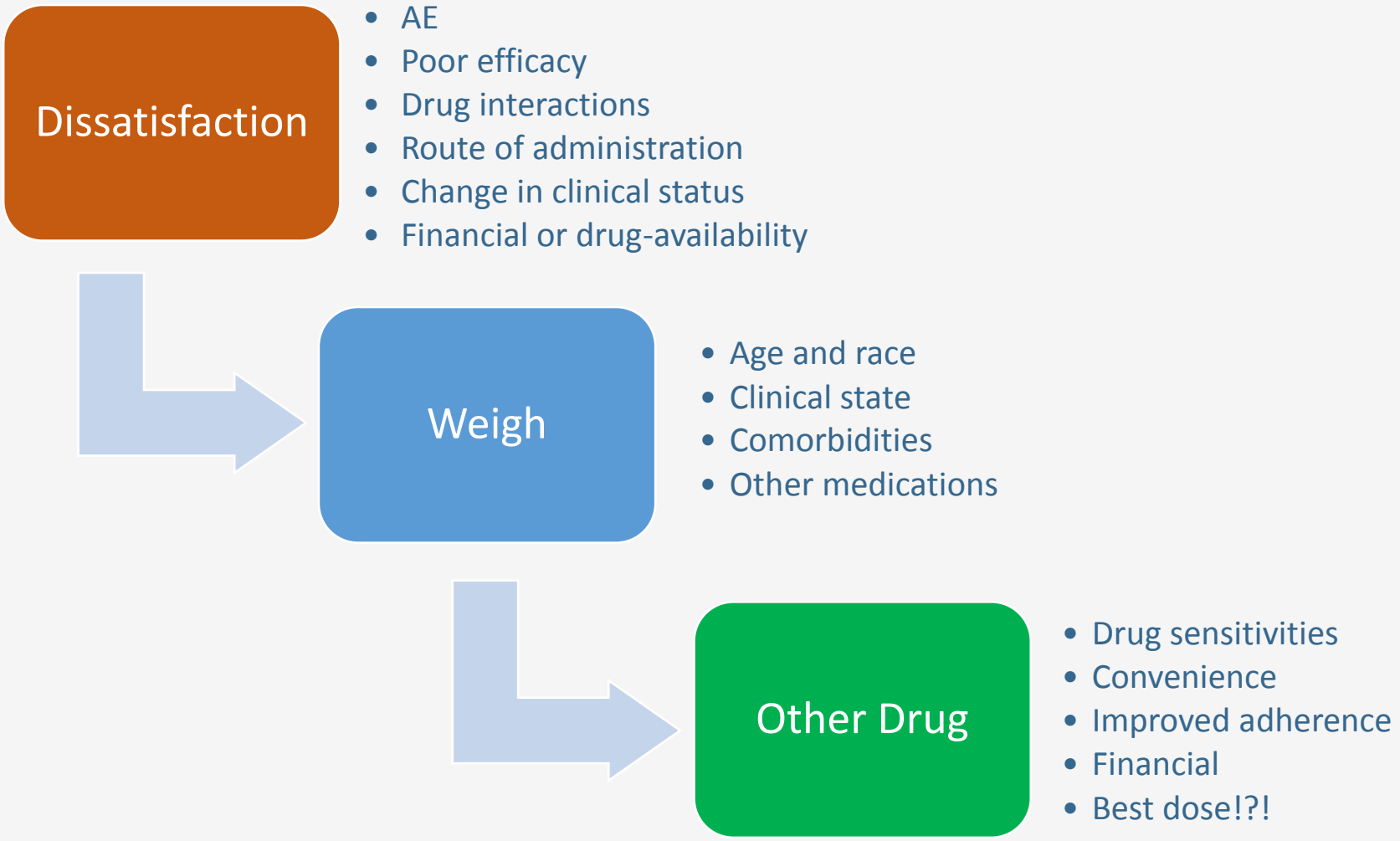
When Analgesia is Inadequate



Converting From Immediate Release to ER/LA Opioids

- Safety is primary
- Before conversion to a long-acting opioid, use immediate release preparations to titrate to the appropriate 24 hour dose
- Different approaches
  A. Use opioid equianalgesic dose table (EDT, conversion table) to switch
  B. Use cross-titration
     - Slowly decrease old opioid
     - Slowly increase new opioid
     - May take weeks to achieve proper dosing

Switching ER/LA Opioids: Rotation



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

You have decided to switch ER/LA medications. At what dose should the second ER/LA opioid be initiated?

- ◯ Equivalent dose, from the ED table
- ◯ 25–50% reduction of equivalent dose
- ◯ 75% reduction of equivalent dose
- ◯ Initiate as new treatment after wash-out period

Choosing a New Dose

Calculate equianalgesic dose of new opioid from EDT

Reduce calculated equianalgesic dose
- Generally: 25–50% reduction
- Methadone: 75–90% reduction
- Use clinical judgment

~50% reduction if patient

- Receives a high dose of current opioid
- Elderly or medically frail

~25% reduction if patient

- Is staying on current opioid but switching to a different administration route

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

Guidelines for Opioid Rotation

If switching to **methadone:**

- Reduce calculated equianalgesic dose by **75–90%**
- For patients on very high opioid doses, be cautious converting to methadone ≥ 100 mg/d
  - Consider inpatient monitoring, including serial EKG

If switching to **transdermal formulation:**

- **Fentanyl**: use equianalgesic dose ratios in the PI
- **Buprenorphine**: follow instructions in the PI

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

Guidelines for Opioid Rotation

Titrate new opioid dose

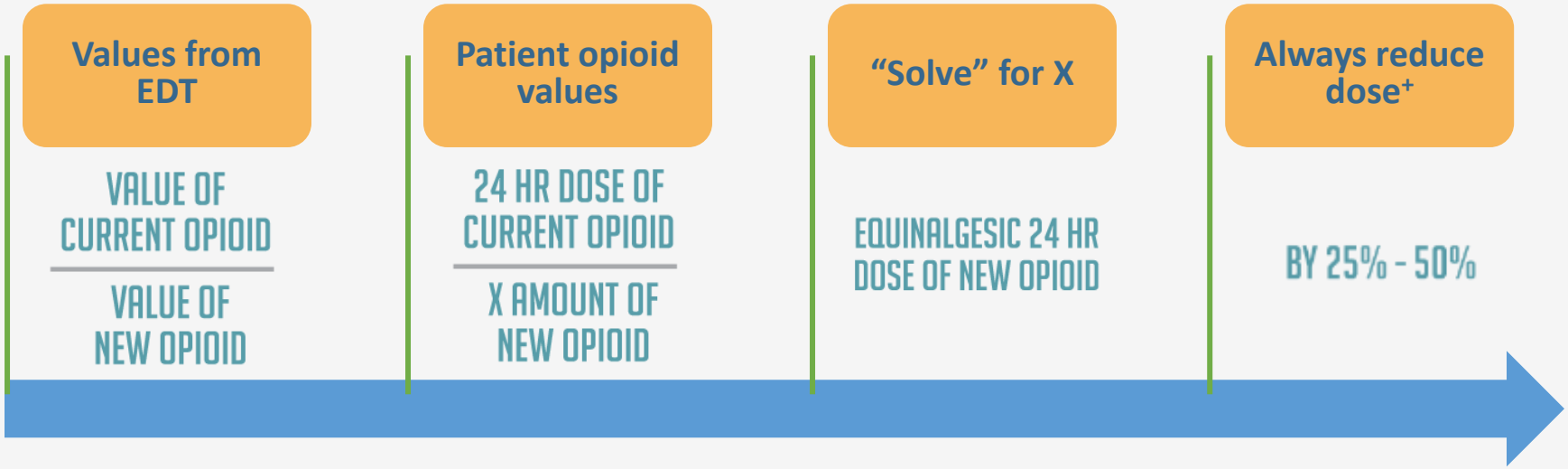
Frequently assess: Analgesia → AEs → Withdrawal symptoms

Break Through Pain

- Use a short-acting, immediate release preparation at 5–15% of total daily opioid dose
- If oral transmucosal fentanyl is used for BTP, always begin at lowest dose
- NEVER use ER/LA opioids for BTP

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

Opioid Rotation: Summary



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 methadone, reduce dose by 75–90%

‡If oral transmucosal fentanyl used as rescue, begin at lowest dose irrespective of baseline opioid

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

ER/LA Opioid-Induced Respiratory Depression

Chief hazard of opioids

- May lead to respiratory arrest & death
- Greatest risk after initiation or dose increase
- Alcohol, sedatives, hypnotics, etc

Reduced urge to breathe & decreased respiration rate

- Shallow breathing
- CO_2 retention can exacerbate opioid sedating effects

Instruct patients/ family

- Symptoms
- Call 911
- Dangerous polypharmacy

Chou R, et al. *J Pain.* 2009;10:113-130.
Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 2012.
www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf

Opioid Exit Strategy – Possible Paths

Patient's behavior consistent with drug addiction	Patient unable or unwilling to cooperate with outpatient taper	No apparent addiction problem Patient able to cooperate with office-based taper
• Refer for addiction management or comanagement	• Provide limited and closely monitored prescriptions while referring to more intensive services	• Taper gradually over 1-2 months • Implement non-opioid pain management (psychosocial support, CBT, PT, non-opioid analgesics)

CBT, cognitive behavioral therapy; PT, physical therapy.

Katz, N. *Patient Level Opioid Risk Management: A Supplement to the PainEDU.org Manual*. Newton, MA: Inflexxion, Inc; 2007.

Webster LR, Dove B. *Avoiding Opioid Abuse While Managing Pain: A Guideline for Practitioners.* 1st Edition. North Branch, MN: Sunrise Press; 2007.

Taper Dose When Discontinuing

Avoid withdrawal symptoms in opioid dependent patients

Optimal setting

- Outpatient in absence of unstable medical or psychiatric conditions or unsafe patterns of behavior
- Higher risk patients may need a more structured setting

When aberrant drug-related behaviors continue, may need

- Close monitoring and enforced tapering or
- Discontinued prescription and referral to detox or
- Agonist therapy

May use a range of approaches

- Slow…10% dose reduction/week
- Rapid…25–50% reduction every few days

Chou R, et al. *J Pain.* 2009;10:113-130.
Department of Veterans Affairs, Department of Defense. *VA/DoD Clinical Practice Guideline for Management of Opioid Therapy*

Taper Dose When Discontinuing

Factors that influence the reduction rate:

- Reason for discontinuation
- Medical and psychiatric comorbidities
- Initial weaning rate
  - Faster at high doses (eg, > 200 mg/d morphine equivalent)
  - Slower at low doses (eg, 60-80 mg/d morphine equivalent)
- Monitor withdrawal symptoms

After taper:

- Continue to treat pain with non-opioids
- Treat psychiatric disorders
- Assess for and treat addiction-related aberrant behaviors

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

Module 2 Key Messages

- Best analgesic choice depends on patient and condition
  - Non-opioid analgesia
  - Immediate-release opioid
  - ER/LA opioid
- Rotation/conversion is not an exact science but protocols give guidance
- ER/LA are not for breakthrough pain
- Respiratory depression is rare but serious
- Opioids should be discontinued by tapering

Managing Therapy with ER/LA Opioid Analgesics

Module 3

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  - Maladaptive behavior, poor coping

Pain Assessment

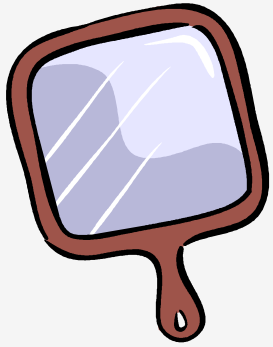
- **Current pain**
  - Numeric rating scale
  - Visual analog scale
  - Faces scale
- **Pain history**
- **PQRS Measure #131**

Patients sometimes assume that **you don't believe their pain complaints**

They may exaggerate pain scores

Self-Reflection on Patient Management

How often do you use quantitative scales for pain, functional status, and adverse events?



	Never			Sometimes			Always
	1	2	3	4	5	6	7
Pain	◯	◯	◯	◯	◯	◯	◯
Function	◯	◯	◯	◯	◯	◯	◯
AEs	◯	◯	◯	◯	◯	◯	◯

CDC HRQOL Healthy Days Measure

1. Would you say that, in general, your health is:

2. Now thinking about your PHYSICAL HEALTH, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?

3. Now thinking about your MENTAL HEALTH, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?

4. During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation?

http://www.cdc.gov/hrqol/hrqol14_measure.htm#1. Accessed Jan 2014.

Side Effect Rating Scale: FIBSER

Frequency, Intensity, and Burden of Side Effects Rating

Frequency

- % time present
- None→ always
- 0-6 scale

Intensity

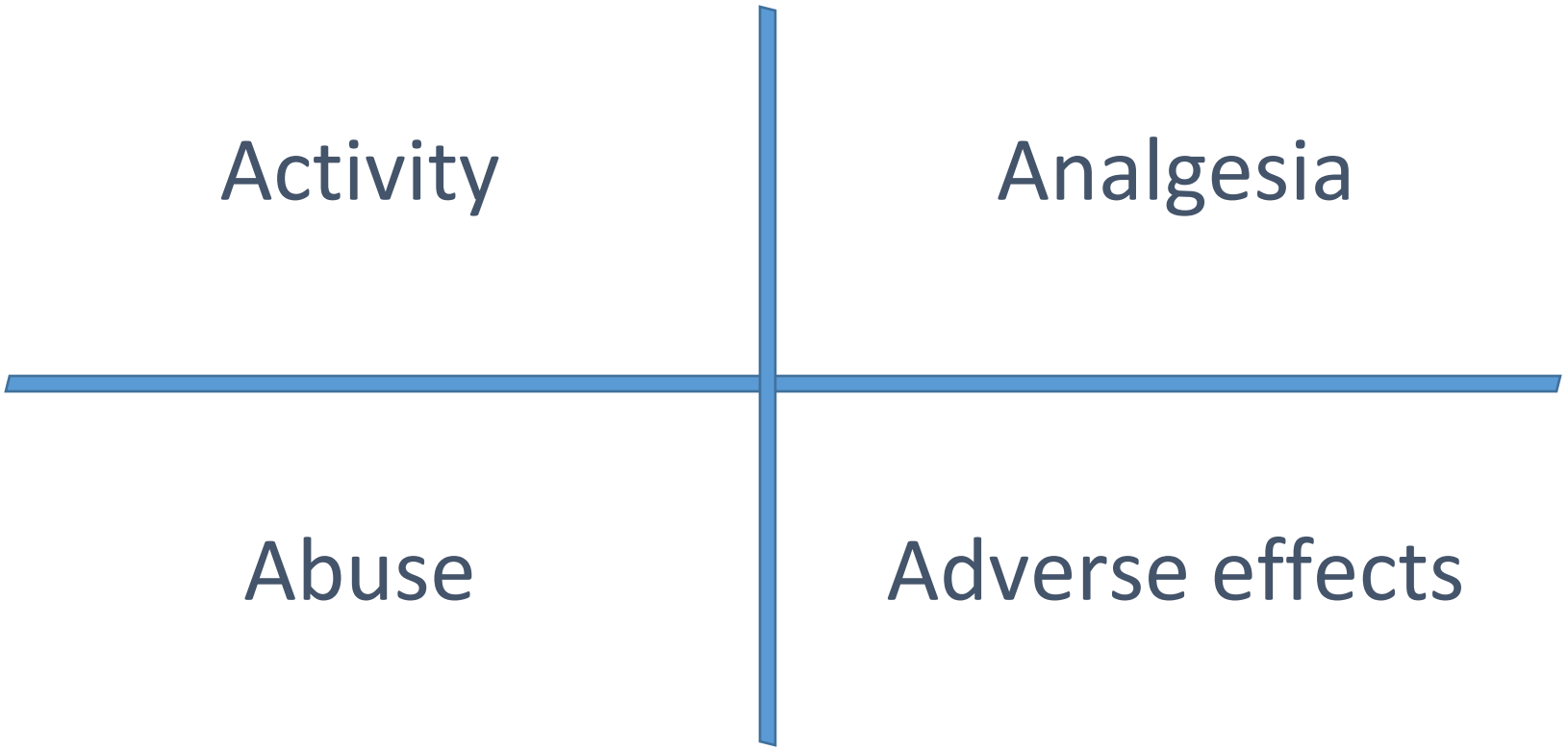
- Severity
- None→ intolerable
- 0-6 scale

Impact

- Degree of interference
- None→ nonfunctional
- 0-6 scale

Wisniewski SR, et al. *J Psychiatr Pract*. 2006;12(2):71-79.
http://www.medscape.org/viewarticle/752781. Accessed Jan 2014.

The four ‘A’s of pain reassessment



Patient Prescriber Agreements

Informed Consent

Communication process between patient and provider, including:

- Potential risks and benefits
  - Side effects (both short- and long-term)
  - Tolerance and physical dependence
  - Drug interactions and over-sedation
  - Impaired motor skills
  - Misuse, dependence, addiction, and overdose
  - Evidence of benefit
- Physician's prescribing policies and expectations
  - Number and frequency of refills
  - Policy on early refills and replacement of lost or stolen medications
- Specific reasons for changing or discontinuing opioid therapy, including violation of the treatment agreement

www.fsmb.org. Accessed Jan 2014.

Patient Prescriber Agreements
Written Opioid Treatment Agreement

Treatment Goals

- Pain
- Function

Roles Responsibilities

- Visits
- Monitoring
- Medication safeguards

Grounds for Continuation

- Progress towards goals
- Tolerable AEs
- Adherence to agreement

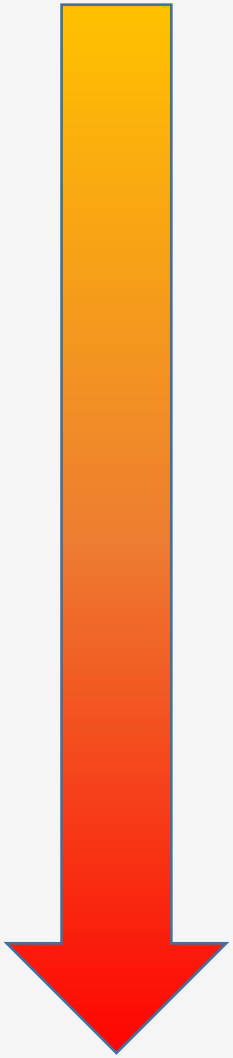
Decision

_____, Patient _____Date

_____, Provider _____Date

Cheatle MD, et al. *J Pain Symptom Manage*. 2012;44(1):105-116.

Red Flags of Aberrant Behavior



- Requests for increase opioid dose
- Requests for specific opioid by name, “brand name only”
- Nonadherence with other recommended therapies (eg, PT)
- Running out early (ie, unsanctioned dose escalation)
- Resistance to change therapy despite AE (eg, over-sedation)
- Deterioration in function at home and work
- Cigarette smoking
- Nonadherence with monitoring (eg, pill counts, urine drug tests)
- Multiple “lost” or “stolen” opioid prescriptions
- Illegal activities – forging scripts, selling opioid prescription

Modified from Portenoy RK. *J Pain Symptom Manage*. 1996;11(4):203-217.

Rationale for Urine Drug Testing (UDT)

Prior to Therapy

- Prior drug use
- Other drug use

During Therapy

- Adherence
- Legal requirement
- Grounds for referral
- Frequency per provider

UDT Stages

SCREENING

- Immunoassay
- Drug class
- Qualitative (+/-)
- Lab or POC

CONFIRMATION

- GC/MS or LC/MS
- Specific, definitive
- Quantitative
- Lab

SAMHSA. *Clinical Drug Testing in Primary Care.* Technical Assistance Publication (TAP) 32. HHS Publication No.(SMA) 12-4668. Rockville, MD: SAMHSA, 2012.

Specific Windows of Drug Detection

Drug in Urine	Time
Amphetamines	≤ 2 d
THC – Single use – Chronic use	 1-3 d ≤ 30 d
Benzoylecgonine after cocaine use	2-4 d
Opiates (morphine, codeine)	2-3 d
Methadone – EDDP (methadone metabolite)	≤ 3 d ≤ 6 d
Benzodiazepines (depending on drug and dose)	Days to weeks

Moeller KE, et al. *Mayo Clin Proc*. 2008;83(1):66-76.

Interpretation of Confirmed Results

Positive Result

Demonstrates recent use

- Most drugs have detection times of 1-3 d
- Chronic use of lipid-soluble drugs: test positive for ≥ 1 week

Does not diagnose

- Drug addiction, physical dependence, or impairment
- Metabolism can alter results

Can't 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

Milone MC. *J Med Toxicol*. 2012;8(4):408-416.

Interpretation of UDT Results

- Use UDT results in conjunction with other clinical information
- Investigate unexpected results

Discuss with the lab

Discuss with the patient

A positive result is probably ….

a positive result.

- Document results, interpretation, and action
- May necessitate closer monitoring and/or referral to a specialist

Screening for Substance Abuse

- **Pain Assessment and Documentation Tool (PADT)**
  - 17 Y/N questions
  - Plus pain and function sections
- **Current Opioid Misuse Measure (COMM)**
  - 17 questions
  - 5 item Likert scale

Passik SD, et al. *Clin Ther*. 2004;26(4):552-561.
https://www.nhms.org/node/128 Accessed Jan 2014.
Butler SF, et al. *Pain*. 2007;130(1-2):144-156.
http://www.painedu.org/. Accessed Jan 2014.

Recognizing Addiction

- DSM-5 Criteria for Substance Use Disorder[1]
  - Tolerance
  - Withdrawal
  - Taken more/longer than intended
  - Desire/unsuccessful efforts to quit use
  - Great deal of time taken by activities involved in use
  - Use despite knowledge of problems associated with use
  - Important activities given up because of use
  - Recurrent use resulting in a failure to fulfill important role obligations
  - Recurrent use resulting in physically hazardous behavior (eg, driving)
  - Continued use despite recurrent social problems associated with use
  - Craving for the substance

≥ 2 items → Dx

≥ 6 items → severe case

- Pain Medicine Questionnaire[2] (PMQ, 26 self-report items)
- Screener and Opioid Assessment for Patients with Pain[3] (SOAPP, 24 self-report items)

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth edition*. Arlington,VA: American Psychiatric Publishing(2013).
2. Adams LL, et al. *J Pain Symptom Manage.* 2004;27(5):440-459.
3. Butler SF, et al. *Pain*. 2004;112(1-2):65-75.

Case

- You have started a 49-year-old married mother of 2 grown children on a short-acting opioid for failed back syndrome. She got little relief from the first dose you prescribed and little relief from 3 months of a higher dose
  - Your staff points out that she has requested early refills twice
- Her son calls about his mother's treatment
- He reports that she is uncommunicative, spending more time in bed and on the sofa, and not leaving the house for social events and church as was her custom. This information conflicts with the patient's reports to you that she is
  - Functioning as before
  - Having lots of pain
- A random UDT is positive for **your opioid** and **a benzodiazepine**
- At the next visit the patient reports that she is
  - Functioning as before
  - Having lots of pain
- Her physical exam is unchanged
- You decide to speak candidly with her about her care

Confidence in Patient Management

What conclusion(s) can you make on the basis of the UDT? (choose all that apply)

- ❑ She is taking the opioid as directed
- ❑ She may be abusing other drugs
- ❑ She is not taking the opioid as directed
- ❑ She may be addicted

Common Adverse Events

Nausea/Vomiting	• Tend to self-resolve • Switch opioid • Antiemetic
Sedation	• Tends to self-resolve • Decrease dose
Constipation	• Laxative • Bowel stimulant • Switch opioid
Pruritus	• Tends to self-resolve • Antihistamines • Switch opioid

Many patients report being allergic to pain medication, especially opioids

Swegle JM, et al. *Am Fam Physician*. 2006;74(8):1347-1354.
Benyamin R, et al. *Pain Physician.* 2008;11(2 Suppl):S105-S120.

Universal Precautions for Prescribing Controlled Substances

1. Make a Diagnosis with Appropriate Differential
2. Psychological Assessment Including Risk of Addictive Disorders
3. Informed Consent
4. Treatment Agreement
5. Pre- and Post-Intervention Assessment of Pain Level and Function
6. Appropriate Trial of Opioid Therapy +/– Adjunctive Medication
7. Reassessment of Pain Score and Level of Function
8. Regularly Assess the "Five A's" of Pain Medicine
   - Analgesia
   - Adverse effects
   - Affect
   - Activity
   - Aberrant behavior
9. Periodically Review Pain Diagnosis and Comorbid Conditions, including Addictive Disorders
10. Documentation

Adapted from Gourlay DL, et al. *Pain Med.* 2005;6(2):107-112.

Module 3 Key Messages

- Set specific analgesic and functional goals
- Use a PPA as a framework
- Document discussions, patient commitments, actions, results
- Refer patients for addiction and abuse treatment as needed
- Identify and manage adverse events

Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

Module 4

Learning Objectives

- Appropriately assess patients for the treatment of pain with ER/LA opioid analgesics, including analyzing risks versus potential benefits
- Assess patient's risk of abuse, including substance use and psychiatric history
- Identify state and federal regulations on opioid prescribing
- Incorporate strategies to effectively initiate therapy, modify dosing or discontinue use of ER/LA opioid analgesics in patients with pain
- Manage ongoing therapy with ER/LA opioid analgesics
- Incorporate effective counseling for patients and caregivers about the safe use of ER/LA opioid analgesics
- Discuss general and product-specific drug information related to ER/LA opioid analgesics

Patient Counseling Document: The DOs of ER/LA Opioids

- READ the medication guide
  - Take your medicine exactly as prescribed
  - Store your medicine in a safe place away from children
  - Flush unused medicine down the toilet
  - Seek help if you do not understand something

- REPORT side effects
  - Call your health care provider
  - Report to the 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 health care provider
  - If the medication does not control your pain
  - About side effects
  - About all your medicines: Rx, OTC, vitamins, and supplements

http://www.er-la-opioidrems.com/IwgUI/rems/pcd.action. Accessed Jan 2014.

Patient Counseling Document: The DON'Ts of ER/LA Opioids

DON'T give your medicine to others

DON'T take medicine unless it was prescribed for you

DON'T stop taking your medicine without talking to your health care provider

DON'T break, chew, crush, dissolve, or inject your medicine

DON'T drink alcohol while taking this medicine

http://www.er-la-opioidrems.com/IwgUI/rems/pcd.action. Accessed Jan 2014.

Reflection on Clinical Practice

How do you use the ER/LA opioid prescribing information when counseling a patient with chronic pain? (choose all that apply)

- ❑ I don't generally refer to it
- ❑ I use it to discuss dosing
- ❑ I use it to discuss side effects and warnings
- ❑ I use to structure the patient discussion
- ❑ I give a copy to patients

http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed Jan 2014.

Product-Specific Information

- Drug **Prescribing Information** documents include critical information
  - Indications, usage
  - Dosage forms and strengths, administration
  - Contraindications, warnings, precautions
  - Common adverse reactions, drug interactions
  - Specific populations
  - Counseling information, medication guide
- Easily available: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

One of your patients travels a lot and has an irregular lifestyle. She is scrupulously adherent; her testimony is supported by UDTs. Airline seats and lack of exercise have exacerbated her back pain and she has developed tolerance to oxycodone. What is your recommendation?

- ◯ Increase her oxycodone dose
- ◯ Convert to a transdermal formulation
- ◯ Taper her oxycodone and seek a non-opioid analgesic

Special Warnings for 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 and death
  - Applesauce or feeding tube may be appropriate (consult PI)

- Use of other CNS depressants with ER/LA opioids can cause overdose and death
  - Sedative-hypnotics and anxiolytics
  - Alcohol
  - Illegal drugs
- Use other CNS depressants, including other opioids, under the instruction of their prescriber
- Do not abruptly stop or reduce the ER/LA opioid dose

Medication Guide

- Each PI contains detailed patient instructions about dosing, custody, precautions, disposal, etc
- Lay language, should be shared with patients verbally and in printed form
- Patient literacy and/or language barriers must be identified and addressed

Medication Guide
KADIAN® (key-dee-uhn)
(morphine sulfate) extended-release capsules, CII

KADIAN is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about KADIAN:

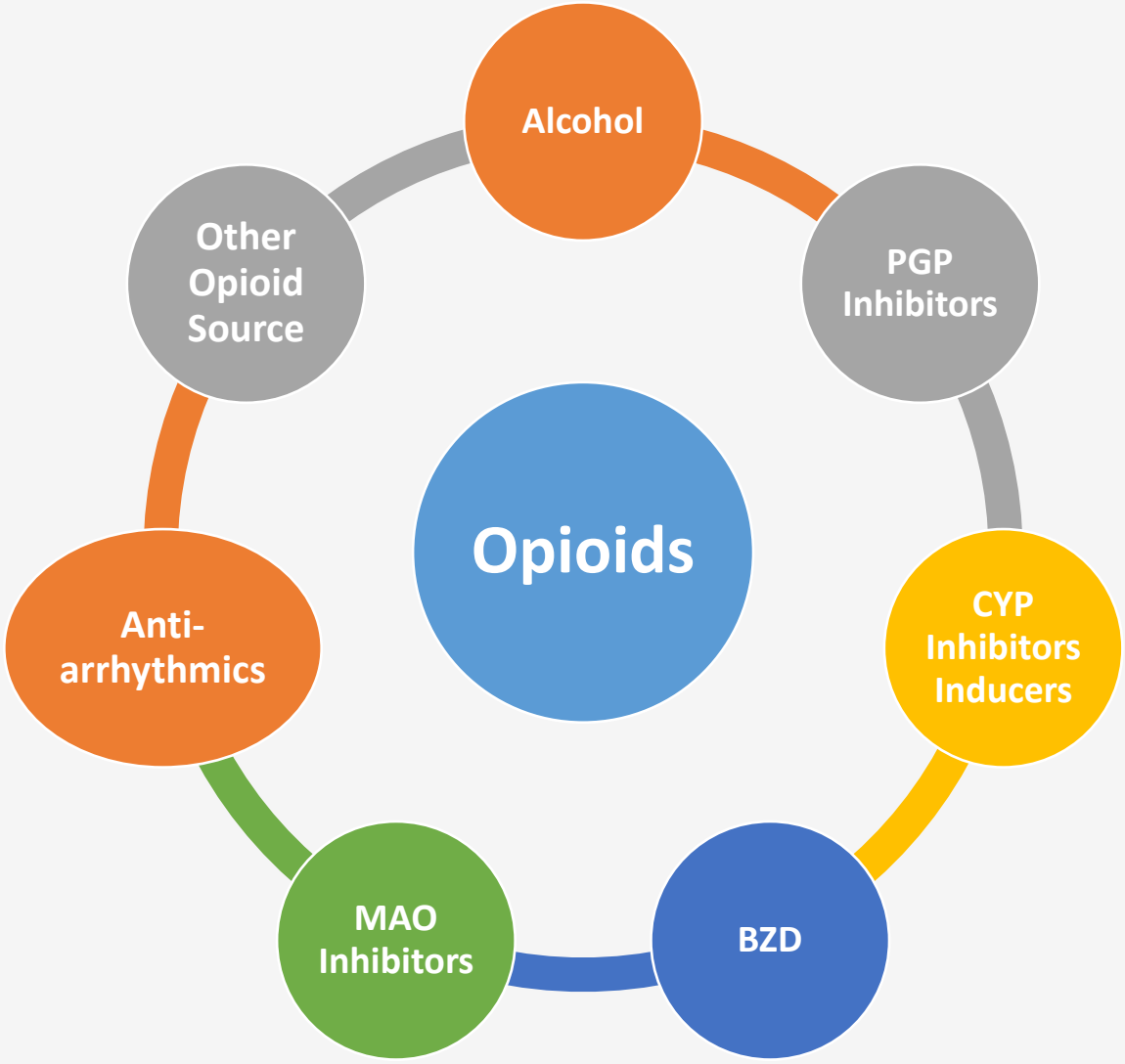
- **Get emergency help right away if you take too much KADIAN (overdose).** When you first start taking KADIAN, when your dose is changed, or if you take too much (overdose), serious or life threatening breathing problems that can lead to death may occur.
- Never give anyone else your KADIAN. They could die from taking it. Store KADIAN away from children and in a safe place to prevent stealing or abuse. Selling or giving away KADIAN is against the law.

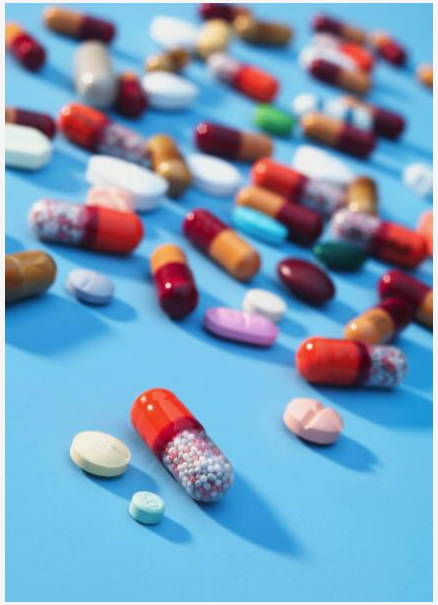
Do not take KADIAN if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Accessed April 2014.

Review All Medications:
What Other Drugs Might Impact Treatment?





Specific Drug Interactions

Product	Alcohol*	PGP Inhibitors	CYP 3A4 Inhibitors/ Inducers	CYP 450 Inhibitors/ Inducers	Benzo-diazepines	MAO Inhibitors	Class IA + III Antiarrhythmics
Morphine sulfate ER (Avinza)	✓	✓					
Morphine sulfate ER (Kadian)	✓	✓					
Morphine sulfate CR (MS Contin)		✓					
Morphine sulfate ER-Naltrexone (Embeda)	✓	✓					
Oxycodone HCl (OxyContin)			✓				
Oxymorphone HCl (Opana ER)	✓						
Hydromorphone HCl (Exalgo)							
Methadone (Dolophine)				✓	✓		✓
Tapentadol (Nucynta ER)	✓					✓	
Fentanyl Transdermal (Duragesic)			✓				
Buprenorphine Transdermal (Butrans)			✓		✓		✓

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013 www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf. Accessed January 2014.

PGP: P-glycoprotein
MAO: monoamine oxidase
*Including medications containing alcohol

Diversion in the Home

Own the Prescriptions

- Note how many pills in each prescription bottle or packet
- Take inventory of all prescription drugs in your home
- Track refills for all household members
- Keep meds in a safe place, not the bathroom cabinet

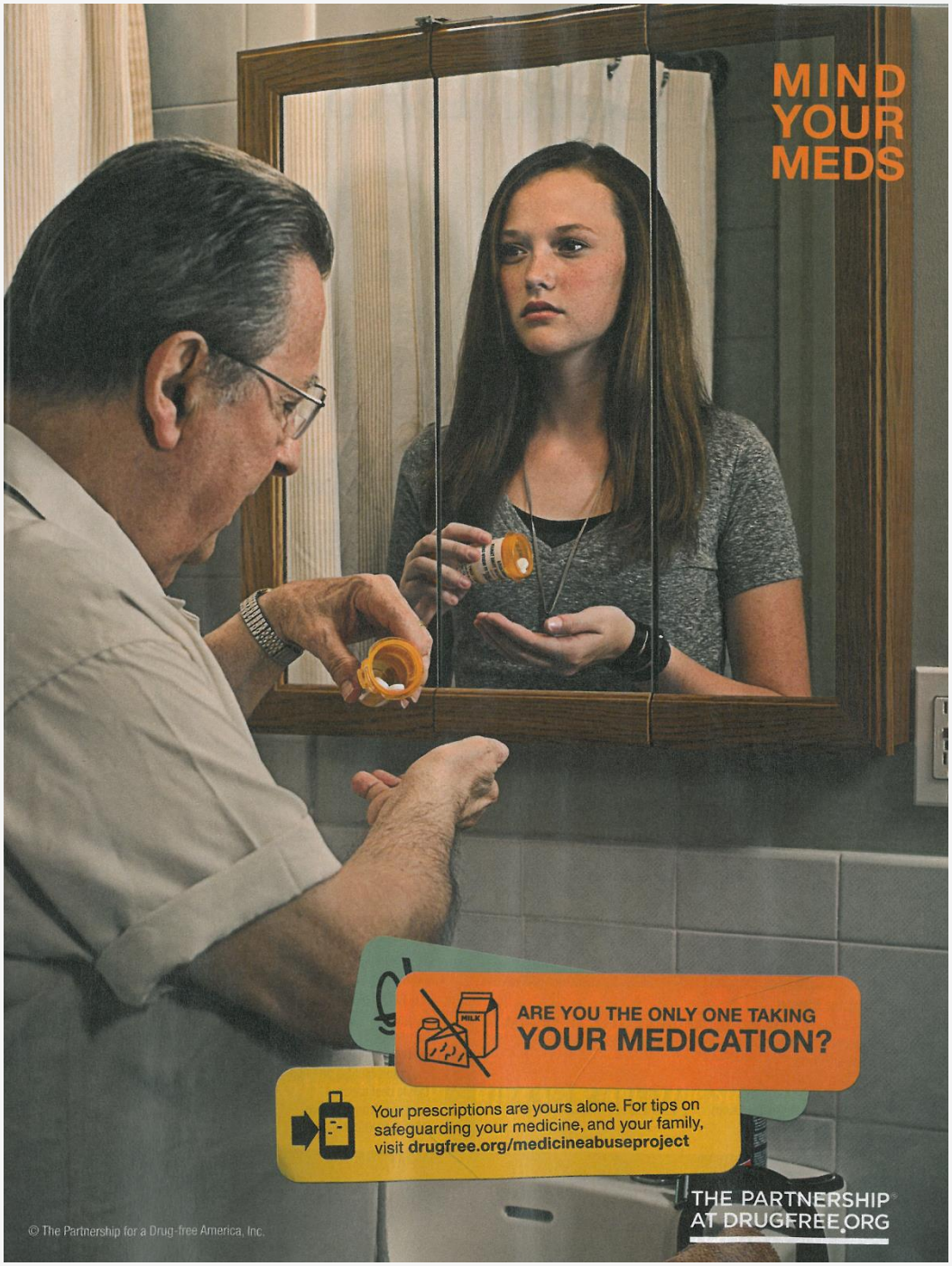
Know Their Weaknesses

- Teens: adventure
- Elderly: drug naïveté

Discard Expired or Unused Meds

Adapted from The Partnership at DrugFree.org. *Rx Abuse: Not in My House*. http://notinmyhouse.drugfree.org/steps.aspx . Accessed January 2014.

Public Awareness Campaign



When to Discontinue Opioids

- Severe unmanageable adverse effects
- Serious or persistent nonadherence to the treatment plan
- Illegal or unsafe behaviors
- Misuse suggestive of addiction to prescribed medication
- Lack of effectiveness
- Patient preference
- Decreased level of pain in stable patients
- Goals of treatment are not met

http://www.healthquality.va.gov/cot/. Accessed Jan 2014.

Tapering Opioids: General Considerations

- Individualize; faster or slower tapering may be warranted
- Complete evaluation prior to initiation of the taper
  - Current treatment plan
  - Psychological conditions
  - Other relevant factors should be completed
- Clear written and verbal instructions should be given to patients and their families to minimize withdrawal symptoms

http://www.healthquality.va.gov/cot/. Accessed Jan 2014.

Tapering Opioids: Patients to Refer

- High risk to engage in aberrant behaviors (eg, parasuicidal acts; dealing/selling medications; severe impulse control disorders)
- Complicated withdrawal symptoms
- Opioid addiction
- Refer to an addiction or pain specialist!

http://www.healthquality.va.gov/cot/. Accessed Jan 2014.

Tapering Opioids: Patient Considerations

- Do not treat withdrawal symptoms with opioids or benzodiazepines after discontinuing opioids
- Consider tapering opioids in patients who have received regularly scheduled opioids at greater than the recommended starting doses for more than a few days
- Non-daily, as-needed opioids do not usually need tapering
- Patient-specific factors
  - Risk of precipitating withdrawal
  - Level of anxiety about discontinuing
  - Duration of opioid therapy (longer use→ slower taper)
  - Medical and psychological comorbidities
  - Clinical need for rapid taper

http://www.healthquality.va.gov/cot/. Accessed Jan 2014.
agencymeddirectors.wa.gov/Files/OpioidGdline.pdf. Accessed Jan 2014.

Tapering Opioids: Specific Considerations

- Taper by 20–50% per week for patients who are not addicted
- A patient needs 20% of the previous day's dose to prevent withdrawal symptoms
- Consider adjuvant agents such as antidepressants to manage irritability and sleep disturbance, or antiepileptics for neuropathic pain
- Patient on fentanyl should be rotated to a different opioid, either long-acting morphine or methadone
  - Once the patient is converted, the same guidelines will apply

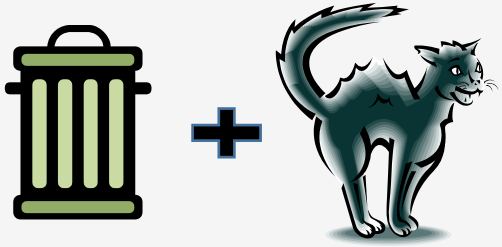
http://www.healthquality.va.gov/cot/. Accessed Jan 2014.
agencymeddirectors.wa.gov/Files/OpioidGdline.pdf. Accessed Jan 2014.

How should patients dispose of expired or unused opioids?

Trash

Flush down toilet

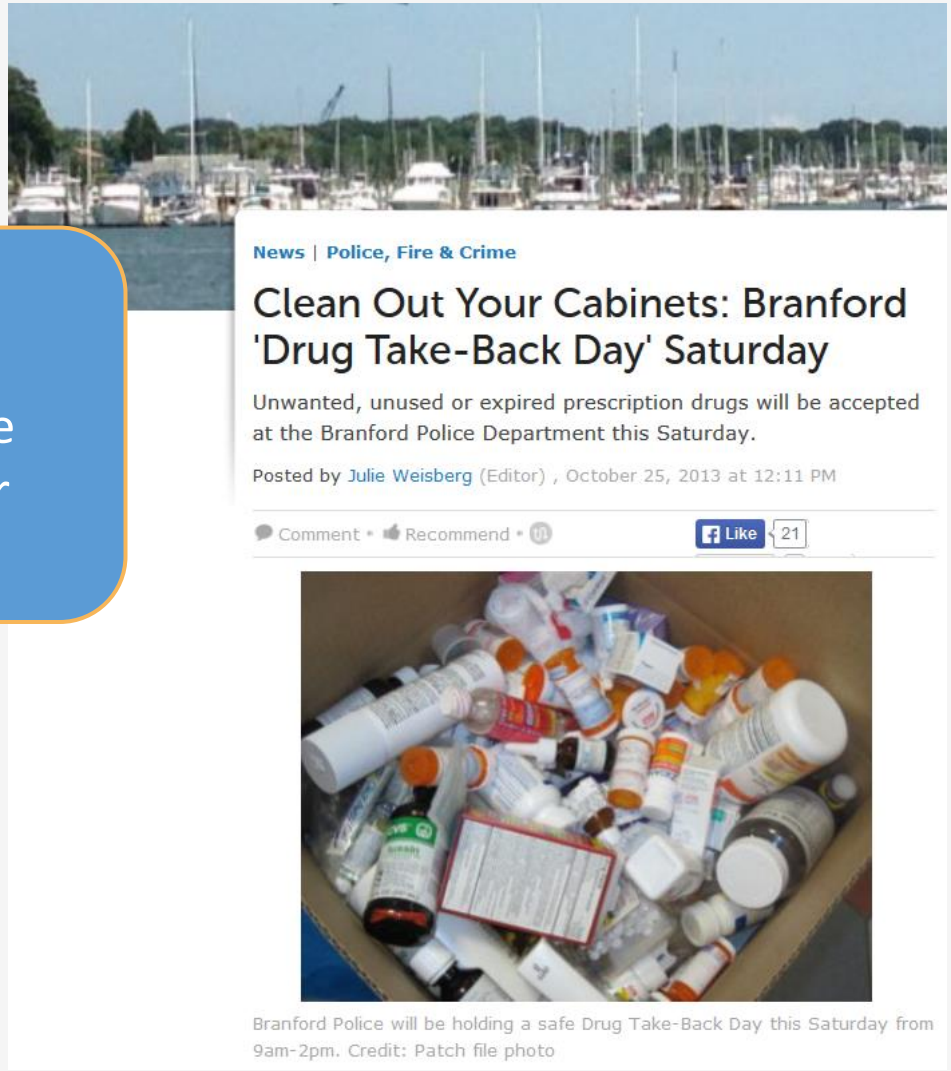
Community drug collection



Mix with kitty litter and put into trash

First Choice: Community Drug Take-Back

- National Prescription Drug Take-Back Day: “Got Drugs?”
- More than 5000 sites participate
- Check with local government for day/location



News | Police, Fire & Crime

Clean Out Your Cabinets: Branford 'Drug Take-Back Day' Saturday

Unwanted, unused or expired prescription drugs will be accepted at the Branford Police Department this Saturday.

Posted by Julie Weisberg (Editor) , October 25, 2013 at 12:11 PM

Comment • Recommend • Like 21

Branford Police will be holding a safe Drug Take-Back Day this Saturday from 9am-2pm. Credit: Patch file photo

www.fda.gov/consumer. www.awarerx.org. Accessed Jan 2014.
http://www.deadiversion.usdoj.gov/drug_disposal/takeback/index.html. Accessed January 2014.

FDA Drug Disposal Guidelines

- Follow the prescription drug labeling
- Community drug take-back programs
- Container: scratch out all identifying information on the label
- Do not give your medicine to friends
- When in doubt, talk to your pharmacist

Dispose of unused ER/LA opioids by flushing down the toilet

http://www.fda.gov/forconsumers/consumerupdates/ucm101653.htm. Accessed Jan 2014.
www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf. Accessed Jan 2014.

Module 4 Key Messages

- Use a **Patient Counseling Document** to communicate
- Refer to drug-specific **Prescribing Information**
  - Includes a **Medication Guide** for patients
  - Proper disposal of drugs
- An exit strategy is critical
  - Know when to discontinue opioids
  - Know how to taper opioids
  - Know when to refer to a specialist

General Drug Information for ER/LA Opioid Analgesic Products

Module 5

Learning Objectives

- Appropriately assess patients for the treatment of pain with ER/LA opioid analgesics, including analyzing risks versus potential benefits
- Assess patient's risk of abuse, including substance use and psychiatric history
- Identify state and federal regulations on opioid prescribing
- Incorporate strategies to effectively initiate therapy, modify dosing or discontinue use of ER/LA opioid analgesics in patients with pain
- Manage ongoing therapy with ER/LA opioid analgesics
- Incorporate effective counseling for patients and caregivers about the safe use of ER/LA opioid analgesics
- Discuss general and product-specific drug information related to ER/LA opioid analgesics

Drug Information Common to ER/LA Opioid Analgesics

Limitations of usage

- Not for as-needed analgesia
- Not for mild pain or pain not expected to persist for an extended duration
- Not for use in treating acute pain

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013 www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf. Accessed Jan 2014.

Drug Information Common to ER/LA Opioids

Key Instructions

- Titrate a dose that provides adequate analgesia and minimizes adverse reactions
- Times required to reach steady-state plasma concentrations are product specific (Refer to PI for titration interval)
- Continually reevaluate patient to assess pain control and adverse effects
- Consult drug PI for dosage reduction with hepatic or renal impairment

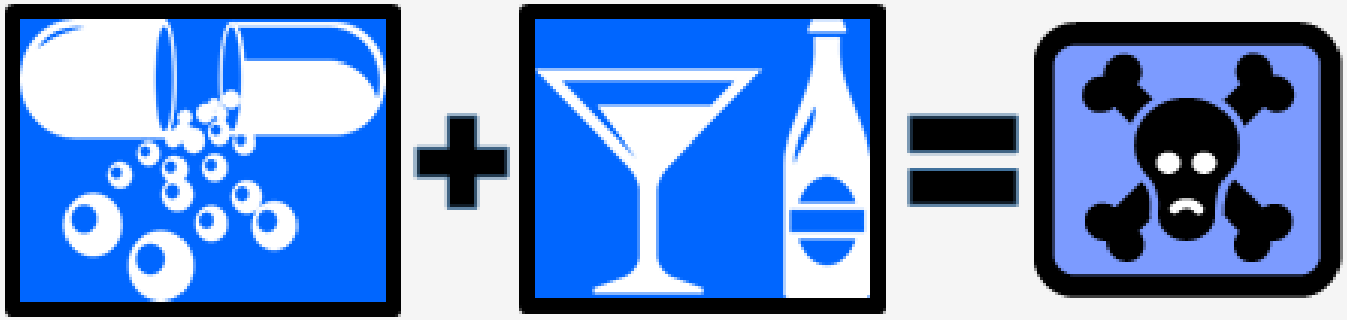
FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013 www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf. Accessed Jan 2014.

A 32-year-old patient who suffered multiple fractures in a motor vehicle accident at age 16 has chronic pain. He is on metoprolol, NSAIDs, gabapentin, and alprazolam but needs increased pain relief. What is the best next step?

- ◯ Taper the alprazolam before ER/LA opioid initiation
- ◯ Initiate an ER/LA opioid but monitor for respiratory depression
- ◯ Begin with a medication reconciliation to avoid drug-drug interactions
- ◯ Try a different non-opioid analgesic first

ER/LA Opioids: Solid Oral Dosage Forms

- Swallow tablets and capsules **WHOLE**
  - ~~**CRUSHING CHEWING BREAKING CUTTING DISSOLVING**~~
- Some capsules can be opened and *sprinkled* on applesauce (see PI)
- Exposure of some products to **alcohol** may result in rapid absorption of a potentially fatal dose of opioid ("dose dumping")



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ER/LA Opioids: Transdermal Dosage

- Application
  - Rotate location of application
  - Prepare skin
    - Clip (don't shave) hair; wash only with water
- Safety
  - Strenuous exertion or external heat exposure may lead to increased absorption and possible overdose
  - Monitor patients with **fever** for signs/symptoms of increased opioid exposure
  - Handle and dispose appropriately
    - Avoid exposure of caregivers/children
  - **Do not cut, damage, chew or swallow**
  - Products with metal foil backings are not safe for MRIs

FDA. Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics. 04/2013 www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf. Accessed Jan 2014.

ER/LA Opioid Analgesics Drug Interactions

CNS Depressants

ER/LA Opioid Analgesics

Concurrent Use

- Sedatives
- Hypnotics
- General anesthetics
- Antiemetics
- Phenothiazines
- Other tranquilizers
- Alcohol

↑ Risk of:

- Respiratory depression
- Hypotension
- Profound sedation
- Coma

Reduce the initial dose of one or both agents

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ER/LA Opioid Analgesics Drug Interactions

Partial agonists and mixed agonist/antagonist analgesics

ER/LA Opioid Analgesics

Concurrent Use

- Buprenorphine
- Pentazocine
- Nalbuphine
- Butorphanol

- May reduce analgesic effect
- Precipitate withdrawal symptoms

Avoid concurrent use

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ER/LA Opioid Analgesics Drug Interactions

Antiarrhythmic Agents

- **Methadone**
- **Buprenorphine**

Concurrent Use

Antiarrhythmic Agents such as:

- Class IA
  - Quinidine
  - Procainamide
  - Disopyramide
- Class III
  - Sotalol
  - Amiodarone
  - Dofetilide

- **May cause QTc prolongation/ arrhythmia**

Avoid use of these opioids in patients with long QT Syndrome or those taking antiarrhythmic medications

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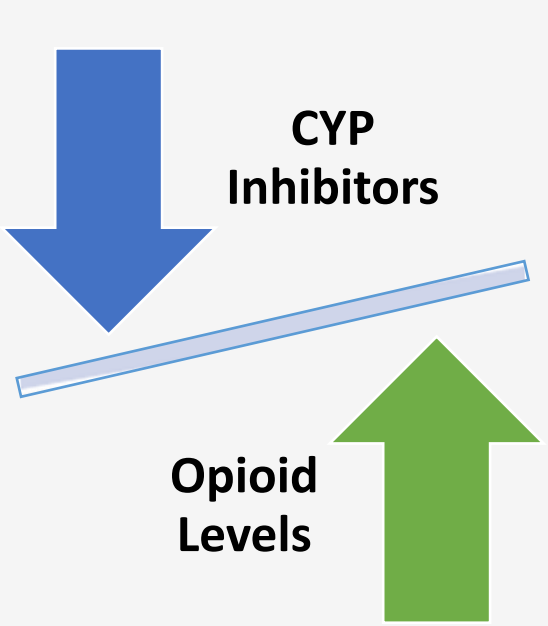
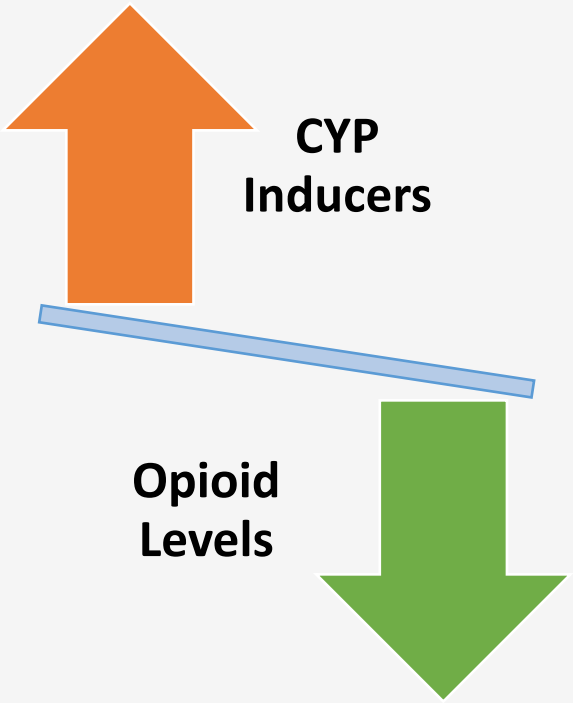
ER/LA Opioid Analgesics Drug Interactions

CYP Inhibitors/Inducers may impact blood levels of ER/LA opioids





!! Consult product-specific information !!

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ER/LA Opioid Analgesics Drug Interactions

Drug	Potential Risk
Alcohol; medications with alcohol	• Some ER opioid formulations may rapidly release opioid when exposed to alcohol ("**dose dump**") • Some drug levels may increase without dose dumping when exposed to alcohol • See individual PI
Monoamine oxidase inhibitors (MAOIs)	• Using opioids with MAOIs may increase **respiratory depression** • May cause **serotonin syndrome**
Diuretics	• Opioids can reduce diuretic efficacy by inducing **ADH**
Skeletal muscle relaxants	• Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and increase **respiratory depression**
Anticholinergic medications	• Concurrent use increases the risk of **urinary retention** and **severe constipation/paralytic ileus**

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ER/LA Opioid Analgesics

Tolerance to sedating and respiratory depressant effects of opioids is critical to the safe use of certain products/strengths/doses

- Products used **ONLY** in opioid-tolerant patients
  - Transdermal fentanyl
  - Hydromorphone HCl ER

- For other products, patients must be opioid tolerant *before* using
  - Certain strengths
  - Certain daily doses
  - **Refer to individual PI**

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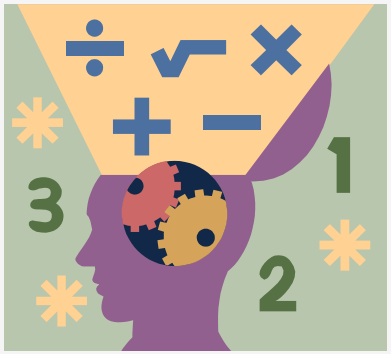
ER/LA Opioid Analgesics

Relative Potency to Morphine

- Intended as a ***general guide***
- Follow conversion instructions in individual PI
- Incomplete cross-tolerance and inter-patient variability require conservative dosing when converting from 1 opioid to another
  - Halve the calculated comparable dose; titrate new opioid as needed



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Module 5 Key Messages

- Prescribers should be knowledgeable about general characteristics, class adverse effects, and drug interactions for ER/LA opioid analgesic products
  - This information provides the foundation for assimilation of product-specific information and the safe/effective use of ER/LA opioid analgesics

Specific Drug Information for ER/LA Opioid Analgesic Products

Module 6

Learning Objectives

- Appropriately assess patients for the treatment of pain with ER/LA opioid analgesics, including analyzing risks versus potential benefits
- Assess patient's risk of abuse, including substance use and psychiatric history
- Identify state and federal regulations on opioid prescribing
- Incorporate strategies to effectively initiate therapy, modify dosing or discontinue use of ER/LA opioid analgesics in patients with pain
- Manage ongoing therapy with ER/LA opioid analgesics
- Incorporate effective counseling for patients and caregivers about the safe use of ER/LA opioid analgesics
- Discuss general and product-specific drug information related to ER/LA opioid analgesics

Informed Treatment Decisions

Consider product characteristics that align with patient needs

Drug substance

- Formulation
- Strength

Dosing interval

Key instructions

- Titration
- Limitations of usage
- Product conversion information

Specific drug interactions

Product-specific safety concerns

Use in opioid-tolerant patients

Potency relative to oral morphine

DailyMed: www.dailymed.nlm.nih.gov
Drugs@FDA: www.fda.gov/drugsatfda

A Look at Different ER/LA Opioid Analgesic Products

- Compare and contrast
  - Relative potency of ER/LA opioid agents
  - Dosing frequency
  - Use based on opioid exposure
  - Specific drug interactions
- Specific characteristics

Oral

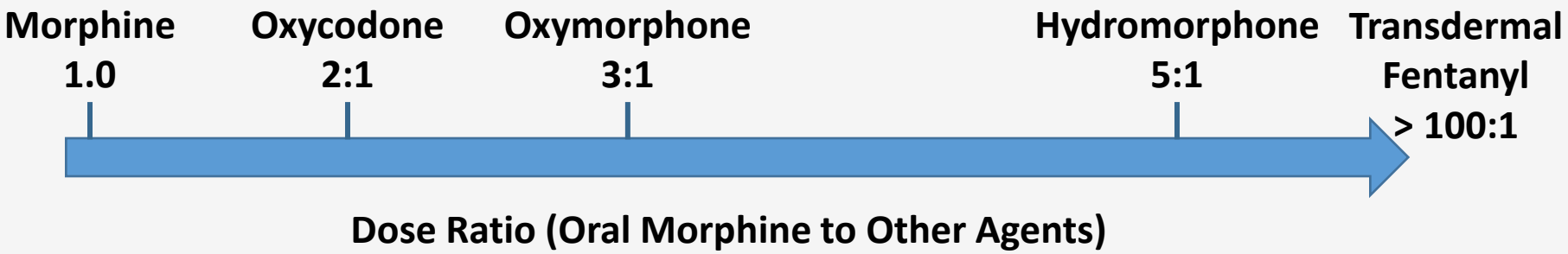
- Morphine sulfate (4)
- Oxycodone
- Oxymorphone
- Hydromorphone
- Methadone
- Tapentadol

Transdermal

- Buprenorphine
- Fentanyl

Relative Potency to Oral Morphine

Important to consult PIs for use of opioids as first agents and for conversion/rotation procedures



Methadone
- Varies contingent on prior opioid exposure

Not Established
- Buprenorphine
- Tapentadol

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Dosing Frequency

Product	Every 8 or 12 hours	Every 12 hours	Once/Day or Every 12 hours	Once/Day	Every 3 Days	Every 7 Days
Methadone (Dolophine)	✓					
Morphine sulfate CR (MS Contin)	✓					
Tapentadol (Nucynta ER)		✓				
Oxymorphone HCl (Opana ER)		✓				
Oxycodone HCl (OxyContin)		✓				
Morphine sulfate ER (Kadian)			✓			
Morphine sulfate ER-Naltrexone (Embeda)			✓			
Morphine sulfate ER (Avinza)				✓		
Hydromorphone HCl ER (Exalgo)				✓		
Fentanyl Transdermal (Duragesic)					✓	
Buprenorphine Transdermal (Butrans)						✓

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A patient you are treating for chronic pain is on multiple medications and suffers from alcoholism. What is your first step in initiating an ER/LA opioid?

- ◯ Start at the lowest dose of the opioid you are most familiar with
- ◯ Select an opioid and consult the PI
- ◯ Select an ER/LA opioid with minimal interactions with current medications
- ◯ Consider patient preferences

Specific Drug Interactions

Product	Alcohol*	PGP inhibitors	CYP 3A4 inhibitors/ inducers	CYP 450 inhibitors/ inducers	Benzo-diazepines	MAO inhibitors	Class IA + III antiarrhythmics
Morphine sulfate ER (Avinza)	✓	✓					
Morphine sulfate ER (Kadian)	✓	✓					
Morphine sulfate CR (MS Contin)		✓					
Morphine sulfate ER-Naltrexone (Embeda)	✓	✓					
Oxycodone HCl (OxyContin)			✓				
Oxymorphone HCl (Opana ER)	✓						
Hydromorphone HCl ER (Exalgo)							
Methadone (Dolophine)				✓	✓		✓
Tapentadol (Nucynta ER)	✓					✓	
Fentanyl Transdermal (Duragesic)			✓				
Buprenorphine Transdermal (Butrans)			✓		✓		✓

PGP: P-glycoprotein
MAO: monoamine oxidase
*Including medications containing alcohol

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Morphine Sulfate ER: *Avinza*

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

Dosing Interval	• Once/day
Instructions	• Initial dose in opioid non-tolerant patients is 30 mg • Titrate using a **minimum of 3-day intervals** • **Swallow capsule whole** (do not chew, crush, or dissolve) • May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately • Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid
Specific Drug Interactions	• **Alcoholic beverages** or **medications containing alcohol** may result in the rapid release and absorption of a potentially fatal dose of morphine • **PGP inhibitors** (eg, quinidine) may increase the absorption/exposure of morphine sulfate by about 2-fold
Use in Opioid Tolerant Patients	• **90 mg and 120 mg** capsules are for use in **opioid-tolerant patients <u>only</u>**
Product-Specific Safety Concerns	• None

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Morphine Sulfate ER: *Avinza*

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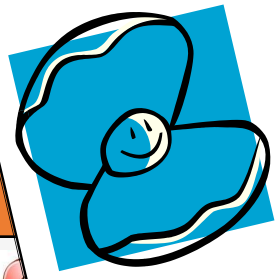
	…iconol may result in …potentially fatal dose of morphine …dine) may increase the absorption/exposure of …date by about 2-fold
…olerant Patients	• **90 mg and 120 mg** capsules are for use in **opioid-tolerant patients only**
Product-Specific Safety Concerns	• None

Clinical Pearl:

- Can be sprinkled on applesauce; good for hospice or patients with difficulty in swallowing



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Morphine Sulfate ER-Naltrexone: *Embeda*

20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg Capsules

Dosing Interval	• Once/day or every 12 hours
Instructions	• Initial dose as first opioid: 20 mg/0.8 mg • Titrate using a **minimum of 3-day intervals** • **Swallow capsules whole** (do not chew, crush, or dissolve) • Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms • May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately
Specific Drug Interactions	• **Alcoholic beverages** or **medications containing alcohol** may result in the rapid release and absorption of a potentially fatal dose of morphine • **PGP inhibitors** (eg, quinidine) may increase the absorption/exposure of morphine sulfate by about 2-fold
Use in Opioid Tolerant Patients	• **100 mg/4 mg capsule** is for use in **opioid-tolerant patients only**
Product-Specific Safety Concerns	• None

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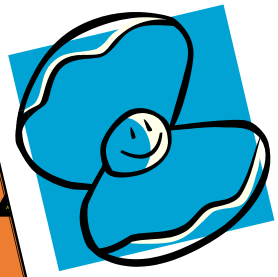
Morphine Sulfate ER-Naltrexone: *Embeda*

20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, and 100 mg/4 mg Capsules

Dosing Interval	• Once/day or every 12 hours
	• Initial dose as first • Titrat
	dose of may increase the absorption/exposure inate by about 2-fold
Patients	• **100 mg/4 mg capsule** is for use in **opioid-tolerant patients only**
Product-Specific Safety Concerns	• None

Clinical Pearls:

- Naltrexone - deterrent for intravenous abuse
- Voluntarily recalled March 2011, may become available in Q2 2014
- Dosage titration should only occur at 3-day intervals



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Oxycodone Hydrochloride CR: *OxyContin*

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

Dosing Interval	• Every 12 hours
Instructions	• Opioid-naïve patients: initiate treatment with 10 mg every 12 hours • Titrate using a **minimum of 1 to 2 day intervals** • **Hepatic impairment**: start with one third to one half the usual dosage • **Renal impairment** (creatinine clearance < 60 mL/min): start with one half the usual dosage • Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. • **Swallow tablets whole** (do not chew, crush, or dissolve) • Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth
Specific Drug Interactions	• **CYP3A4 inhibitors** may increase oxycodone exposure • **CYP3A4 inducers** may decrease oxycodone exposure
Use in Opioid Tolerant Patients	• **Single dose greater than 40 mg** or **total daily dose greater than 80 mg** are for use in **opioid-tolerant patients only**
Product-Specific Safety Concerns	• Choking, gagging, regurgitation, tablets stuck in the throat, **difficulty swallowing the tablet** • Contraindicated in patients with gastrointestinal obstruction
Relative Potency to Oral Morphine	• ~ **2:1** oral morphine to oxycodone oral dose ratio

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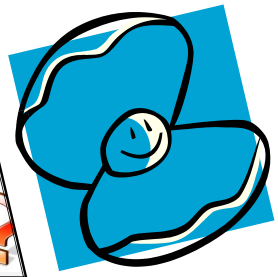
Oxycodone Hydrochloride CR: *OxyContin*

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

Dosing Interval	• Every 12 hours
Instruction	• Opioid-naïve patients: initiate treatment with 10 • Titrate using a **minimum of 1 to 2 d** • **Hepatic impairment**: st • **Renal impa**
	daily dose greater than 80 mg are for use in
	gagging, regurgitation, tablets stuck in the throat, **difficulty swallowing the tablet** • Contraindicated in patients with gastrointestinal obstruction
Relative Potency to Oral Morphine	• ~ **2:1** oral morphine to oxycodone oral dose ratio

Clinical Pearls:

- Tablet "ghosts" may appear in stool
- Use with caution in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction



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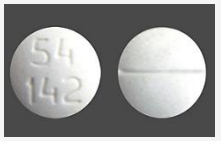
Methadone Hydrochloride: *Dolophine*

5 and 10 mg Tablets



Dosing Interval	• Every 8 to 12 hours
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 and death**. Use low doses according to the table in the full prescribing information • **High inter-patient variability** in absorption, metabolism, and relative analgesic potency • Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (CFR, Title 42, Sec 8)
Specific Drug Interactions	• Pharmacokinetic drug-drug interactions with 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 and torsade de pointes • **Benzodiazepines** may increase respiratory depression
Use in Opioid Tolerant Patients	• Refer to full prescribing information
Product-Specific Safety Concerns	• QTc prolongation and torsade de pointe • **Peak respiratory depression occurs later and persists longer than analgesic effect** • Clearance may increase during pregnancy • False positive urine drug screens possible
Relative Potency to Oral Morphine	• Varies depending on patient's prior opioid experience

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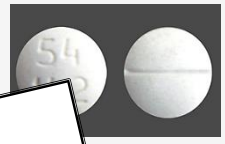
Methadone Hydrochloride: *Dolophine*

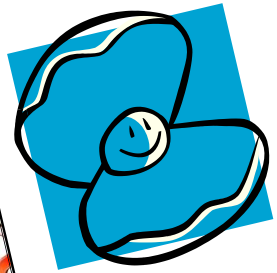


5 and 10 mg Tablets

Dosing Interval	• Every 8 to 12 hours
Instructions	• Initial dose in opioid non-tolerant • **Conversion of opioid**

Clinical Pearls:

- Good for nociceptive/neuropathic pain conditions--but requires caution
- Double-check your conversions
- There may be prolonged respiratory depression with methadone compared to other opioids
- Titrate dose at weekly intervals because of long half-life



longer than analgesic effect

possible

depending on patient's prior opioid experience

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Fentanyl: *Duragesic*

12, 25, 50, 75, and 100 mcg/hr Transdermal System

Dosing Interval	• One transdermal system every 3 days (72 hours)
Instructions	• Use product specific information for dose conversion from prior opioid • Use 50% of the dose in mild or moderate hepatic or renal impairment, **avoid use in severe hepatic or renal impairment** • Application – Apply to intact/non-irritated/non-irradiated skin on a flat surface – Skin may be prepped by clipping hair, washing site with water only – Rotate site of application – Titrate using **no less than 72 hour intervals** – **Do not cut** • **Avoid exposure to heat** • Avoid accidental contact when holding or caring for children • Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet • **Specific contraindications:** – Patients who are not opioid-tolerant – Management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time – Management of post-operative pain, including use after out-patient or day surgery – Management of mild pain

Continued on next slide …

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Fentanyl: *Duragesic* (continued)

12, 25, 50, 75, and 100 mcg/hr Transdermal System

Dosing Interval	• One transdermal system every 3 days (72 hours)
Specific Drug Interactions	• **CYP3A4 inhibitors** may increase fentanyl exposure • **CYP3A4 inducers** may decrease fentanyl exposure
Use in Opioid Tolerant Patients	• **All doses of fentanyl** are indicated for use in **opioid-tolerant patients <u>only</u>**
Product-Specific Safety Concerns	• Accidental exposure due to **secondary exposure** to unwashed/unclothed application site • Increased drug exposure with **increased core body temperature or fever** • Bradycardia • Application site skin reactions
Relative Potency to Oral Morphine	• See individual product information for conversion recommendations from prior opioid

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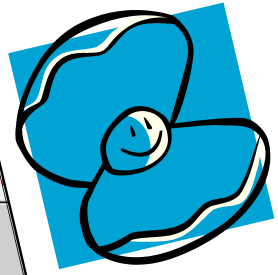
Fentanyl: *Duragesic* (continued)

12, 25, 50, 75, and 100 mcg/hr Transdermal System

Dosing Interval	• One transdermal system every 3
Specific Dr	
	…otted application
	…re body temperature or fever
	…kin reactions
…ency …Oral Morphine	• See individual product information for conversion recommendations from prior opioid

Clinical Pearls:

- Good for late-stage pain
- Do not use in opioid naïve patients
- Residual drug in patch after use
  - Potential for abuse
  - Dispose of properly



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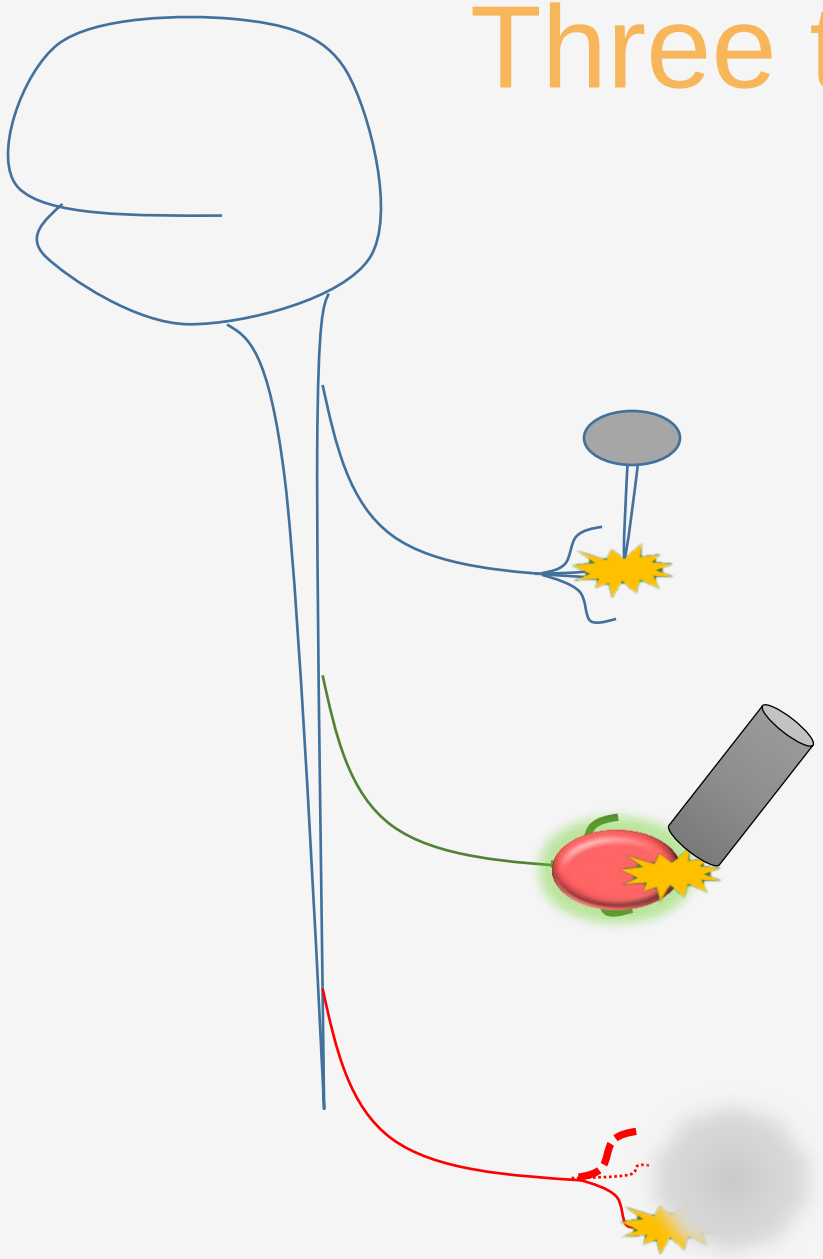
Three types of pain



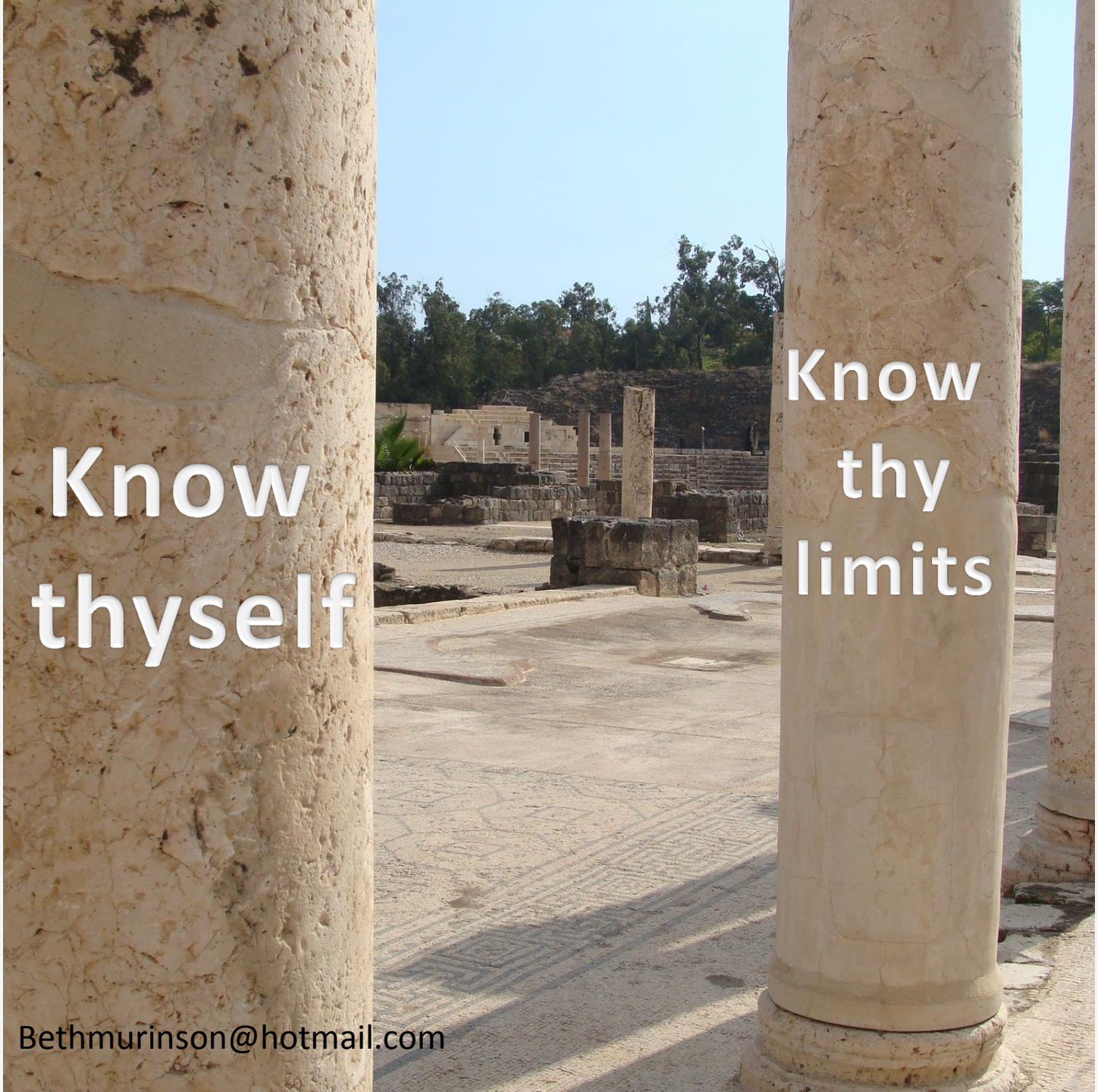
NOCICEPTIVE: ‘normal’ pain sensing in **response to threats** in the environment; sharp

INFLAMMATORY: increased pain sensing that raises sensitivity to normal levels of pressure and activity; aching

NEUROPATHIC: abnormal pain in response to things that normally ‘do’ and ‘don’t’ hurt; burning, zinging, tingling.

Types of pain medications

NSAIDS and STEROIDS	NEURO-ACTIVE: ANTI-DEPRESS.	NEURO-ACTIVE: ANTI-CONVUL.	OPIOIDS	NEURO-ACTIVE: LOCAL ANESTH. AND OTHERS
Ibuprofen, Naproxen, Etodolac, Ketorolac, etc.	Nortriptyline, amitriptyline; venlafaxine, duloxetine, etc.	Gabapentin, pregabalin, carbemazepine, topiramate, etc.	Morphine, oxycodone, codeine, Fentanyl, etc.	Lidocaine, Acetaminophen Tramadol, Musc. relaxants
Work especially well for inflammatory pain but also good for mild-moderate nociceptive pain	Take time to start working but quite effective and generally safe for long-term use	Work especially well for neuropathic (nerve) pain, work well together with other agents	Work well for short periods, but effect wears off quickly and potency declines with use	Work through various pathways, often used alone or in combination with other medications
NSAIDs: GI bleeding, renal Steroids: not for long term use	Some may increase suicide risk, need to monitor use	May increase dizziness, impair thinking	Very dangerous: many deaths each year	Side effects vary but should be reported if suspected
As needed and limited courses	Must take daily for drug to work	Recommended for daily dosing	Not ideal for daily use	Dosing varies with drug



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Module 6 Key Messages

- Safe prescribing of ER/LA opioid analgesics requires knowledge of product-specific information
- Product factors to consider when formulating individualized treatment plans:

Safety

Dosing

Tolerance

Formulation

Potency

Key Instructions

Drug interactions

Thank you for participating!

- Please take the posttest
- Please fill out the evaluation