A Comprehensive Approach to the Safe Management of Extended-Release/Long-Acting Opioids

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Learning Objectives

At the conclusion of this activity, participants should be able to:

• Describe how to counsel patients and caregivers on the safe use of ER/LA opioid analgesics, including proper storage and disposal

• Review how to safely initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics

• Explain general and product-specific drug information concerning ER/LA opioid analgesics

• Identify patients who are candidates for treatment with ER/LA opioid analgesics

• Describe how to minimize the risks of opioid abuse, addiction, and diversion while managing patients who are receiving ongoing therapy with ER/LA opioid analgesics

Pain: A Public Health Issue
Important Points for Consideration

- Understand the prevalence of chronic pain
- Understand effect of pain on QOL and economics
- Understand the trends in opioid prescribing

Pain Affects 100 Million Americans

The Cost to America in $ Billions

Cancer vs Diabetes vs Heart vs Pain

Nearly 2 Million People Age 12 or Older Either Abused or Were Dependent on Prescription Opioids

Number of Substance Abuse Treatment Admissions
Emergency Department Visits

<table>
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<th>Year</th>
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<th>Benzodiazepines</th>
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<tr>
<td>2013</td>
<td>143,546</td>
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Emergency Department Visits

18,000 Deaths in 2014


Dueling Crises

FDA Task Force to Address Opioid Misuse

Recognizing the Barriers in Effective Pain Management

- Understand physician and patient barriers to treatment
- Understand the 8 principles of safer opioid prescribing

20 Years of Expanded Opioid Prescribing

- What have we learned?
  - Something fundamental about the clinical use of opioids?
  - OR
  - Something fundamental about the problems of our health care system?
The Problem With Insurance

• The Role of the Health Insurance Industry in Perpetuating Suboptimal Pain Management

Bio-Psych-Social Model

• Of all approaches to the treatment of Pain, none has a stronger evidence basis for efficacy, cost-effectiveness than interdisciplinary care

Interdisciplinary Programs

Access to Interdisciplinary Care

Coverage by Type of Health Insurance

Shareholder Pain is the Worst Pain

• The fiduciary obligation of health insurers is not to its enrollees, but to its share-holders

• Concern with cost-containment (and, in most cases, profitability) inherent in the "business ethic" under which the health insurance industry operates trumps any sense of perceived responsibility to ameliorate enrollee suffering
**Insurer Mechanisms to Limit Care**

- Limitations on physical therapy
- Limited cognitive behavioral therapy coverage
- Limited coverage for evidence-based alternative therapies
- Independent medical examiners (IME)
- When IME supports patient – rarely not re-hired
- No or limited reimbursement of REMS activities
- No reimbursement for increased work load

**Major Reasons for Opioid-Associated Deaths**

- Over-prescribing (Physician)
  - Starting dose too high
  - Dose escalation too rapid
  - Over reliance on conversion tables
  - Inadequate risk assessment
- Non-adherence (Patient)
  - To control pain
  - To “cope”
  - Substance abuse
- Unanticipated co-morbidities
  - QT prolongation
  - Pharmacogenetics & methadone metabolism
  - Sleep disordered breathing

**Responsible Opioid Prescribing**

- Patient evaluation, including risk assessment
- Treatment plans that incorporate functional goals
- Informed consent and prescribing agreements
- Periodic review and monitoring of patients
- Referral and patient management
- Documentation
- Compliance with state and federal law

**Pain Assessment Issues to Evaluate and Document With Every Patient**

- Pain intensity, onset, location, duration, and quality
- Pain-related disabilities and other comorbidities
- Prior pharmacologic and nonpharmacologic treatments
- Current medications/allergies
- Medical, psychiatric, and social history
- Substance abuse history
- Risk level for aberrant drug-related behavior

- In addition, regarding those being considered for opioid analgesic therapy
  - Is the pain acute or chronic?
  - Will opioid therapy be short or long-term?

- Inform patient of risks, benefits, and alternatives to opioid therapy
- Initiate patient care agreement

**FSMB Model Policy Guidelines**

- Evaluation of the Patient
  - Medical history and physical exam must be obtained, evaluated, and documented in the medical record
- Treatment Plan
  - Should state objectives that will be used to determine treatment success and indicate any future diagnostic evaluations or treatments
- Informed Consent and Agreement for Treatment
  - Discuss the risks and benefits of therapy; specify that prescriptions should be obtained from one physician and one pharmacy; if patient is high risk, consider using written patient agreement
- Periodic Review
  - Review course of pain treatment and any new information regarding etiology of pain or patient’s health. Continuation or modification of therapy depends on physician’s evaluation of progress toward treatment objectives
- Consultation
  - Refer as necessary for additional evaluation and/or treatment to meet objectives
- Medical Records
  - Should include history and physical exam; diagnostic, therapeutic, and lab results; evaluations/consultations; treatment objectives; discussion of risks and benefits; informed consent; treatments; medications; instructions and agreements; periodic reviews

**REMS, APS/AAPM Guidelines, and State Medical Board Policies**

- REMS will not replace existing federal and state policies regarding opioid prescribing
- APS/AAPM guidelines are consistent with state medical board guidelines
- Check with your local medical board for particular guidelines/policies pertaining to your state
- Implementation of REMS principles into current practice is intended to advance responsible use of opioid therapy in order to
  - Ensure safe use of opioids
  - Improve patient outcomes and minimize adverse events
  - Keep access to opioid therapy available to people with pain

**Compliance With Controlled Substances Law and Regulations**

- See Physician Manual of the US Drug Enforcement Administration for state-specific rules and regulations

*See 2009 APS/AAPM Guideline Section 1.1-1.3, 2.1-2.2, 6.1-6.2*
Eight Opioid Prescribing Principles for Providers®
Help Minimize Harm Prescribing Opioids and Other Psychotherapeutics

1. Assess patients for risk of abuse before starting opioid therapy and manage accordingly.
2. Watch for and treat comorbid mental disease if present.
3. Conventional conversion tables can cause harm and should be used cautiously when rotating (switching) from one opioid to another.
4. Avoid combining benzodiazepines with opioids, especially during sleep hours.
5. Start methadone at a very low dose and titrate slowly regardless of whether your patient is opioid tolerant or not.
6. Assess for sleep apnea in patients on high daily doses of methadone or other opioids and in patients with a predisposition.
7. Tell 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, post-operative, or trauma-related pain.

Assess Patients for Risk of Abuse Before Starting Opioid Therapy & Manage Accordingly

1. BEST PRACTICES

Oreos As Addictive As Cocaine? For Rats, At Least


Vulnerability to Opioid Addiction

Individuals respond differently to opioid exposure:
- No addictive disease with exposure
- Addictive disease after opioid exposure
- No addictive disease due to lack of exposure

Genetic Vulnerability to Addiction?

| Fischer 344 | Abstinence | Drug rejecting |
| Lewis        | Poly-substance Abuse | Drug seeking |
| Sprague-Dawley | Average | Drug neutral |

Level of Abuse in Stressful Environments

| Low | Moderate | High |
| Drug-abusing behavior | Level of stress | Patient stress level |
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Screening Tools to Assess Patient Risk Before Prescribing Opioids

- Use one of several available tools to assess patient risk of developing problematic drug-taking behaviors
  - Based on biological, social, & psychiatric risk factors

<table>
<thead>
<tr>
<th>Tool</th>
<th># of Items</th>
<th>Administered by</th>
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<tbody>
<tr>
<td>Opioid Risk Tool</td>
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<td>Patient</td>
</tr>
<tr>
<td>SOAPP® Screener &amp; Opioid Assessment for Patients with Pain</td>
<td>24, 14, or 5</td>
<td>Patient</td>
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<tr>
<td>DIRE Diagnosis, Intractability, Risk, &amp; Efficacy Score</td>
<td>7</td>
<td>Clinician</td>
</tr>
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</table>

- Implement a plan according to risk level
  - Eg, for high-risk patients, refer for psychiatric evaluation or co-manage with a chemical dependency expert prior to opioid trial

Clinical Case #1

RH is a 76-year-old male with right hip OA and severe coronary artery disease (not a surgical candidate). No personal history of addiction. Family history of alcoholism. Had been using hydrocodone/APAP for last year. Still has daily intermittent pain. Concerned about continued use and the risk of addiction.

Clinical Case #2

KT is a 42-year-old female with complex regional pain syndrome (CRPS) with compound ankle fracture post motor vehicle accident. She is on hydrocodone/APAP and is requesting oxycodone/APAP. Stressed, depressed, using alcohol and marijuana. Sexually abused as a preadolescent.

Clinical Case #3

BD is a 46-year-old male with failed back syndrome. Used street drugs when in college and treated for alcoholism. Sober for the last 15 years, attends AA regularly. Smokes ¼ pack of cigarettes per day (reduced from 2 packs a day more than a year ago). Working full time and providing for a family of 3 children. No family history of addiction; no other psychiatric illness.

All of These Patients Could Potentially Benefit from a Trial of Chronic Opioid Therapy (1 of 2)

A chronic opioid therapy trial should only be considered when potential benefits are likely to outweigh risks. A comprehensive history and physical examination, including an assessment of psychosocial factors, is always necessary:

- Risk assessment should be conducted even if the patient is already receiving opioid therapy.
- Opioid therapy can be considered in well-selected patients with history of substance abuse, psychiatric issues, or serious aberrant drug-related behaviors only if highly structured conditions are in place.

See 2009 APS/AAPM Guideline Sections 1.1-1.3

All of These Patients Could Potentially Benefit from a Trial of Chronic Opioid Therapy (2 of 2)

- Always rely on your clinical judgment when deciding whether a patient should or should not receive opioid therapy—risk assessment tools should be used as a guide.
- Implement opioid therapy as a component of a multimodal, interdisciplinary treatment plan that may include psychological and functional restoration interventions.
- Managing the conversion from short-acting to long-acting opioid therapy

See 2009 APS/AAPM Guideline Sections 1.1-1.3
Managing Risk and Referral

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<tr>
<th>Lower Risk</th>
<th>Moderate Risk</th>
<th>Higher Risk</th>
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</thead>
<tbody>
<tr>
<td>Primary Care Patients</td>
<td>Primary Care Patients with Specialist Support</td>
<td>Pain Specialist Patients</td>
</tr>
</tbody>
</table>

ORT Score: 0-3
- No past or current history of substance use disorders
- No family history of prior or current substance use
- No major or untreated mental illness
- Present UDT
- PMP consistent
- Pain mild to moderate

ORT Score: 4-7
- May be a past history of addiction or other disorders
- May be family history of problems, they can vary in type and severity
- May have past or current untreated mental illness
- Usually consistent UDT
- No serious pain

ORT Score: 8+
- Active substance use disorders
- Major untreated psychopathology
- Present UDT
- Protein added
- Active pain
- UDT inconsistent
- Pain moderate to severe

Identify Misuse Once Opioid Treatment Begins

- Periodic monitoring for effects on analgesia, daily activities, adverse events, ADRBs, cognition, function, & QOL can be assisted by tools

<table>
<thead>
<tr>
<th>Tool</th>
<th># of Items</th>
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<tr>
<td>PADT Pain Assessment &amp; Documentation Tool</td>
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<td>COMM Current Opioid Misuse Measure</td>
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Watch for & Treat Comorbid Mental Disease if Present

BEST PRACTICES

Overlapping Effects

Psychiatric Disorders

50% overlap

Pain Disorders

Addiction Disorders

60% overlap

Comorbid Pain & Mental Disease

- Co-occurrence of mental health disorders with chronic pain place patient at high risk for:
  - Misuse
  - Drug-drug interactions
  - Overdose
- Assess for the presence of mental disease before initiating opioid therapy
  - When indicated, consult with experts in mental health fields to co-ordinate care

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### An Olympian Challenge: Managing a Critical Interplay

**A “trio diagnosis”**
- Addiction disorder
- Psychiatric disorder
- Pain disorder


### Why Suicide? Non-Pain Patients

- Escape from severe suffering
- Only option
- Hopelessness
- Permanent solution


### Conventional Conversion Tables Can Cause Harm & Should Be Used Cautiously When Rotating (Switching) From One Opioid To Another

**BEST PRACTICES**

- Equianalgesic tables provide insufficient guidance to determine the equivalent doses of different opioids
  - Individual consideration is necessary for every patient


### Steps in Opioid Rotation

- Slowly decrease one opioid while slowly titrating the new opioid to effect


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Steps in Opioid Rotation

1. In most cases, the complete switch can occur within 3-4 weeks.
2. If you are not experienced in switching opioids in patients on long-term opioid therapy, seek expert consultation.

Avoid Combining Benzodiazepines with Opioids, Especially During Sleep Hours

Best Practices

Most Common Drugs Involved in Overdoses in the United States

- In 2013, there were 43,982 drug overdose deaths:
  - 22,767 (51.8%) were related to pharmaceuticals
  - 16,235 (71.3%) involved opioid analgesics
  - 6,973 (30.6%) involved benzodiazepines
- People who died of drug overdoses often had a combination of benzodiazepines & opioids in their bodies.
- In 2011, ~1.4 million ED visits involved nonmedical use of pharmaceuticals:
  - 501,207 visits involved anti-anxiety & insomnia medications
  - 420,040 visits involved opioid analgesics

Benzodiazepines & Chronic Pain Patients

- Enhance the respiratory depressant effects of opioids:
  - Frequently co-prescribed with opioids (up to 50% of patients)
  - In 1 population, 80% of patients prescribed high-dose opioids were co-prescribed benzodiazepines
  - More common in chronic pain patients with substance use disorders
- Consider an alternative:
  - For anxiety disorders
  - When a sleep aid is indicated, e.g., an anticonvulsant or low-dose trazodone
  - For patients with neuropathic pain, low-dose trazodone at bedtime may be dualy beneficial.
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**Concurrent Illicit Drug Use**

- Respondents can indicate multiple options.

**Start Methadone At A Very Low Dose & Titrate Slowly Regardless Of Whether Your Patient Is Opioid Tolerant Or Not**

5. **BEST PRACTICES**

- Methadone contributed to nearly 1 in 3 prescription opioid deaths in 2009.
- 5,000 people die every year of overdose related to methadone.
- 6 times as many people died of methadone overdose in 2009 than a decade before.

**Death Rate from Overdose Caused by a Single Prescription Painkiller**

**Simulated Methadone Dosing**

**Legal Review of Opioid Deaths: Methadone**

- Starting doses 20-140 mg/day
  - Most <30 mg/day
  - ~80% opioid tolerant
  - ~80% died within 4 days of first methadone
  - Snoring common
  - Occasional upper respiratory infection/flu onset preceded death
Initiating Methadone

• Consider starting patients, whether or not they are opioid naïve, on ≤15 mg/day in divided doses (q8h)
• Increase the total daily dose by no more than 25%-50%, no more frequently than weekly

If you are not experienced prescribing methadone, consult with a clinician who is.

Assess for Sleep Apnea In Patients on High Daily Doses of Methadone or Other Opioids & in Patients With a Predisposition

Assess for Sleep Apnea

• Refer the following patients for formal sleep apnea evaluation
  – Patients who require >50 mg/day of methadone
  – Patients who require >150 mg/day of morphine equivalent dose of other opioids
  – Patients with a predisposition or risk factors for sleep apnea
• At risk patients may require inpatient evaluation to monitor for & determine safety of opioid therapy

Tell patients on long-term opioid therapy to reduce opioid dose during upper respiratory infections or asthmatic episodes
Reduce Opioid Dose During

• Because of a decreased margin of safety, advise patients to reduce their daily opioid doses by ≥30% during events with acute respiratory tract compromise
  – These include:
    • Flu
    • Pneumonia
    • Upper respiratory infections
    • Cigarette use
    • Chronic obstructive pulmonary disease
    • Asthmatic episodes

Avoid Using Long-acting Opioid Formulations For Acute, Post-operative, Or Trauma-related Pain

Reserve Long-Acting Opioids for Opioid-Tolerant Patients

• Reserve long-acting/extended-release opioids, including transdermal patches, for patients who have developed tolerance to opioids
  – i.e., who already take regular, daily, around-the-clock opioids
• Do not use for acute, postoperative, or trauma-related pain

REMS: Extended Release Opioids and Abuse Deterrent Formulations: What Prescribers Need to Know

Overview

• Review risks/benefits of opioid use of chronic pain management
• Review REMS for opioid ER/LA formulations
• Introduce Abuse Deterrent Formulations (ADFs)
  – Physical and pharmacologic barriers
• Review those ADF’s
  – Currently available
  – In development
### Analgesic Options

- Although formal pain management treatment protocols are lacking, most experts propose conservative nonpharmacological modalities as primary and adjunctive treatment, with opioids reserved for those patients who fail to respond to other therapies.

### Overview

- Health care professionals who prescribe extended-release (ER), controlled-release (CR) and long-acting (LA) opioids are in a key position to balance the benefits of pain relief against the risks of:
  - **AE's**
    - Constipation, somnolence, nausea, pruritus…
  - Serious adverse outcomes
    - Abuse, addiction, unintentional overdose and death

### Opioids

- Relieve pain
- Improve function
- Improve QoL
- Play an important role in acute and chronic pain management and palliative care
- Can be misused
- Can be abused
- Can lead to or worsen preexisting addiction
- Are diverted for illicit use
- Contribute to overdose related respiratory depression and death

### Opioid Therapy: Benefits and Risks

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Reduction in pain</th>
<th>Reduction in pain-related impairment</th>
<th>Improved function and quality of life</th>
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</thead>
<tbody>
<tr>
<td>Risks</td>
<td>Sedation/confusion</td>
<td>Nausea/dizziness</td>
<td>Constipation</td>
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</tbody>
</table>

**BEFORE** starting a trial of opioid therapy, benefits/risks, alternatives to opioid therapy, and patient concerns should be discussed.

### Complexities of Opioid Therapy

- Variable response, partial efficacy
  - Receptor subtypes
- AE profile
  - Constipation, sedation, nausea
- OIH (opioid-induced hyperalgesia)
- Endocrine dysfunction (hypogonadism)
- Respiratory depression, sleep-disordered breathing
- Drug-drug interactions
- Abuse, misuse and diversion
- Regulatory concerns, fears

### Other Considerations with Opioids

- Food effect
- QTc interval prolongation
- Heat
- Alcohol effect
- P450 metabolism
- T½ (methadone)
- Renal or Liver dysfunction
- Tampering and ADF’s (abuse deterrent formulations)
ER-LA REMS

• In April 2011, FDA announced a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of extended-release and long-acting (ER/LA) opioid analgesics outweigh the risks.
• The REMS supports national efforts to address the prescription drug abuse epidemic.

As part of the REMS, all ER/LA opioid analgesic companies must provide:

• Education for prescribers of these medications, provided/supported through CME activities
• Information that prescribers can use when counseling patients about the risks and benefits of ER/LA opioid analgesic use

The FDA Blueprint for Prescriber Education: REMS

• Concepts for safe prescribing
  – Be familiar with how to initiate therapy, modify dose, and discontinue use
  – Converting patients between opioid products
  – Understanding the general characteristics and toxicities of specific opioids (ie. methadone)
  – Managing drug-drug interactions with opioids
  – Anticipating and managing opioid AE’s

What Are the Options for ER-LA Opioids?

- Duragesic
- Dolophine
- MS Contin
- Kadian
- Oramorph
- Embeda
- Oxycontin
- Opana ER
- Exalgic
- Butrans
- Nucynta ER
- Belbuca
- Zohydro ER
- Targin ER
- Hysingla ER

All versions including generic covered by REMS program. For more detailed information, please see the FDA Blueprint pages 7-17 located at:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/ERLA_opioids_2015-10-23_FDA_Blueprint.pdf

Although We Have Equianalgesic Reference Tables

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<td>Levoorphanol (Levo-Dromoran®)</td>
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<tr>
<td>Codeine</td>
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<td>200</td>
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</tbody>
</table>

Relative Abuse Risk

| Opioid | Relative Abuse Risk
|--------|---------------------|
| Morphine | Low
| Hydromorphone | Low
| Methadone | Low
| Oxycodone | Low
| Levoorphanol | Low
| Oxyphenera | Low
| Meperidine | Low
| Codeine | Low

All versions including generic covered by REMS program. For more detailed information, please see the FDA Blueprint pages 7-17 located at:
http://www.accessdata.fda.gov/drugsatfda_docs/rems/ERLA_opioids_2015-10-23_FDA_Blueprint.pdf
Patients Usually Have A Variable Response To Medications

ESPECIALLY TO ANALGESICS

ESPECIALLY TO OPIOIDS

Who Misuses/Abuses Opioids and Why?

Nonmedical Use
• Recreational abusers
• Patients with disease of addiction

Medical Use
• Pain patients seeking more pain relief
• Pain patients escaping emotional pain

And There Are Serious Risks:
Opioid Analgesic Overdoses = Public Health Epidemic

• Opioid analgesics are among the most commonly misused or abused pharmaceuticals
• Overdose deaths from prescription painkillers have increased
  – 16,651 in 2010; >4x # in 1999

Improper use of any opioid can result in serious side effects, including overdose and death

A Multifaceted Approach to Addressing Opioid Abuse

A collaborative approach is necessary

HCPs
Patients
Government
State + Federal
Industry

By mitigating opioid abuse, it may be possible to decrease abuse in the community and decrease patient risk

What Can Industry Do?

...and drug manufacturers should modify opioid painkillers so that they are more difficult to tamper with and/or combine them with agents that block the effect of the opioid if it is dissolved and injected.

What are the Most Common Methods of Abuse?

Primary routes of opioid abuse:
• Oral
• Intranasal (snorting)
• Parenteral (IV, IM, SC)
• Smoking

Primary forms of opioid manipulation:
• Crushing or grinding into small particles or powder
• Dissolving in a solvent (e.g., alcohol, acetone)
• Extraction by exposure to hot or cold temperatures
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Abuse-Deterrent Opioids
Evaluation and Labeling: April 2015

- Replaces January 2013 Draft Guidance
- Explains FDA’s current thinking about the studies that should be conducted
- Makes recommendations about how those studies should be performed and evaluated
- Outlines how to describe studies and their implications on product labeling


Industry’s Approaches to Abuse-Deterrent Opioids

The FDA Has Identified 7 Categories of Abuse-Deterrent Technologies

- Agonist/Antagonist Combos
  - May curb euphoria when formulation compromised
  - Antagonist may be formulated to be clinically active only when tampered with
- Aversion
  - Substances may be added to create unpleasant effects when tampered with or taken at higher doses
- Delivery System
  - Drug-release designs or method of drug delivery can offer resistance to abuse
- New Molecular Entities and Prodrugs
  - May require enzymatic activation, different receptor binding profiles, slower CNS penetration, or other novel effects
- Physical/Chemical Barriers
  - May prevent chewing, crushing, cutting, grating, or grinding
  - May resist extraction by solvents
- Combination
  - Use of 2 or more technologies in 1 product to deter abuse
- Novel Approaches
  - Use of technologies not captured by any of the above

Examples of ADFs Currently Available

- OxyContin®
- Targiniq™ ER
- Hysingla® ER
- Embeda®
- Oxaydo®
- Suboxone®
- Zohydro® ER
- Xtampza ER®

Examples of ADFs Currently Available

- OxyContin®
  - April 5, 2010 - FDA approved Purdue Pharma L.P.’s reformulation of OxyContin® (oxycodone HCl controlled-release)
  - The reformulation met FDA criteria for bioequivalence to the original formulation
  - While similar in appearance to the original formulation, the reformulated tablets have a different marking (“OP”) than the currently marketed tablets (marking “OC”) and the 60 mg and 80 mg tablets are slightly larger in size than the currently marketed tablets
  - Purdue elected to reformulate OxyContin® in an effort to make the tablet more difficult to manipulate for the purpose of intentional misuse and abuse
  - However, this formulation of OxyContin is still subject to abuse, diversion, overdose or addiction

Formulations In Development

- Oxycodone ER Crush-resistant & gelling (Egalet)
- Oxycodone ER Beads in tablet (TEVA)
- Oxycodone ER Naltrexone antagonist (Pfizer)
- Oxycodone ER Naltrexone antagonist (Elite)
- Oxycodone ER Crush-resistant & gelling (Inspirion)
- Oxycodone Pro-drug Under development (Signature Therapeutics)
- Remoxy Gel capsule (Pain Therapeutics)
- Oxycodone/APAP IR (Mallinckrodt)
Formulations In Development

- Hydrocodone/APAP IR (Mallinckrodt)
- Hydrocodone ER Crush-resistant & gelling – (Egalet)
- Hydrocodone ER Beads in tablet (TEVA)
- Pro-drug IR – (KemPharm)

Specific Abuse Deterrent Opioid Examples Under Review

- ER oxycodone combined with opioid-receptor agonist naltrexone1
  - If tablets are crushed, naltrexone is released, counteracting the oxycodone
- ER hydrocodone using a manufacturing process that coats drug particles in polymer layers2
  - Protects against “dose-dumping” via crushing or dissolving tablets in water or alcohol

Summary of ADF Opioids

- Several technologies are currently available or being developed
- Abuse-deterrent opioid technologies provide additional barriers to manipulation
- The FDA has published guidance on how these formulations may be evaluated
- In the absence of Category 4 (postmarket) studies, premarket studies provide insight into what methods of manipulation the product may resist

Prescribers of ER/LA Opioids Should Balance:

The benefits of prescribing ER/LA opioids to treat pain
The risks of serious adverse outcomes

All Prescribers Play an Active Role in Reducing the Risks Associated With Opioids

- ADF DO NOT Replace a Comprehensive Assessment
- Be familiar with Opioid REMS
- When opioids are being considered as part of a chronic pain treatment plan:
  - Establish diagnosis
  - Perform a history and physical
  - Order and evaluate the results of relevant diagnostic tests
  - Complete an appropriate risk assessment PRIOR to prescribing
  - Monitor the patient regularly on an ongoing basis
  - PDMP, UDT, Tools
  - Prescribe opioids as part of a multimodal treatment regimen

APS/AAPM Clinical Guidelines For The Use Of Chronic Opioid Therapy In Chronic Noncancer Pain (2009)

- Patient selection and risk stratification
- Informed consent and opioid management plans
- Initiation and titration of COT
- Monitoring
- Dose escalations, high-dose opioid therapy, opioid rotation, indications for discontinuations of therapy
- How to deal with high-risk patients

APS, American Pain Society; AAPM, American Academy Of Pain Medicine; COT, chronic opioid therapy


### APS/AAPM Clinical Guidelines For The Use Of Chronic Opioid Therapy In Chronic Noncancer Pain (2009) (cont’d)

- Opioid-related adverse effects
- Use of psychotherapeutic co-interventions
- Driving and work safety
- Identifying a medical home and when to obtain consultation
- Breakthrough pain
- Opioids in pregnancy
- Opioid policies

APS, American Pain Society; AAPM, American Academy Of Pain Medicine


### Implementing Informed Consent and Opioid Treatment Agreements

- Informed consent is conceptually separate from an opioid treatment agreement
- Opioid treatment agreement can be a valuable tool that facilitates discussion, education, and structuring of care between clinician and patient (and other caregivers)
- Creates a durable record of patient and clinician responsibilities and expectations which can be referred to on an ongoing basis over the course of treatment
- May also be used as part of an overall opioid management plan to set boundaries and guidelines for opioid treatment
- Documentation of goals of treatment is also important and serves as a basis for assessment of the effectiveness of therapy

### Components of the Informed Consent Form

- Potential adverse effects of opioids, including but not limited to sleepiness, constipation, nausea, itching, respiratory depression, inadequate pain relief, and risk of addiction
- Definitions and descriptions of tolerance, physical dependence, and addiction
- Alternative treatments discussed or tried
- Discussion of the risks for low testosterone in men and risks of pregnancy-related concerns of opioid therapy in women who may become pregnant
- Description of the counseling regarding operating heavy machinery, driving, etc., while taking opioids, particularly during initiation and dose changes
- Signatures of the prescribing clinician and patient, dated

Sample informed consent form available in APS/AAPM guidelines

[See 2009 APS/AAPM Guideline Sections 2.1-2.2]

### Components of the Opioid Treatment Agreement

- Widely used but not evidence based
- Reminder: opioids are just one modality in multifaceted approach to achieving goals of therapy
- Prohibited behaviors, and grounds for tapering or discontinuation
- Obtaining opioids from one prescriber and filling prescriptions at one pharmacy
- Limitations on prescriptions (eg, weekly or bimonthly instead of monthly amounts)
- Urine drug testing
- Schedule for office visits and procedure for emergency issues
- Refill and dose-adjustment procedures; maintaining adherence
- Safe storage and disposal of opioids; missed/missing doses
- Exit strategy
- May contain elements of Informed Consent discussion

Sample patient care agreement available in APS/AAPM guidelines

[See 2009 APS/AAPM Guideline Sections 2.1-2.2]

### Use Patient Counseling Documents

- Secure prescriptions the same way as other valuables in the home, like jewelry or cash
- Take prescription medications out of the medicine cabinet and hide them in a place only you know about
- Encourage relatives and friends to secure their medications
- If possible, keep all medicines in a safe place
- An existing fire safe or gun safe
- Use a cut-proof bag designed for travel safety
- Locking medicine box or cabinet
- Patients should always be in a position to know if any pills are missing

- Take note of how many pills are in each prescription bottle or pill packet
- Keep track of your refills for your own medication, as well as for other members of the household
- Make sure friends and relatives—especially grandparents—are aware of the risks and regularly monitor their own medicines

### Safe Storage of Opioids

<table>
<thead>
<tr>
<th>Monitor</th>
<th>Secure</th>
</tr>
</thead>
<tbody>
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<td></td>
</tr>
</tbody>
</table>
**Safe Disposal of Opioids**

- Do not flush prescription drugs down the toilet or drain unless the label or accompanying patient information specifically instructs you to do so.
- Prescription drugs not labeled to be flushed may be able to be disposed of at community drug take-back programs. If a drug take-back program is not available:
  1. Take your prescription drugs out of their original containers.
  2. Mix drugs with an undesirable substance (eg, cat litter or used coffee grounds).
  3. Put the mixture into a disposable container with a lid or a sealable bag.
  4. Conceal or remove any personal information, including Rx number, on the empty containers by covering it with black permanent marker or duct tape, or by scratching it off.
  5. Place the sealed container with the mixture, and the empty drug containers, in the trash.

*Information regarding drugs that should be flushed is available at: [http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/en suringsafeuseofmedicine/safedisposalofmedicines/ucm186187.htm#Flush_List](http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/en suringsafeuseofmedicine/safedisposalofmedicines/ucm186187.htm#Flush_List).*

**Opioids are One Small Portion of Rx, Which is One Small Portion of TX**

- Intervventional Approaches
- Pharmacotherapy
- Physical Medicine and Rehabilitation
- Psychological Support
- Multimodal Therapeutic Strategies for Pain and Disability
- Complementary and Alternative Medicine
- Lifestyle Changes

**Consider Prescribing Naloxone**

- Multiple formulations available
- Instruct patients to use in case of suspected opioid related respiratory depression emergency
- Candidates:
  - All patients?
  - ER/LA opioids
  - History of abuse, addiction, treatment
  - High risk comorbidities

**To Continue or Discontinue Opioid Therapy**

- Continue opioid therapy if there is:
  - Effective pain relief
  - Improvement in physical and/or psychosocial functioning
  - Acceptable side effects and patient compliance
- Have an exit strategy prepared. Consider discontinuing if there is:
  - Lack of pain reduction
  - Lack of functional and/or psychosocial improvement
  - Unacceptable side effects or unacceptable patient compliance
- Distinguish between abandoning opioid therapy and abandoning the patient:
  - Taper opioids with or without specialty assistance


**Short v Long-acting Opioid**

<table>
<thead>
<tr>
<th></th>
<th>Rapid or Short-acting Opioids</th>
<th>Long-acting Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Fast-acting; appropriate for acute pain, breakthrough pain</td>
<td>May be more appropriate for patients with a constant pain component; analgesic stability</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Need for repetitive dosing</td>
<td>Delayed onset of action</td>
</tr>
</tbody>
</table>

Reserve Long-Acting Opioids for Opioid-Tolerant Patients

- Reserve long-acting/extended-release opioids, including transdermal patches, for patients who have developed tolerance to opioids
  - i.e., who already take regular, daily, around-the-clock opioids
- Do not use for acute, postoperative, or trauma-related pain


How Do We Decide on Using an Opioid?

- Match your analgesic to pain intensity AND temporal nature
- This means you need more than a static 0-10 pain score!

REMS: ER/LA Opioid Products

- Avinza® morphine sulfate ER capsules
- Butrans® buprenorphine transdermal system
- Dilaudid™ morphine sulfate intramuscular injection
- Duragesic® fentanyl transdermal system
- Hynza® morphine sulfate/naltrexone ER capsules
- Hymetazone® transdermal system
- Hyromorph® morphine sulfate/naltrexone ER tablets
- Hydromorphone/hydrochloric acid ER tablets
- Hydroxyzine hydrochloride ER tablets
- Hydroxyzine hydrochloride hydrobromide ER tablets
- Javaluna® transdermal system
- MS Contin® morphine
- Norco® ER oxycodone/acetaminophen ER tablets
- OxyContin® oxycodone hydrochloride ER tablets
- Targin® oxycodone hydrochloride/naloxone hydrochloride ER tablets
- Transderm Perlin® transdermal system

REM: Keep Up To Date With Important Safety Label Changes

- Revised Indication
  - For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
- Revised Warnings
  - Addiction, Abuse and Misuse
  - Life Threatening Respiratory Depression
  - Accidental Ingestion
  - Cytochrome P450 3A4 Interaction
- New Warning: Neonatal Opioid Withdrawal Syndrome

CHECK EACH PRODUCT’S PI/LABEL

Patient Centered Approach

“IT IS MUCH MORE IMPORTANT TO KNOW WHAT SORT OF A PATIENT HAS A DISEASE THAN WHAT SORT OF A DISEASE A PATIENT HAS.”
— Sir William Osler
Improving the Management of Pain Through Patient Engagement

The Goal of Chronic Pain Management

- The goal of pain management is:
  - For the patient to live as full and meaningful a life as possible with their chronic pain
- This goal is sometimes codified in the 4 As for the purposes of monitoring progress and goes beyond the simple provision of analgesia
  - The 4 As can be used to engage patients in the process of assessing their own outcomes and recognizing too how their clinicians understand success or failure in opioid therapy

Setting the Stage: Teaching the Patient about the Desired Outcome: The 4 A’s

- Analgesia (pain relief)
- Activities of Daily Living (psychosocial functioning)
- Adverse effects (side effects)
- Aberrant drug taking (addiction related outcomes) (may be more appropriate as “ambiguous noncompliance behaviors”)

Goals of Treatment

- Increased functioning
  - QOL issue, improved sleep, mood and ability to fulfill roles
- Increased comfort
  - Reduced pain rating, distinguish between usual pain and flares
- Decentralization of medications
  - Stress that medications are important but not the only way to recover and live with chronic pain
  - Monitor for compliance with other modalities
- Compliant drug-taking and appropriate attention to substance abuse and recovery activities, as necessary
- Patient satisfaction

Why is Patient Engagement Essential in Pain Management?

- The population of patients with persistent pain is tremendously diverse
  - Subgroups require a variety of strategies to allow them to realize the benefits of opioids and other interventions
- Pain occurs in not only diverse but complex human beings
  - Pain is often complicated by depression and the negative life consequences it brings
  - Many patients require comprehensive management that goes beyond the relief that opioids and other strictly medical interventions can bring to encompass extensive lifestyle changes
  - Have drug therapy be the sole focus can lead to overuse and a range of compliance problems as people seek to get more from their medications than they can bring and ignore the need for other interventions
- Pain and its complications interferes with function and living a normal life

Chronic Pain Interferes With Function

- While the physician is principally involved in reducing interference from pain intensity generally via their use of medical interventions, pain related interference also arises from the other complications of pain that require patient engagement
Chronic Pain Interferes With Function

• Pain can lead to avoidance and anhedonia, creating a vicious cycle
• This cycle is often complicated by overuse of medications that further fails to resolve functional stagnation

Why Risk Pain Flare?

Sacrifice Enjoyable Activity

Development of Bland Life

Treatment With Complex Patients

Treatments need to be comprehensive - involve patient and family in multiple efforts, including:

Medical
Psychological
Rehabilitation

Best Use of Multimodal Treatment

• When reasonable attempts at management are not leading to good pain management outcomes in all domains
• When patients show consistent failure to improve functionally
• When, upon documentation with the 4 As, patients consistently engage in potentially aberrant behaviors

Best Use of Multimodal Treatment

• When your screening programs indicate the presence of a mental disorder such as depression or anxiety

Depression
Anxiety

Best Use of Multimodal Treatment

• When faced with the chronically dysfunctional patient (angry patients or those with pervasive personality disorders)

Roles For the Pain Management Provider

How Do You Become A Change Agent For Patient

1. Cheerleader
2. Coach
3. Guru
4. Enforcer
The physician who makes the referral for multimodal pain treatment has an important role in encouraging the patient, applauding their efforts, and acknowledging progress made.

- Must overcome the tendency to view these other aspects of care as "dealt with" once the referral is made to the psychologist or physical therapist.
- Ministrations of other team members can be seen as mysterious (especially where psychotherapy is concerned) and progress in those areas is usually not carefully monitored.
- Showing active interest and reinforcing the patient’s efforts goes a long way.

If progress is not gauged and integrated, the patient soon gets the message that these other aspects of care are secondary and compliance is not essential.

- Closely related to the cheerleader role (and not just metaphorically).
- The Coach Role is important when a higher degree of input is needed to motivate the patient and some pointed direction is warranted.
- At times, the coach may need to be demanding and tough, but within the confines of a therapeutic relationship and not quite crossing over into the enforcer role.

The physician as coach:
- laying out the game plan
- following its success
- modifying it when necessary
- anticipating and overcoming new obstacles that arise over time.
Coaches are Theorists on Human Motivation whether Behavioral and Cognitive: William James

- William James (Principles of Psychology from the 1890's) an early behaviorist?
  - “If you want to be a church-going person, go to church”

Coach cont’d

- Self view and good habit formation is set in motion behaviorally and not from intention
- Development of a self view as a well, healthy or athletic person starts not with the head but with the feet

Coach cont’d

- James believed that we lay down neural pathways, that sustain behavior and change our self-perception
- Thus, coaching the patient to have his feet take him to the gym, can actually lay down the habit
  - in some instances, going through the motions, if sustained for even a short while, can lead to the development of the desired habit

Guru

- The physician can become the “spiritual leader” for the multimodal approach

Guru cont’d

- Referrals will not be effective if the physician does not believe in them and embody them for the patient
- The physician can be a role model in terms of
  - lifestyle
  - mental and physical self-care
  - stress management
  - attitudes (ie, openness to trying new things, etc)

Enforcer

- While strong-arming patients isn’t recommended, you must recognize that prescribing pain medications is a position of power that can be used to motivate the patient and gain compliance with the hope that extrinsic limit setting will lead to an internal adaptation of its principles
**Enforcer cont’d**

- While we hope pain patients buy in to multimodal treatment because they have internalized the goals of care and are intrinsically motivated to develop a more healthy approach to life, this is not always the case.

- May need to make compliance with other aspects of care a prerequisite for further prescribing of controlled substances:
  - Pain meds are not completely benign
  - In some cases, it is only via multimodal therapy that the risks to the patient are mitigated
- The hope is that once the patient has become more compliant with non-drug aspects of care and realized benefits from this compliance, they will then become intrinsically motivated.
- **Being in the Enforcer role too often is an Rx for burnout.**

**Patient Engagement and Opioid Limit-setting**

- Patients need to be taught that opioids and other controlled substances are different than other medications.
- Unilateral dose escalation in the face of pain flare can appear innocent but it is a slippery slope for many patients.
- Poor compliance is dangerous not only to individual patients but the entirety of the patients' community.

**Patient Engagement and Urine Drug Testing**

- Patients can use UDT for their own decision making and to help them monitor and change behavior.
- It is the only objective way to document their adherence if there is ever a question raised about the appropriateness of their opioid therapy.
- Must be de-stigmatized and presented in a clinical, not forensic, way.

**BURNOUT**

- Patients who fail to follow our recommendations are actually thwarting our creativity.
- Parenting (ie, constant limit-setting) is an exhausting job.
- Working as Enforcer is a recipe for burnout.
- Look at difficult patients as a challenge rather than a pain.
- Patient engagement protects physicians against burn out.

**Assessing Motivation to Change**

- Focus on Motivation to Change.
- Prochaska and DiClemente (1992) have delineated a useful, empirically derived framework for classifying motivational level for behavior change.
- These levels include:
  - Precontemplation—no intention to change behavior in the foreseeable future.
  - Contemplation—developing awareness of the need for change.
  - Preparation—planning to take action within the next 30 days.
  - Action—steps taken to modify some behavior, experience or environment.
  - Maintenance—consistently engaging in new healthful behaviors.

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A Comprehensive Approach to the Safe Management of Extended-Release/Long-Acting Opioids

Stages of Change

- **Pre-contemplation**: Not interested in changing 'risky' lifestyle
- **Contemplation**: Thinking about change
- **Action**: Making changes
- **Commitment**: Ready to change
- **Maintenance**: Maintaining change
- **Relapse**: Relapsing back
- **Exit**: Maintaining 'safer' lifestyle

The Unique Contribution

**Motivation to Change**

- Find where the patient is in this motivational system and begin the process of moving forward with interventions meant for each level
  - Education and awareness raising: used for someone in pre-contemplation stage
  - Client self empowerment: used for someone in contemplation stage
  - Behaviour change strategies: used for someone in action/maintenance stage
- This model is very useful in primary health care and pain management settings


The Unique Contribution

**Motivation to Change**

- Problems should also be anticipated so that they don’t undo the chrysalis of motivation that is forming


The Unique Contribution

**Motivation to Change**

- But if we glibly recommend they go to the gym and work out without preparing them, this difficult behavioral change might be short-lived


The Unique Contribution

**Motivation to Change**

- For example, physically healthy patients who are sedentary who begin an exercise regimen will not report feeling as well as they did on the first day of the program until day ten (Smith, 1991).

Summary

• The pain population is diverse – psychological issues are important to note and their management requires careful assessment and tailored approaches that recognizes this diversity
• Psychological and psychiatric assistance can be invaluable for those hard-to-manage patients
• Overall, we must focus on multimodal treatment and keep communication active between all parties

Questions?

Please remember to complete the post-activity assessment for this session located in the front of your syllabus.

Your participation in this assessment allows Rockpointe and Global to report de-identified numbers to the FDA.

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