LEARNING OBJECTIVES

• Brief overview of commonly used opioids

• Appropriate use of opioids
  • FDA Blue Print/ Prescription Guidelines ER/LA OPIOID REMS
  • Role of opioid analgesics in reducing pain and restoring patient function.
  • Opioid selection, titration, rotation, conversion, and dose tapering.
  • Clinical strategies for preventing abuse and diversion with opioids while effectively managing chronic pain.
Dr. Stephen Anthony, 64, of Davie, Florida, pled guilty to conspiring to distribute and dispense large amounts of oxycodone without a legitimate medical purpose and outside the usual course of professional practice.

Dr. Anthony also pleaded guilty to money laundering and income tax evasion.

Anthony faces a maximum term of imprisonment of five years on the drug charge, ten years on the money laundering charge and 5 years on the tax evasion charge.
A prominent Delaware County doctor has been arrested for allegedly selling prescriptions for unneeded pain medications.

Dr. Lenwood Wert of Lansdowne is charged with more than 500 felony counts.

Delaware County District Attorney Jack Whelan said Wert operated a pill mill out of his office, which is attached to his large white home in the borough.
OPIOID MIS-USE ... AN EPIDEMIC

- 2010 National Survey on Drug Use and Health:
  - > 35 million Americans age 12 & older estimated to use an opioid analgesic for non-medical use some time in their life — an increase from about 30 million in 2002.

- 2009: Nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.

- 2008: Nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.
FDA BLUEPRINT “REMS”

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

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

III. Managing Therapy with ER/LA Opioid Analgesics

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

V. General Drug Information for ER/LA Opioid Analgesic Products

VI. Specific Drug Information for ER/LA Opioid Analgesic Products

FDA Blueprint for Prescriber Education for ER & LA Opioid Analgesics (08/2014)
“An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

Barash et al, 4th ed; 1441
100 MILLION AMERICANS SUFFER FROM CHRONIC PAIN

1 in 3 Americans (Back pain is the most common cause)

- Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education: Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education and Research. The National Academies Press, 2011.
- Principles for Safe Opioid Prescribing- L Webster, MD
CHRONIC PAIN

- Adults age 45-64 years were the most likely to report pain lasting more than 24 hours (30%).

- 25% of young adults age 20-44 reported pain.

- Adults age 65 and over were the least likely to report pain (21%).

Chronic Pain increases with age

- Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education: *Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education and Research*. The National Academies Press, 2011.
- *Principles for Safe Opioid Prescribing*- L Webster, MD
KEY FINDINGS FROM THE 2006 VOICES OF CHRONIC PAIN SURVEY

• More than half of respondents (51%) felt they had little or no control over their pain.

• Impact on Quality of Life
  • 60% experienced breakthrough pain one or more times daily, severely impacting their quality of life and overall well-being.

• Almost two-thirds (59%) reported an impact on their overall enjoyment of life.

• More than three quarters of patients (77%) reported feeling depressed.

• 70% said they have trouble concentrating.

• 74% said their energy level is impacted by their pain.

• 86% reported an inability to sleep well.

• Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education: Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education and Research. The National Academies Press, 2011.
• Principles for Safe Opioid Prescribing- L Webster, MD
PSYCHOSOCIAL CONSEQUENCES

Poor Pain Control

• Negative emotions
• Anxiety
• Depression
• Sleep deprivation
• Existential suffering
  • May lead patients to actively seek ending life


OPIOIDS
HISTORICAL
<table>
<thead>
<tr>
<th>PHENANTHRENE ALKALOIDS (OPIATES)</th>
<th>SEMI-SYNTHETIC</th>
<th>SYNTHETIC</th>
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<tbody>
<tr>
<td>Morphine</td>
<td>Hydrocodone</td>
<td>Demerol</td>
</tr>
<tr>
<td>Codeine</td>
<td>Hydromorphone</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Thebaine <em>(most toxic)</em></td>
<td>Oxycodone</td>
<td>Methadone</td>
</tr>
<tr>
<td></td>
<td>Oxymorphone</td>
<td>Tramadol</td>
</tr>
<tr>
<td></td>
<td>Heroin</td>
<td></td>
</tr>
</tbody>
</table>
OPIUM POPPY  \( (PAPAVER\; SOMNIFERUM) \)
OPIUM

• Traditional method:
  • Scratch ("score") the immature seed pods (fruits) by hand

• Contains up to 12% Morphine

• Dried latex also includes:
  • Codeine and
  • Non-narcotic alkaloids – Papaverine, Thebaine, Noscapine
NOMENCLATURE

- **Opium** (poppy tears, *lachryma papaveris*) is the dried latex obtained from the un-ripened seed capsules of the poppy.

- **OPIATE**: any agent derived from opium.

- **OPIOID**: refers to all substances (exogenous and endogenous) with morphine like properties.

- Generic term for class of agents is “**OPIOID**”.
• Unchanged since ancient times

• 6 major Opium alkaloids

• 3 Phenanthrene Alkaloids:  
  *(Under International Control)*
  • Morphine
  • Codeine
  • Thebaine (most toxic)

• NOT *under International Control:*
  • *Papaverine*
  • *Narcotine*
  • *Narceine*

Selective breeding of the *Papaver somniferum* plant
OFTEN CONVERTED INTO HEROIN, WHICH IS LESS BULKY, TWICE STRENGTH, EASIER TRANSPORT
HEROIN (DI-ACETYL MORPHINE) [C-I]

- Synthesized by C.R. Alder Wright in 1874
- Heroin is about twice as potent as Morphine*.

HEROIN
(DI-ACETYL MORPHINE) [C-I]

(Big H, Black Tar, Chiva, Hell Dust, Horse, Negra, Smack, and Thunder)

- Highly addictive
- The most rapidly acting of the opiates.
- Short half life
- Withdrawal may be as quick as 4 hrs after last use
• Depends on Purity…

• 1 bag Heroin = 100 mg

• Assuming 20% heroin/ bag = ~20 mg Heroin

• Heroin is about twice as potent as Morphine.

• 1 bag Heroin = ~40 mg Morphine
ADDICTION VS DEPENDENCE
**TOLERANCE:**
- With continued use, progressively more and more opioid is necessary to produce the same effect.

**PHYSICAL DEPENDENCE:**
- A state of adaptation that is manifested by a drug class.
- Specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, and/or administration of an antagonist.

**PSUEDOADDICTION:**
- A drug-seeking behavior that simulates true addiction, which occurs in patients with pain who are receiving inadequate pain medication.

**ADDICTION:**
- A psychic or physical state characterized by compulsive behavior to obtain a drug in order to experience psychic effects despite full knowledge of its harmful effects.
ADDICTION

• The 5 C’s
  • Chronic
  • Compulsive use
  • Control impaired
  • Craving
  • Continued use despite harm
• Binding affinity correlates with analgesic potency

• Only L isomer exhibits analgesic activity

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<tr>
<th>OPIOIDS</th>
<th>Binding Affinity</th>
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<tr>
<td>Sufentanil</td>
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<td>Fentanyl</td>
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<tr>
<td>Morphine</td>
<td>5.7</td>
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<tr>
<td>Alfentanil</td>
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<tr>
<td>Meperidine</td>
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# OPIOID Receptors & Clinical Effects

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<tr>
<th>Receptor</th>
<th>Effect</th>
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</thead>
<tbody>
<tr>
<td>MU (μ)</td>
<td></td>
</tr>
<tr>
<td>MU₁</td>
<td>Supraspinal Analgesia</td>
</tr>
<tr>
<td></td>
<td>Most naturally occurring opiates</td>
</tr>
<tr>
<td>MU₂</td>
<td>Spinal Analgesia</td>
</tr>
<tr>
<td></td>
<td>Respiratory Depression</td>
</tr>
<tr>
<td></td>
<td>Slowing gastric transit</td>
</tr>
<tr>
<td></td>
<td>Pruritus, Nausea, Vomiting</td>
</tr>
<tr>
<td></td>
<td>Most Cardiovascular effects</td>
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<tr>
<td></td>
<td>Physical Dependence</td>
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<tr>
<td></td>
<td>Euphoria</td>
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<tr>
<td>Delta (δ)</td>
<td>Modulation of MU-receptor activity</td>
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<tr>
<td></td>
<td>Spinal Analgesia</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Kappa (κ)</td>
<td></td>
</tr>
<tr>
<td>Kappa₁</td>
<td>Spinal Analgesia</td>
</tr>
<tr>
<td></td>
<td>Diuresis</td>
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<tr>
<td></td>
<td>Sedation</td>
</tr>
<tr>
<td></td>
<td>Miosis</td>
</tr>
<tr>
<td>Kappa₂</td>
<td>Low Potential for abuse</td>
</tr>
<tr>
<td>Kappa₃</td>
<td>Supraspinal Analgesia</td>
</tr>
<tr>
<td>Sigma (Σ)</td>
<td>No Analgesia</td>
</tr>
<tr>
<td></td>
<td>Dysphoria</td>
</tr>
<tr>
<td></td>
<td>Hypertonia</td>
</tr>
<tr>
<td></td>
<td>Respiratory &amp; Vasomotor Stimulation</td>
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<tr>
<td></td>
<td>Mydriasis</td>
</tr>
</tbody>
</table>

*Bonica’s Management of Pain, 3rd Edition*
**INTRINSIC ACTIVITY**

- Pure Agonists

- Partial Agonists
  - Ceiling effect
  - Concomitant administration of a partial and full agonist reduces (antagonizes) the effect of the full agonist

- Mixed Agonist-Antagonists
  - Ceiling effect
  - Concomitant administration of a partial and full agonist reduces (antagonizes) the effect of the full agonist
BUPRENORPHINE
(SUBUTEX, SUBOXONE, BUTRANS) [ C-III ]

- Semi-synthetic derivative of Thebaine
- Suboxone (Naloxone added)
- Highly lipophilic, ~96% protein bound
- **Buprenorphine (Mean half-life): 37h**
  - Mean half-life of Naloxone: 1.1h
  - 20-30X potency of Morphine
- Poor oral bioavailability and moderate sublingual bioavailability.

- Used for Opioid detoxification & Maintenance programs
  - Formulations for opioid addiction treatment are in the form of sublingual tablets.
- May cause a "precipitated withdrawal syndrome"

---

www.FDA.gov; buprenorphine.samhsa.gov; Likar 2006; Bickel et al. 1988; Boas & Villager 1985; Tyers 1980
BUPRENORPHINE [C-III ]
(SUBUTEX, SUBOXONE, BUTRANS)

POST-OP PAIN CONTROL IN A SUBOXONE PATIENT

• SLOW initial binding c.f. other opioids such as Fentanyl (Boas & Villager, 1985)

• Buprenorphine achieves effective analgesia at low receptor occupancy (5-10%), so onset similar (Tyers, 1980)

• Low plasma concentration sufficient to provide pain relief

• Strong binding to the $\mu$-receptor

• Slow dissociation from the $\mu$-receptor

www.FDA.gov; buprenorphine.samhsa.gov; Likar 2006; Bickel et al. 1988; Boas & Villager 1985; Tyers 1980
SCHEDULING
CONTROLLED SUBSTANCES ACT 1970

- Legislation created 5 Schedules based on:
  - Abuse & Dependency potential
  - Acceptable medical use

- “Narcotic drugs” defined, not by pharmacology

A. High potential for abuse

B. Most dangerous w/ potentially severe physical or psychological dependence

C. No currently accepted medical use in treatment in the United States.

D. There is a lack of accepted safety
   i. Heroin
   ii. Marijuana (changing / state by state)
   iii. LSD
   iv. Ecstasy
   v. Mescaline
**SCHEDULE - II**

A. High potential for abuse

B. Less abuse potential than schedule-I

C. Accepted medical use in treatment in the United States, or currently accepted medical use with severe restrictions

i. Cocaine (topical anesthetic)

ii. PCP - phencyclidine

iii. Hydrocodone**

iv. Morphine

v. Hydromorphone

vi. Methadone

vii. Oxycodone

viii. Fentanyl

ix. Codeine

- + ASA or APAP = C-III
- Add Expectorant = C-V

SCHEDULE - III

A. Potential for abuse less than the drugs or other substances in schedules I and II.

B. Currently accepted medical use in treatment in the United States.

i. Codeine (<90 mg/dose unit) (Tylenol #3, #4)

iii. Ketamine

iv. Buprenorphine

v. Anabolic steroids

vi. Marinol

SCHEDULE – IV

Low potential for abuse or risk for dependence

- Benzodiazepines
- Ambien
- Talwin
- Tramadol**
- Soma

SCHEDULE – V

Lower potential for abuse or risk for dependence than schedule-IV

- Antitussive (<200 mg Codeine per 100 ml)
- Promethazine + codeine
- Anti-diarrheal
- Lomotil with atropine
- Anti-neuropathic
- Pregabalin
PURE AGONISTS
CODEINE [C-II]

- Opiate (occurring naturally in poppy)
- Most Rx opioid in world

- 10% dose demethylated to morphine
  - Fractional reason for analgesia

- Low affinity for opioid receptor
- Limited by:
  - Low potency
  - Perceived freq. of n/v
8 to 14 percent of the dry weight of opium

Hepatic: Phase II conjugation

Renal excretion:
- Morphine-3-glucuronide (40%)
- Morphine-6β-glucuronide (10%)

Morphine: Hydrophillic, does not cross BBB

M6G concentration in CSF is 20-80% that of morphine.
  - Accumulation in Renal failure

MORPHINE
( _MS CONTIN, KADIAN, AVINZA_) [C-II]

PHARMACOKINETICS

- IM: Peak plasma conc.: 20 min
- IV: Redistribution ½ life between 1.5 & 4.4 min
- Terminal elimination half-life: 1.7-3.3 hrs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Loading Dose (mg)</th>
<th>Demand Dose (mg)</th>
<th>Lockout Interval (min)</th>
<th>Continuous Infusion (mg/hr)</th>
<th>4-hr Limit (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone</td>
<td>0.25-0.5</td>
<td>0.1-0.5</td>
<td>5-10</td>
<td>0.2-0.5</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>5-10</td>
<td>0.5-3</td>
<td>5-12</td>
<td>1-10</td>
<td>20-30</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.025-0.075</td>
<td>0.015-0.05</td>
<td>3-10</td>
<td>0.02-0.1</td>
<td>0.2-0.4</td>
</tr>
</tbody>
</table>
SEMI-SYNTHETICS
HYDROCODONE [C-II]

• Used for moderate-severe pain

• 1.5x less potent than Oxycodone

• Does NOT undergo extensive first-pass hepatic metabolism

• Historically, 2nd most abused opioid after Oxycodone

With Acetaminophen (Tylenol)
Norco (5,7.5,10)
Anexia (5/500, 7.5/325)
Lortab 2.5, 5, 7.5, 10/325)
Vicoden (5/500)
Vicoden ES
Loricet (7.5, 10/325)

Vicoprofen (Ibuprofen 200/7.5 hydrocodone)
Zohydro ER / Hysingla ER
### OXYPHEDRINE  [C-II]

<table>
<thead>
<tr>
<th>μ</th>
<th>δ</th>
<th>κ₁</th>
<th>κ₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Potency = Morphine**
  
  1mg Morphine = 0.8mg Oxycodone (PO)

- **Half-life**: 2-3 hrs
- **DoA**: 4-5 hrs
- **Adv**: Fewer side effects than Morphine
- **D/A**: One of the most abused prescription opioid
- **Oxycontin (reformulated summer 2010)**

- **Percocet**
  
  (Oxycodone 5/ APAP 325 mg)

- **Percodan**
  
  (Oxycodone 5/ASA 325 mg)

- **Roxyedone/ OXY IR**
Total Number of Opioid Prescriptions Dispensed by U.S. Retail Pharmacies, 1991–2010

Source: SDI's Vector One®: National (VONA)
PERCENT CHANGES BETWEEN 2004 & 2008

Source: 2008 (08/2009 update) SAMHSA Drug Abuse Warning Network (DAWN)
HYDROMORPHONE [C-II]

- 6-8x as potent as Morphine

- **Active metabolite:** Hydromorphone-3-glucuronide which is excreted by kidneys

- Accumulates in renal failure

- **Palladone: Hydromorphone ER**
  - *Purdue voluntarily suspended sales*
  - *Palladone + alcohol results in dangerous increases in peak plasma conc*
**HYDROMORPHONE [C-II]**

PCA choice considerations:
1. High opioid requirements
2. In patients not responsive/ sensitive to Morphine
3. Less histamine release c.f. Morphine

<table>
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<td>0.02-0.1</td>
<td>0.2-0.4</td>
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</table>
OXYMORPHONE (OPANA) [C-II]

- Faster onset and longer DoA than Morphine
- High affinity for Mu receptors: Slower dissociation from receptors
- 7-10x as potent as Morphine

OPANA IR:
5 & 10mg tabs
SYNTHETICS
FENTANYL (ACTIQUE, DURAGESIC PATCH) [C-II]

μδκ

κ1 κ2

25 mcg/hr Fentanyl Patch = ~60 mg/day Morphine PO

PATIENT-CONTROLLED TRANSDERMAL SYSTEM
• Chemically unlike morphine or heroin

• It has cross-tolerance with other opioids including heroin and morphine

• Higher doses of methadone can block the euphoric effects of heroin, morphine, and similar drugs.

**USES**

1. Severe chronic pain
2. Opioid Dependence
3. Opioid withdrawal syndrome
METHADONE (DOLOPHINE) [C-II]

- Variable Half life: 13-100 hrs (average 21)

- Analgesic duration<<t1/2 (slow terminal elimination)
  - Sequestered and unavailable for analgesia
  - Usually 4-6 hrs

- Usually started at 5 mg bid or tid.

- For pain, cannot prescribe more than 10 mg tabs
- So, 50 mg = 10mg x5

- Titration no less than 5-7 days
# METHADONE  *(DOLOPHINE) [C-II]*

## ADVANTAGES

1. Inexpensive
2. Long-acting
3. Less Euphoria
4. Less Sedation
5. Added NMDA activity
6. Any physician can write for pain treatment
   - Special lic. for Detox

## DISADVANTAGES

1. Major cause of death due to improper prescription practices**
2. QT prolongation
3. Long-acting, Variable metabolism
4. Risk of accumulation
5. Stigma of Heroin maintenance
OTHER SYNTHETICS
DEXTROMETHORPHAN

• D-isomer of Levomethorphan, which is the methyl ether of levorphanol (both opioid analgesics)

• No classic analgesic effects (only L isomer)

• Cough syrup

• NMDA antagonist (neuropathic pain)
  • Need very large dose to obtain: impractical
MEPERIDINE (DEMEROL) [C-II]

- Structurally similar to atropine
  - Tachycardia (unlike most opioids bradycardia)
- Problems with MAO inhibitors
- Normeperidine - Metabolite (CNS excitation) -- seizures
  - Renally cleared
  - Slow excretors normal Cr clearances
- Duration of Action – short (3hrs)

- 1st synthetic opioid synthesized in 1932 by Otto Eislib
- Not on formulary in most hospitals
- Use restricted at TUH for post-op shivering – or needs special override
TRAMADOL  
(ULTRAM, ULTRACET) [C-IV]

- Treat moderate to moderately severe pain

- MoA:
  - Very weak μ-opioid receptor agonist
  - Induces serotonin release
  - Inhibits the reuptake of Norepinephrine

- Converted to O-desmethyltramadol, a significantly more potent μ-opioid agonist

- Molecule similar to Venlafaxine (Effexor)
  - has similar SNRI effects, with antinociceptive effects.
  - May help symptoms of depression, anxiety, and phobias
  - Caution – rx with Effexor – serotonin syndrome
TRAMADOL: ADVERSE REACTIONS

- Nausea, Vomiting, Sweating, Itching and Constipation

- Reduction in SEIZURE threshold:
  - Seizures reported in humans receiving >700 mg
  - Either alone, or in combination w/ other anti-depressants
  - Relative contra-indication with SSRIs/ TCA Rx.
  - Relative contra-indication with h/o seizures.

- Serotonin Toxicity which can be fatal
  - Increased risk when taken with SSRIs
• Schedule II

• Indications:
  • Moderate to severe chronic pain in adults.
  • Neuropathic pain associated with diabetic peripheral neuropathy

• Similar to Tramadol
OPIOID METABOLISM

- Natural Opiate
  - Codeine
  - Hydrocodone
  - Oxycodone
  - Methadone
- Semi-Synthetic Opioid
  - NorFentanyl
  - Hydromorphone
  - Oxymorphone
- Synthetic Opioid
  - Fentanyl
  - 6-MAM (heroin metabolite)
  - Heroin

Key:
- Green: Natural Opiate
- Purple: Synthetic Opioid
- Blue: Semi-Synthetic Opioid
THE OPIOID PRESCRIBING TOOL

8 PRINCIPLES TO MAKE OPIOIDS SAFER

Source: American Academy of Pain Medicine
BACKGROUND

- Accidental deaths increasing
- Prescribers part of the problem
- Addresses the FDA Risk Evaluation Mitigation Strategies (REMS) for ER formulations
  - www.fda.gov
- The need to have RELIABLE solutions…
Increase in Unintentional Overdose Deaths Involving Opioid Analgesics, 1999–2008

Source: Centers for Disease Control and Prevention, National Center for Health Statistics, accessed through CDC WONDER Online Database, released 2011.
THE 8 PRINCIPLES

- Easy to follow
- Endorsed by the American Academy of Pain Medicine (AAPM)
- Associated with 28% decrease in unintentional overdose deaths!
- Currently partnering with other professional organizations

To make opioids safer

Source: American Academy of Pain Medicine
<table>
<thead>
<tr>
<th>R</th>
<th>Respiratory</th>
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<tbody>
<tr>
<td>E</td>
<td>Experience</td>
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<tr>
<td>L</td>
<td>Long Acting</td>
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<tr>
<td>I</td>
<td>Initiating Methadone</td>
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<tr>
<td>A</td>
<td>Apnea</td>
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<tr>
<td>B</td>
<td>Benzodiazepine</td>
</tr>
<tr>
<td>L</td>
<td>Look for co-morbidities</td>
</tr>
<tr>
<td>E</td>
<td>Exercise caution with switching</td>
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Source: American Academy of Pain Medicine
<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
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<tbody>
<tr>
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<tr>
<td>Flu</td>
<td>Reduce Dose</td>
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<td>Infirmed</td>
<td>Reduce Dose</td>
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Source: American Academy of Pain Medicine
### EXPERIENCE (2)

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<td><strong>Assess for Risk</strong></td>
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<tr>
<td>ORT, SOAPP, etc</td>
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<tr>
<td><strong>Biologic Risk Factors</strong></td>
</tr>
<tr>
<td>Age, Gender, Pain, Smoking, Family &amp; Personal history of Substance Abuse</td>
</tr>
<tr>
<td><strong>Social Risk Factors</strong></td>
</tr>
<tr>
<td>Legal problems, MVAs, DUIs, Unemployed, Isolated</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
</tr>
<tr>
<td>Mental health d/o, Coping skills, Loci of control</td>
</tr>
</tbody>
</table>
OXYCODONE & VICODIN REMAIN THE TWO MOST FREQUENTLY ABUSED OPIOIDS

After Marijuana, Prescription and Over-the-Counter Medications* Account for Most of the Commonly Abused Drugs

Prevalence of Past-Year Drug Use Among 12th Graders

Categories are not mutually exclusive

SOURCE: University of Michigan, 2010 Monitoring the Future Study

* Nonmedical Use
BIOLOGICAL RISK FACTORS: GENDER

• For women, 7 in 10 prescription drug deaths include pain killers.

• Women are more likely to die of overdoses on medicines for mental health conditions.

• Antidepressants + pain killers can be especially dangerous.

Every 3 minutes, a woman goes to the emergency department for prescription painkiller misuse or abuse.

Women between the ages of 25 and 54 are most likely to go to the emergency department because of prescription painkiller misuse or abuse.
BIOLOGICAL RISK FACTORS: GENDER

www.cdc.gov
**LONG ACTING (3)**

<table>
<thead>
<tr>
<th>Key elements from guide here</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AVOID ER/LR for Acute Pain</strong></td>
</tr>
<tr>
<td>Monitor</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
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<tr>
<td></td>
</tr>
</tbody>
</table>

Source: American Academy of Pain Medicine
URINE DRUG TESTING
TUH:
Lab 5610

Amphetamines 1000ng/mL Screen: NEGATIVE
Barbiturates: NEGATIVE
Benzodiazepines: NEGATIVE
Cocaine (Metab.) (Abnormal):
- POSITIVE
Marijuana Metabolite (Abnormal):
- POSITIVE
Methadone:
- NEGATIVE
Methaqualone: NEGATIVE
Opiates:
- NEGATIVE
Phencyclidine: NEGATIVE
Propoxyphene: NEGATIVE
OPIOID METABOLISM

Natural Opiate
- Codeine
- Heroin
- Morphine
- 6-MAM (heroin metabolite)
- Hydrocodone
- Hydromorphone
- Oxycodone
- Oxymorphone
- Methadone
- EDDP
- Fentanyl
- NorFentanyl

Semi-Synthetic Opioid
- Hydrocodone
- Hydromorphone
- Oxymorphone

Synthetic Opioid
- Methadone
- EDDP
- Fentanyl
- NorFentanyl
1. Self-escalation
2. Running out of medications early
3. Exhibiting addictive behaviors
   • Missing appointments and multiple phone calls for early refills
   • Insisting on more drugs
4. Selling or diverting medications in any manner
5. Losing the medication or prescription
6. Getting opioids from another source
7. UDS (Urine Drug Screen) positive for any illegal drugs
8. UDS negative for prescribed drugs
9. Refusal or postponing Urine Drug Screen other than insurance reasons
### Key elements from guide here

<table>
<thead>
<tr>
<th>PHARMACOKINETIC</th>
<th>Variable half-life: 12-100 hrs</th>
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</thead>
<tbody>
<tr>
<td>INITIATION</td>
<td>Starting dose &lt;15 mg/day</td>
</tr>
<tr>
<td>TITRATION</td>
<td>Dose escalation q7 days</td>
</tr>
<tr>
<td>P450</td>
<td>Unknown slow metabolizers</td>
</tr>
<tr>
<td>DRUG-DRUG INTERACTION</td>
<td>P450 inhibitors</td>
</tr>
</tbody>
</table>

*Source: American Academy of Pain Medicine*
GROWTH OF METHADONE USE FOR PAIN & METHADONE OVERDOSES

DEATH RATE FROM OVERDOSES CAUSED BY A SINGLE PRESCRIPTION PAINKILLER

Source: Substance Abuse and Mental Health Services Administration, Center for Behavioral Statistics and Quality, Drug Abuse Warning Network Medical Examiner Component, 2009.
Why have methadone overdoses increased?

As methadone prescriptions have increased, so have the number of methadone overdoses. But many people who die of painkiller overdoses don't have a prescription. How can this be?

It's because some of these prescriptions are illegally sold or given to people who use them for nonmedical reasons. This is known as diversion.

Diversion is a major factor in the prescription drug abuse epidemic. More careful prescribing will help reduce diversion and save lives.
Simulated Methadone Dosing

- α (analgesic)
- β (non-analgesic)

Blood level

Hours

Toxicity

Analgesia

LEGAL REVIEW OF OPIOID DEATHS: METHADONE

• Starting doses 20-140 mg/day
  • Most <30 mg/day

• ~90% opioid tolerant

• ~80% died within 4 days of first Methadone

• Snoring common

• Occasional URI/flu onset preceded death

### Key elements from guide here

<table>
<thead>
<tr>
<th>SLEEP DISORDERED BREATHING</th>
<th>Screen for OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Screen for CSA</td>
</tr>
<tr>
<td></td>
<td>Screen for Hypoxemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RISK INCREASED</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>Sedatives and Hypnotics</td>
</tr>
<tr>
<td></td>
<td>High Dose</td>
</tr>
</tbody>
</table>

*Source: American Academy of Pain Medicine*
Chronic Opioid Use is a Risk Factor for the Development of Central Sleep Apnea and Ataxic Breathing

James M. Walker, Ph.D., Robert J. Farney, M.D., Steven M. Rhondeau, M.D., Kathleen M Boyle, B.S., Karen Valentine, B.S., Tom V. Cloward, M.D., and Kevin C. Shilling, M.D.

Adapted from Webster L, Principles to make opioids safer, ISIS 2013
## Key elements from guide here

**AVOID BENZO'S WITH OPIOIDS**

- Increases opioid toxicity
- Adds to risk for Sleep Apnea
- Contributes to Hypoxemia
- Contributes to Cognitive Impairment
- Contributes to Falls

**Source:** American Academy of Pain Medicine
# Look for Co-Morbidities (7)

<table>
<thead>
<tr>
<th>Mental Health Disorders</th>
<th>Bipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General Anxiety Disorders</td>
</tr>
<tr>
<td></td>
<td>ADHD</td>
</tr>
<tr>
<td></td>
<td>PTSD</td>
</tr>
<tr>
<td></td>
<td>Pre-Adolescent Sexual Abuse</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
</tr>
<tr>
<td></td>
<td>Chemical Coper</td>
</tr>
</tbody>
</table>

Source: American Academy of Pain Medicine
LEVEL OF ABUSE IN STRESSFUL ENVIRONMENT

### Key elements from guide here

<table>
<thead>
<tr>
<th>OPIOID ROTATION</th>
<th>INITIATION OF NEW OPIOIDS</th>
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</thead>
<tbody>
<tr>
<td>Conversion Tables Flawed</td>
<td>Assume Opioid Naïve</td>
</tr>
<tr>
<td>Don't use Equianalgesic Tables</td>
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</tr>
</tbody>
</table>

**Source:** American Academy of Pain Medicine
<table>
<thead>
<tr>
<th>DRUG</th>
<th>PO (mg)</th>
<th>IV (mg)</th>
<th>PATCH</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUPRENORPHINE</td>
<td>0.3-0.4</td>
<td></td>
<td>5-10 mcg/hr</td>
<td></td>
</tr>
<tr>
<td>CODEINE</td>
<td>200</td>
<td>130</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYDROCODONE</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYDROMORPHONE (DILAUDID)</td>
<td>7.5</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>METHADONE **</td>
<td>10</td>
<td>5</td>
<td></td>
<td>Exponential conversion ratios at higher doses</td>
</tr>
<tr>
<td>MEPERIDINE (DEMEROL)</td>
<td>300</td>
<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MORPHINE (MS CONTIN)</td>
<td>30</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXYCODONE (OXYCONTIN)</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXYMORPHONE (OPANA)</td>
<td>10</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FENTANYL PATCH</td>
<td>60 mg MORPHINE PO/ 24 hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(25 mcg / hr)</td>
<td>40 mg OXYCODONE PO/ 24 hr</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**When switching between classes of opioids, decreasing by 30-50% may be appropriate.**

** Higher Morphine equivalent daily dosing ratios for Methadone are exponential (range from 2:1, 4:1, 8:1, 12:1, 15:1, 20:1) **

USE IN OPIOID-TOLERANT PATIENTS

Patients considered opioid tolerant are those receiving, for one week or longer:

• AT LEAST 60 MG ORAL MORPHINE/ DAY
• 25 mcg transdermal fentanyl / hour
• 30 mg oral Oxycodone / day
• 8 mg oral Hydromorphone / day
• 25 mg oral Oxymorphone / day
8 RELIABLE PRINCIPLES
1. Assess patients for risk of nonmedical use or medical misuse before starting opioid therapy and manage accordingly.

2. Watch for and treat co-morbid mental disease when it occurs.

3. Conventional conversion tables may cause harm when rotating (switching) from one opioid to another.

4. Avoid combining benzodiazepines with opioids, especially during sleep hours.

Source: American Academy of Pain Medicine
5. If using methadone as a secondary or tertiary agent, start with a low dose and titrating very slowly.

6. Assess for sleep apnea in patients on high daily doses of methadone or other opioids and in patients with a predisposition.

7. Instruct patients on long-term opioid therapy to reduce opioid dose during upper respiratory infections or asthmatic episodes.

8. Avoid using long-acting opioid formulations for acute, postoperative or trauma-related pain.

Source: American Academy of Pain Medicine
BREAK : NEXT TOPIC - REMS
ER / LA OPIOID REMS
RiskMAPs - 2005

- Risk Minimization Action Plans
- Precursor REMS
- Guide to the development REMS
- Goal – minimize the risks of certain products while maintaining their benefits.

RiskMAPs - 2005

5 separate components

• Medication guides
• Communication plan
• Assure safe use
• Implementation of system
• Timetable for submission

REMS: RISK EVALUATION AND MITIGATION STRATEGY

- **Strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA).**

- Ensure that the benefits of a drug outweigh its risks.

- FDA has required a REMS for extended-release and long-acting (ER/LA) opioid analgesics, among other classes.

- Plan for incorporating short acting – in evolution.
2007 FDA AMENDMENTS ACT (FDAAA)

• Afforded the FDA ability to enforce post marketing risk management strategies for prescription medications

• Program designed –
  • Improve prescriber education
  • Patient awareness of opioid safety
  • Minimize risk of addiction, unintentional overdose, and deaths

• REMS - July 2012, the FDA approved a classwide REMS for ER and LA opioids

ORGANIZATIONS REMS
SUMMARY ER/LA OPIOID REMS
Patient Assessment and Treatment with ER/LA opioid Therapy
DOCUMENTATION IS EVERYTHING
DOCUMENTATION

- All patient interactions (Visits / phone calls)
- Assessment and Diagnosis
- Risk Stratification (abuse hx, elderly, mental illness)
- Testing and Results
- Treatment Plans
HISTORY – GOVERNMENTAL EXPECTATIONS

- General and Specific Pain
- Past treatments and records
- Risk Assessment
  - (tools, scoring, and ranking)
- Physical Exam
- Selection decision and diagnosis
ASSESS RISK

- Prescription drug abuse
- Illegal substances
- Alcohol and tobacco
  - Does not prohibit ER/LA opioids – may require specialty referral
- Family substance abuse
- Sexual abuse

Achieving Safe Use While Improving Patient Care, Core-Rems Collaboration for Rems Education
SOCIAL HISTORY RELEVANT

- Marital status
- Legal history
- Behavior problems
- Employment
- Cultural history
OPIOID RISK TOOLS

“helpful for risk stratification, though more validation and prospective outcome studies are needed to understand how their use predicts and affects clinical outcomes”

OPIOID RISK TOOL – “ORT”

- Completed as part of the interview
- Completed and scored while making opioid treatment decisions
- Documents level of monitoring required
- When: initial visit and prior to opioid treatment

- 0-3 Low Risk
- 4-7 Moderate
- 8+ High

### Mark each box that applies

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Family hx of substance abuse</td>
<td></td>
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<tr>
<td>Alcohol</td>
<td>1</td>
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<tr>
<td>Illegal Drugs</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>2. Personal hx of substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Illegal Drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>3. Personal hx of substance abuse</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4. Hx of preadolescent sexual abuse</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5. Psychologic disease</td>
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<tr>
<td>ADD, OCD, bipolar, schizophrenia</td>
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<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Scoring totals:
INITIATING OPIOID TRIAL - CAUTION

• **Elderly**

  respiratory depression
  cachetic / dehabilitated
  start ½ to 1/3 starting dose

  Constipation – bowel regimen
  Caregiver management - reliable?
INITIATING OPIOID TRIAL - CAUTION

• Pregnant
  • Newborn
    • Low birth weight
    • Premature
    • Opioid withdraw syndrome
  • Encourage non opioid approach to treatment
    Anticipate and manage risk to newborn
INITIATING OPIOID TRIAL - CAUTION

• **Pediatrics**
  - Safety and Effectiveness most ER/LA – unestablished
  - Transdermal Fentanyl approved children >2yrs
  - Focus on Safety
  - Primarily used in treatment of life threatening conditions
  - Consult palliative or pediatric pain specialist

PEARLS FOR PRACTICE

Document Everything

Conduct a Comprehensive H&P
  • General and Pain Specific

Assess Risk and Expected Benefits

Determine whether a Therapeutic Trial is Appropriate

Achieving Safe Use While Improving Patient Care, Core-Rems Collaboration for Rems Education
MANAGING THERAPY WITH ER/LA OPIOIDS

• Informed Consent
  • Analgesic and Functional goals of treatment
  • Expectations
  • Potential risks
  • Alternatives to opioids
  • Education on opioids
  • Patient and prescriber responsibilities

Document signed by both patient and prescriber at time of opioid prescribed

Achieving Safe Use While Improving Patient Care, Core-Rems Collaboration for Rems Education
ER/LA OPIOID CANDIDATE

“OPIOID TOLERANT?”

Yes, when taking at least

- 60mg oral morphine/day
- 25mcg transdermal fentanyl/hr
- 30mg oxycodone/day
- 8mg hydromorphone/day
- 25mg oxymorphone/day

Still requires caution when rotating from IR to a different ER/LA opioid

Achieving Safe Use While Improving Patient Care, Core-Rems Collaboration for Rems Education
PEARLS FOR PRACTICE

Establish Informed Consent to Treatment

Counsel Patients on Proper Use

  Appropriate use of medications
  Consequences of inappropriate use

Educate the Whole Team

  Patients, Family, caregivers

Tools and Documents Can Help with Counseling

  Use them

Achieving Safe Use While Improving Patient Care, Core-Rems Collaboration for Rems Education
MONITORING
URINE DRUG SCREENING

Considered a necessary tool to use when prescribing opioids for non-cancer chronic pain by:

- DEA
- State Regulators
- Pain Societies
WHO?

- **New patients** to be started on opioids
- Patients already taking opioids
- **Change** in treatment
- Resisting full evaluation
- Requesting **specific** drug
- Abherent behavior
- Mental health issues
- Tobacco and alcohol use
<table>
<thead>
<tr>
<th>Patient Information</th>
<th>Result Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Name</td>
<td>Abnormal</td>
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<tr>
<td>Sex</td>
<td>Female</td>
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<tr>
<td>DOB</td>
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<td>SSN</td>
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<tr>
<td>Status</td>
<td>Final result (6/26/2013 1:21 PM)</td>
</tr>
<tr>
<td>Provider Status</td>
<td>Reviewed</td>
</tr>
</tbody>
</table>

**URINE DRUG TESTING**

**TUH:**
Lab 5610

- **Amphetamines 1000ng/mL Screen:** NEGATIVE
- **Barbiturates:** NEGATIVE
- **Benzodiazepines:** NEGATIVE
- **Cocaine (Metab.) (Abnormal):** POSITIVE
- **Marijuana Metabolite (Abnormal):** POSITIVE
- **Methadone:** NEGATIVE
- **Methaqualone:** NEGATIVE
- **Opiates:** NEGATIVE
- **Phencyclidine:** NEGATIVE
- **Propoxyphene:** NEGATIVE
OPIOID METABOLISM

Natural Opiate
- Codeine
- Hydrocodone
- Oxycodone
- Methadone
- Fentanyl
- Morphine
- Hydromorphone
- Oxymorphone

Semi-Synthetic Opioid
- Hydrocodone
- Hydromorphone
- Oxymorphone

Synthetic Opioid
- Heroin
- NorFentanyl
- EDDP

6-MAM (heroin metabolite)
PEARLS FOR PRACTICE

• Initiation of Opioids as a Therapeutic Trial
• Anticipate ER/LA Induced Respiratory Depression
  can be life threatening
• Conservative and Thoughtful in dosing
  when initiating, titrating, and rotating opioids
  first calc equinalgesic dose and reduce appropriately
• Discontinue ER/LA slowly and safely
QUESTIONS?