Addressing the Barriers to Effective Pain Management and Issues of Opioid Misuse and Abuse

Alvin J. Mathé, DO
Assistant Professor
Division of Geriatrics
University of North Texas Health Science Center at Fort Worth
Fort Worth, Texas

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Educational Learning Objectives
• Identify the negative impact of persistent pain on health and quality of life, methods to assess pain levels, appropriate use of opioid medications, and documentation required for compliance with regulatory policies
• Integrate appropriate risk assessment strategies for patient abuse, misuse, and diversion of opioids into an overall management approach for acute and chronic pain
• Describe the specific elements of new abuse deterrent technologies associated with opioid therapy, and assess their implications for clinical practice
Prevalence of Recurrent and Persistent Pain in the US

- 1 in 4 Americans suffer from recurrent pain (day-long bout of pain/month)
- 1 in 10 Americans report having persistent pain of at least one year’s duration
- 1 in 5 individuals over the age of 65 report pain persisting for more than 24 hours in the preceding month
  - 6 in 10 report pain persisting > 1 year
- 2 out of 3 US armed forces veterans report having persistent pain attributable to military service
  - 1 in 10 take prescription medicine to manage pain


Multiple Types of Pain

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Nociceptive</td>
<td>- Strains and sprains - Bone fractures - Postoperative</td>
</tr>
<tr>
<td>B. Inflammatory</td>
<td>- Osteoarthritis - Rheumatoid arthritis - Tendinitis</td>
</tr>
<tr>
<td>C. Neuropathic</td>
<td>- Diabetic peripheral neuropathy - Post-herpetic neuralgia - HIV-related polyneuropathy</td>
</tr>
<tr>
<td>D. Noninflammatory/Nonneuropathic</td>
<td>- Fibromyalgia - Irritable bowel syndrome</td>
</tr>
</tbody>
</table>


Long-Term Consequences of Acute Pain: Potential for Progression to Chronic Pain

- Surgery or injury causes inflammation
- Peripheral Nociceptors: Transient Activation, Sustained Activation
- Peripheral Nociceptors: Sustained currents
- Sensitization
- Structural Remodeling
- CNS Neuroplasticity
- Hyperactivity
- CHRONIC PAIN
Neuroplasticity in Pain Processing


Vicious Cycle of Uncontrolled Pain


Breaking the Chain of Pain Transmission

5-HT = serotonin; NE = norepinephrine; TCA = tricyclic antidepressant
Multimodal Treatment

- Physical Medicine and Rehabilitation
- Pharmacotherapy
- Interventional Approaches
- Complementary and Alternative Medicine
- Psychological Support
- Lifestyle Change

Strategies for Pain and Associated Disability

- Opioids, nonopioids, adjuvant analgesics
- Injections, neurostimulation
- Assistive devices, electrotherapy
- Exercise, weight loss

Psychological Support
- Psychotherapy, group support

Components of Chronic Pain

- Chronic pain
  - Baseline persistent pain
  - Breakthrough pain (BTP)
- Each component of chronic pain needs to be independently assessed and managed

Positioning Opioid Therapy for Chronic Pain

- Chronic non-cancer pain: evolving perspective
  - Consider for all patients with severe chronic pain, but weigh the influences
    - What is conventional practice?
    - Are there reasonable alternatives?
    - What is the risk of adverse events?
    - Is the patient likely to be a responsible drug-taker?
Chronic Opioid Therapy Guidelines and Treatment Principles

Patient Selection
Patient Selection and Risk Stratification (1.1-1.3)

Initial Patient Assessment
Informed Consent and Opioid Management Plans (2.1-2.2)
High-Risk Patients (6.1-6.2)

Comprehensive Pain Management Plan
Driving and Work Safety (10.1)
Identifying a Medical Home* and When to Obtain Consultations (11.1-11.2)

Alternatives to Opioid Therapy
Use of Psychotherapeutic Cointerventions (9.1)

Trial of Opioid Therapy
Initiation and Titration of Chronic Opioid Therapy (3.1-3.2)
Methadone (4.1)
Opioids and Pregnancy (13.1)

Patient Reassessment
Monitoring (5.1-5.3)
Dose Escalations, High-Dose Opioid Therapy, Opioid Rotation, Indications for Discontinuation of Therapy (7.1-7.4)
Opioid Policies (14.1)

Continue Opioid Therapy
Monitoring (5.1-5.3)
Breakthrough Pain (12.1)

Implement Exit Strategy
Opioid-Related Adverse Effects (8.1)

Opioid Formulations

<table>
<thead>
<tr>
<th>Type of Drug</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure μ-opioid receptor agonists</td>
<td>Morphine, hydromorphone, fentanyl, oxycodone</td>
</tr>
<tr>
<td>Dual mechanism opioids</td>
<td>Tramadol, tapentadol</td>
</tr>
<tr>
<td>Rapid onset (transmucosal)</td>
<td>Fentanyl, fentanyl, sufentanil, diamorphine</td>
</tr>
<tr>
<td>Immediate release</td>
<td>Tramadol, oxycodone</td>
</tr>
<tr>
<td>Modified release (long acting)</td>
<td>Morphine, methadone, oxycodone</td>
</tr>
<tr>
<td>Available with co-analgesic</td>
<td>Oxycodone, tramadol, codeine</td>
</tr>
<tr>
<td>Only available with co-analgesic</td>
<td>Hydrocodone</td>
</tr>
</tbody>
</table>

*Clinician accepting primary responsibility for a patient’s overall medical care.
Formulation Points to Consider

- Dose-limiting issues and toxicity with co-analgesics
  - 4 g/day acetaminophen limit
- Importance of titration
  - Risk of overdose, challenges of dose conversion during rotation
- Pharmacokinetics versus temporal patterns of pain
- Adherence
- Cost
- Convenience
- Caregiving issues

Domains for Pain Management Outcome: The 4 A’s

- Analgesia
- Activities of Daily Living
- Adverse Events
- Aberrant Drug-Taking Behaviors


Federation of State Medical Boards of the United States, Inc
Model Policy for the Use of Controlled Substances for the Treatment of Pain

FSMB Model Policy

Basic Tenets

• Pain management is important and integral to the practice of medicine
• Use of opioids may be necessary for pain relief
• Use of opioids for other than a legitimate medical purpose poses a threat to the individual and society
• Physicians have a responsibility to minimize the potential for abuse and diversion
• Physicians may deviate from the recommended treatment steps based on good cause
• Not meant to constrain or dictate medical decision-making

FSMB, Federation of State Medical Boards

New Illicit Drug Use United States, 2006

![Chart showing new illicit drug use in the United States in 2006](chart.png)

<table>
<thead>
<tr>
<th>Substance</th>
<th>New Users (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>2,063</td>
</tr>
<tr>
<td>Cocaine</td>
<td>1,112</td>
</tr>
<tr>
<td>LSD</td>
<td>1,112</td>
</tr>
<tr>
<td>PCP†</td>
<td>1,112</td>
</tr>
<tr>
<td>Pain Relievers*</td>
<td>877</td>
</tr>
<tr>
<td>Tranquilizers</td>
<td>850</td>
</tr>
<tr>
<td>Stimulants</td>
<td>845</td>
</tr>
<tr>
<td>Sedatives</td>
<td>793</td>
</tr>
<tr>
<td>Inhalants</td>
<td>267</td>
</tr>
<tr>
<td>Heroin</td>
<td>264</td>
</tr>
<tr>
<td>Heroin (PCP)</td>
<td>91</td>
</tr>
</tbody>
</table>

*533,000 new nonmedical users of oxycodone aged ≥12 years. Past year initiates for specific illicit drugs among people aged ≥12 years.
†LSD, lysergic acid diethylamide; PCP, phencyclidine.


Definition of Terms

- **Misuse**
  - Use of a medication (for a medical purpose) other than as directed or as indicated, whether wilful or unintentional, and whether harm results or not

- **Abuse**
  - Any use of an illegal drug
  - The intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness, eg, getting high

- **Diversion**
  - The intentional removal of a medication from legitimate and dispensing channels

- **Addiction**
  - A primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations
  - Behavioral characteristics include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, craving

- **Pseudoaddiction**
  - Syndrome of abnormal behavior resulting from undertreatment of pain that is misidentified by the clinician as inappropriate drug-seeking behavior
  - Behavior ceases when adequate pain relief is provided
  - Not a diagnosis; rather, a description of the clinical intention

Prevalence of Misuse, Abuse, and Addiction

- Misuse: 40%
- Abuse: 20%
- Addiction: 2% to 5%

Total Pain Population


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

Rx Opioid Users Are Heterogeneous

- Nonmedical Users
- Pain Patients

Risk Factors for Aberrant Behaviors/Harm

<table>
<thead>
<tr>
<th>Biological</th>
<th>Psychiatric</th>
<th>Social</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≤ 45 years</td>
<td>• Substance use disorder</td>
<td>• Prior legal problems</td>
</tr>
<tr>
<td>• Gender</td>
<td>• Preadolescent sexual abuse (in women)</td>
<td>• History of motor vehicle accidents</td>
</tr>
<tr>
<td>• Family history of prescription drug or alcohol abuse</td>
<td>• Major psychiatric disorder (eg, personality disorder, anxiety or depressive disorder)</td>
<td>• Poor family support</td>
</tr>
<tr>
<td>• Cigarette smoking</td>
<td></td>
<td>• Involvement in a problematic subculture</td>
</tr>
</tbody>
</table>

Stratify Risk

- Low Risk
  - No past/current history of substance abuse
  - Noncontributory family history of substance abuse
  - No major or untreated psychological disorder

- Moderate Risk
  - History of treated substance abuse
  - Significant family history of substance abuse
  - Past/current psychological disorder

- High Risk
  - Active substance abuse
  - Active addiction
  - Major untreated psychological disorder
  - Significant risk to self and practitioner

10 Principles of Universal Precautions

1. Diagnosis with appropriate differential
2. Psychological assessment including risk of addictive disorders
3. Informed consent (verbal or written/signed)
4. Treatment agreement (verbal or written/signed)
5. Pre-/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 “Four A’s” of pain medicine: Analgesia, Activity, Adverse Reactions, and Aberrant Behavior
9. Periodically review pain and comorbidity diagnoses, including addictive disorders
10. Documentation

Initial Visits

- Initial comprehensive evaluation
- Risk assessment
- Prescription monitoring assessment
- Urine drug test
- Opioid treatment agreement
- Opioid consent form
- Patient education

McGill Short Form Pain Questionnaire

Results of Short and Long Form tests correlate well for postsurgical pain

$r = 0.67 - 0.86, P \leq 0.002$


Principles of Responsible Opioid Prescribing

- Patient Evaluation
  - Pain assessment and history
  - Directed physical exam
  - Review of diagnostic studies
  - Analgesic and other medication history
  - Personal history of illicit drug use or substance abuse
  - Personal history of psychiatric issues
  - Family history of substance abuse/psychiatric problems
  - Assessment of comorbidities
  - Accurate record keeping

Principles of Responsible Opioid Prescribing

Treatment Plan

• I have resolved key points before initiating opioid therapy
  – Diagnosis established and opioid treatment plan developed
  – Established level of risk
  – I can treat this patient alone/I need to enlist other consultants to co-manage this patient (pain or addiction specialists)

• I have considered nonopioid modalities
  – Pain rehabilitation program
  – Behavioral strategies
  – Non-invasive and interventional techniques

Principles of Responsible Opioid Prescribing

Treatment Plan (cont)

• Drug selection, route of administration, dosing/dose titration
• Managing adverse effects of opioid therapy
• Assessing outcomes
• Written agreements in place outlining patient expectations/responsibilities
• Consultation as needed
• Periodic review of treatment efficacy, side effects, aberrant drug-taking behaviors

Algorithm for the Management of Chronic Pain

Pain frequency

Infrequent Flares < 4 days per week

Interventional Pain Management

Ineffective or Flare

Relaxation

Neuropathic pain, burning quality, nerve injury, neuralgia

Structural etiology with irritable myofascial points

Reconditioning

Body mechanics, stretching, work modification

Stress management

Short-acting opioids

Pain, burning quality, nerve injury, neuralgia

Capsaicin cream

Long-acting opioids

GMNC = tricyclic antidepressants: SSRI = selective serotonin reuptake inhibitors

Medical Records

- Maintain accurate, complete, and current records
  - Medical Hx & PE
  - Diagnostic, therapeutic, lab results
  - Evaluations/consultations
  - Treatment objectives
  - Discussion of risks/benefits
  - Tx and medications
  - Instructions/agreements
  - Periodic reviews
  - Discussions with and about patients

Considerations

- What is conventional practice for this type of pain or pain patient?
- Is there an alternative therapy that is likely to have an equivalent or better therapeutic index for pain control, functional restoration, and improvement in quality of life?
- Does the patient have medical problems that may increase the risk of opioid-related adverse effects?
- Is the patient likely to manage the opioid therapy responsibly?
- Who can I treat without help?
- Who would I be able to treat with the assistance of a specialist?
- Who should I not treat, but rather refer, if opioid therapy is a consideration?
Monitoring Chronic Pain

Review of Efficacy of Therapy


Opioid Treatment Agreement


Differential Diagnosis of Aberrant Drug-Taking Attitudes and Behavior

- Addiction (out-of-control, compulsive drug use)
- Pseudoaddiction (inadequate analgesia)
- Other psychiatric diagnosis
  - Organic mental syndrome (confused, stereotyped drug-taking)
  - Personality disorder (impulsive, entitled, chemical-coping behavior)
  - Chemical coping (drug overly central)
  - Depression/anxiety/situational stressors (self-medication)
- Criminal intent (diversion)

Identifying Who Is at Risk for Opioid Abuse and Diversion

- Predictive tools
- Aberrant behaviors
- Urine drug testing
- Prescription monitoring programs
- Severity and duration of pain
- Pharmacist communication
- Family and friends
- Patients

Signs of Potential Abuse and Diversion

- Request appointment toward end-of-office hours
- Arrive without appointment
- Telephone/arrive after office hours when staff are anxious to leave
- Reluctant to have thorough physical exam, diagnostic tests, or referrals
- Fail to keep appointments
- Unwilling to provide past medical records or names of HCPs
- Unusual stories

However, emergencies happen: not every person in a hurry is an abuser/diverter

Risk Assessment Tools

- Addiction Behaviors Checklist (ABC)
  - Evaluate and monitor behaviors indicative of addiction related to prescription opioids in patients with chronic pain
- Addiction Severity Index (ASI)
  - Assess current and lifetime substance-use problems and prior treatment
- Current Opioid Misuse Measure (COMM)
  - Periodically monitor aberrant medication-related behaviors in patients with chronic pain currently on opioid therapy


Risk Assessment Tools (cont)

- Drug Abuse Screening Test (DAST-10)
  - Screen for probably drug abuse or dependence
- Pain Medication Questionnaire (PMQ)
  - Assess risk for opioid medication misuse in patients with chronic pain
- Screening Instrument for Substance Abuse Potential (SISAP)
  - Identify individuals with possible substance-abuse history
- Opioid Risk Tool (ORT)
  - Predict which patients might develop aberrant behavior when prescribed opioids for chronic pain


Risk Assessment Tools (cont)

- Diagnosis, Intractability, Risk, Efficacy (DIRE)
  - Predict the analgesic efficacy of, and patient compliance to, long-term opioid treatment in the primary care setting
- Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)
  - Predict aberrant medication-related behaviors in patients with chronic pain considered for long-term opioid therapy
    - Empirically-derived, 24-item self-report questionnaire
    - Reliable and valid
    - Less susceptible to overt deception than past version
  - Scoring:
    - 18 identifies 90% of high-risk patients


ORT Validation

Mark each box that applies

1. Family history of substance abuse
   - Alcohol
   - Illegal drugs
   - Prescription drugs
2. Personal history of substance abuse
   - Alcohol
   - Illegal drugs
   - Prescription drugs
3. Age (mark box if 16-45 years)
4. History of preadolescent sexual abuse
5. Psychological disease
   - ADD, OCD, bipolar, schizophrenia
   - Depression

Female  | Male
--- | ---
1 | 1
2 | 2
3 | 3
4 | 4
5 | 5

• Exhibits high degree of sensitivity and specificity

94% of low-risk patients did not display an aberrant behavior
91% of high-risk patients did display an aberrant behavior

N = 185
ADD, attention deficit disorder; OCD, obsessive-compulsive disorder.
SOAPP

Name: Chris Jackson  Date: 9/16/09

Mr. Jackson’s Score = 3

To score the SOAPP, add ratings of all questions. A score of 4 or higher is considered positive.

Please answer the questions before using the following scale:

0 = Never, 1 = Seldom, 2 = Sometimes, 3 = Often, 4 = Very Often

1. How often do you have mood swings? 0 1 2 3 4
2. How often do you smoke a cigarette within an hour after you wake up? 0 1 2 3 4
3. How often have you taken medication other than the way it was prescribed? 0 1 2 3 4
4. How often have you used illegal drugs (for example, marijuana, cocaine, etc.) in the past five years? 0 1 2 3 4
5. How often in your lifetime have you had legal problems or been arrested? 0 1 2 3 4

Please exclude any additional information you wish about the above answers. Thank you.

Risk Assessment Tools Highlights

• ORT, SOAPP & DIRE
  – Best assess abuse potential among those being considered for long-term opioid therapy
• COMM & PMQ
  – Characterize degree of medication misuse or aberrant behavior once opioids are started
• DAST-10 & PMQ
  – More suitable for assessing current alcohol and/or drug abuse than potential for such abuse

Urine Drug Testing

• When to test?
  – Randomly, annually, PRN
• What type of testing?
  – POC, GS/MS
• How to interpret
  – Metabolism of opioids
  – False positive and negative results
• What to do about the results
  – Consult, refer, change therapy, discharge

The Role of UDT

- UDT in clinical practice may
  - Provide objective documentation of compliance with treatment plan by detecting presence of a particular drug or its metabolites
  - Assist in recognition of addiction or drug misuse if results abnormal
- Results are only as reliable as testing laboratory’s ability to detect substance in question


Positive and Negative Urine Toxicology Results

- Positive forensic testing
  - Legally prescribed medications
  - Over-the-counter medications
  - Illicit drugs or unprescribed medications
  - Substances that produce the same metabolite as that of a prescribed or illegal substance
  - Errors in laboratory analysis
- Negative compliance testing
  - Medication bingeing
  - Diversion
  - Insufficient test sensitivity
  - Failure of laboratory to test for desired substances

Urine Drug Testing

- Initial testing done with class-specific immunoassay drug panels
  - Typically do not identify individual drugs within a class
- Followed by a technique such as GC/MS
  - To identify or confirm the presence or absence of a specific drug and/or its metabolites
UDT Immunoassay Screening

- Lab Testing or POCT
  - Drug class
  - High sensitivity, low specificity
  - Rapid results
  - Not quantitative

POCT, point-of-care testing


Detection of Opioids

- Opiate immunoassays detect morphine and codeine
  - Do not detect synthetic opioids
    - Methadone
    - Fentanyl
  - Do not reliably detect semisynthetic opioids
    - Oxycodone
    - Hydrocodone
    - Buprenorphine
    - Hydromorphone
- GC/MS will identify these medications


UDT Laboratory-Based Tests

- GC/MS, LC/ MS, ELISA
  - High sensitivity, high specificity
  - Expensive
  - Quantitative
  - 1-3 days for results

RESULTS OF CONTROLLED SUBSTANCE UDT: WORKPLACE

<table>
<thead>
<tr>
<th>Donor Name: Jack</th>
<th>Specimen ID #: 186021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accession #: None assigned</td>
<td>Reason for test: Random</td>
</tr>
<tr>
<td>Date collected: 04/15/2008</td>
<td>Time collected: 1648</td>
</tr>
<tr>
<td>Date received: 04/15/2008</td>
<td>Date reported: 04/15/2008</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class or Analyte</th>
<th>Result</th>
<th>Screen Cut-Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPHETAMINES</td>
<td>NEGATIVE</td>
<td>1,000 ng/ml</td>
</tr>
<tr>
<td>BARBITURATES</td>
<td>NEGATIVE</td>
<td>200 ng/ml</td>
</tr>
<tr>
<td>BENZODIAZEPINES</td>
<td>NEGATIVE</td>
<td>200 ng/ml</td>
</tr>
<tr>
<td>CANNABINOID</td>
<td>NEGATIVE</td>
<td>50 ng/ml</td>
</tr>
<tr>
<td>COCAINE</td>
<td>NEGATIVE</td>
<td>300 ng/ml</td>
</tr>
<tr>
<td>METHADONE</td>
<td>NEGATIVE</td>
<td>150 ng/ml</td>
</tr>
<tr>
<td>MOPEDS</td>
<td>NEGATIVE</td>
<td>150 ng/ml</td>
</tr>
</tbody>
</table>

Validity Test

<table>
<thead>
<tr>
<th>CREATININE (mmol/L)</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>× 10 mg/dL</td>
<td>≥ 2.0</td>
<td>≥ 20 mg/dL</td>
</tr>
<tr>
<td>SPECIFIC GRAVITY</td>
<td>1.080-1.020</td>
<td>1.003</td>
</tr>
</tbody>
</table>

ELISA, enzyme-linked immunosorbent assay; GC, gas chromatography; LC, liquid chromatography; MS, mass spectrometry.

Heroin  6-MAM

C-6G  Codeine  Morphine  M-3G

Minor  Minor

Hydrocodone  Hydromorphone

Dihydrocodeine  Dihydromorphone

Not comprehensive pathways, but may explain presence of apparently unprescribed drugs


Detection Times of Common Drugs of Misuse

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate Retention Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>48 hours</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Short-acting (eg, secobarbital), 24 hours</td>
</tr>
<tr>
<td></td>
<td>Long-acting (eg, phenobarbital), 2–3 weeks</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3 days if therapeutic dose is ingested</td>
</tr>
<tr>
<td></td>
<td>Up to 4–6 weeks after extended dosage (≥1 year)</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Moderate smoker (4 times/week), 5 days</td>
</tr>
<tr>
<td></td>
<td>Heavy smoker (daily), 10 days</td>
</tr>
<tr>
<td></td>
<td>Retention time for chronic smokers may be 20–28 days</td>
</tr>
<tr>
<td>Cocaine</td>
<td>2–4 days, metabolized</td>
</tr>
<tr>
<td>Ethanol</td>
<td>2–4 hours</td>
</tr>
<tr>
<td>Methadone</td>
<td>Approximately 30 days</td>
</tr>
<tr>
<td>Opiates</td>
<td>2 days</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>Approximately 8 days</td>
</tr>
<tr>
<td></td>
<td>Up to 30 days in chronic users (mean value = 14 days)</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>6–48 hours</td>
</tr>
</tbody>
</table>


Risk Evaluation and Mitigation Strategies

Position of the FDA

- The current strategies for intervening with [the problem of prescription opioid addiction, misuse, abuse, overdose and death] are inadequate
- New authorities granted under FDAAA: [FDA] will now be implementing Risk Evaluation and Mitigation Strategies (REMS) for a number of opioid products
- [FDA expects] all companies marketing these products to [cooperate] to get this done expeditiously
- If not, [FDA] cannot guarantee that these products will remain on the market

Rappaport BA. REMS for Opioid Analgesics: How Did We Get Here? Where are We Going? FDA meeting of manufacturers of ER opioids, FDA White Oak Campus, Silver Spring, MD. March 3, 2009.
## Identifying and Managing Abuse and Diversion

- Assessing risk and aberrant behaviors
- Performing scheduled and random UDTs
- Utilization of PMPs
- Assessing stress and adequacy of pain control
- Developing good communication with pharmacists
- Receiving input from family, friends, and other patients

## Case Study: Opioid Renewal Clinic

What is the impact of a structured opioid renewal program?

- Primary goal: reduce oxycodone SA use to 3% of opioids
- Setting
  - Primary care
  - Managed by nurse practitioner and clinical pharmacist
  - Philadelphia VA pain clinic
- Structured program
  - Electronic referral by PCP
    - Signed Opioid Treatment Agreement
  - UDT
  - Support from multidisciplinary pain team: addiction psychiatrist, rheumatologist, orthopedist, neurologist, and physiatrist
- Multimodal management
  - Opioids
  - NSAIDs and acetaminophen for osteoarthritis
  - Transcutaneous electrical stimulation (TENS) units
  - Antidepressants and anticonvulsants for neuropathic pain
  - Reconditioning exercises

Opioid Renewal Clinic: Results

- OTAs increased: 63 → 214
- Monthly UDTs increased: 80 → 200
- Oxycodone SA use decreased
  - Quarterly costs: $130,000 → $5,000
  - Percent of opioids: 22.5% → 0.4%
- ER visits reduced 73%
- Unscheduled PCP visits reduced 60%
- PCPs satisfied (questionnaire)
  - 171/335 patients referred had aberrant drug-taking behaviors
    - 45% adhered to OTA (resolved aberrant behaviors)
    - 38% self-discharged from ORC
    - 13% referred for addiction treatment
    - 4% consistently negative UDT


Opioid Abuse-Deterrent Strategies Hierarchy

<table>
<thead>
<tr>
<th>Combination Mechanisms</th>
<th>Aversive Component</th>
<th>Physical</th>
<th>Deterrent Packaging</th>
<th>Prescription Monitoring</th>
</tr>
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<tbody>
<tr>
<td>Pharmacologic</td>
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<tr>
<td>Sequestered antagonist</td>
<td>Capsaicin – burning sensation</td>
<td>Difficult to crush</td>
<td>RFID – Protection</td>
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<tr>
<td>Bio-available antagonist</td>
<td>Ipecac – emetic</td>
<td></td>
<td>Tamper-proof bottles</td>
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<tr>
<td>Pro-drug</td>
<td>Denatonium – bitter taste</td>
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Electronic Track and Trace RFID

- Secures integrity of drug supply chain by providing accurate drug "pedigree"
  - A record documenting that the drug was manufactured and distributed under secure conditions.

- RFID technology
  - Tiny radio frequency chip containing essential data in the form of an electronic product code (EPC)
  - Each discrete product unit has a unique electronic serial number
  - Product can be tracked electronically through every step of the supply chain

RFID, radiofrequency identification
**Physical Deterrent: Viscous Gel Base**

- SR oxycodone formulation: Remoxy™
  - Deters dose dumping
  - Accessing entire 12-h dose of CR medication at 1 time
  - Difficult to crush, break, freeze, heat, dissolve
  - The viscous gel-cap base of PTI-821 cannot be injected
  - Resists crushing and dissolution in alcohol or water

**Aversive Component**

- Capsaicin
  - Burning sensation
- Ipecac
  - Emetic
- Denatonium
  - Bitter taste
- Niacin
  - Flushing, irritation

**Pharmacologic Deterrent: Antagonist**

- Oral formulation
- Sequestered antagonist
- Antagonist bioavailable only when agent is crushed for extraction
- SR morphine + naltrexone (Embeda®) FDA approved 2009

Remaining Questions

• How much does the barrier approach deter the determined abuser?
• How much do agonist/antagonist compounds retain efficacy?
• How much do agonist/antagonist compounds pose serious adversity?

Patient Case Studies

Case Study 1

• A 56-year-old healthy male with acute back pain
• Conservative therapy ineffective
• Dx with acute thoracic compression fractures
• Persistent pain 6/10 and activity related pain 10/10
• ORT 5
• UDT consistent therapy
• PMP: no opioids
• Rx started with hydrocodone 10 mg/APAP q 4 hours
• Titrated to 50 mg CR morphine/naltrexone BID
Case Study 1 (cont)

- Monitoring
  - Weekly visits until stable
  - Prescribe only enough medication until next visit
- RX
  - Short acting for BTP
  - CR formulation (with less street attractiveness)
  - Vertebroplasty partially effective
- Six month follow-up
  - Much improved; pain 2/10, => tapered of opioids by 70%
  - No aberrant behaviors
  - PMP showed no aberrant behavior
  - Monthly UDT consistent with therapy

Case Study 2

- 38-year-old female actress with ovarian cancer and peripheral neuropathy from therapy
- ORT score was 9
- Urine drug test: THC, amphetamines
- History of oxycodone addiction, ADD, sexual abuse
- Smokes 1 pack per day since the age of 12
- Consumes 20 drinks per week
- PMP: several opioid prescriptions from different providers

Case Study 2 (cont)

- RX
  - Instructed to D/C THC
  - OTA
  - Pregabalin 600 mg/day
  - Methadone was slowly titrated to 10 mg qid, Education for Safe Use

- Two weeks later
  - Patient said she couldn’t tolerate methadone
  - Asked for oxycodone
  - Pregabalin is causing confusion and severe memory impairment, can’t remember her lines in performance
Case Study 2 (cont)
- High risk determines what type of monitoring/therapy
  - Can oxycodone be safely prescribed?
- Abnormal PMP suggest substance abuse or diversion
  - UDT and PMP role in monitoring? Frequency?
- What to do about THC?
  - What if it is medical marijuana?
- Positive UDT amphetamine due to ADD treatment?
  - Can UDTs differentiate methamphetamine from Adderall®?
- What multi-therapeutic approaches should be taken?
- Should opioids be prescribed?

Conclusion
- Use of opioids may be necessary for pain relief
- Balanced multimodal care
  - Use of opioids as part of complete pain care
  - Anticipation and management of side effects
  - Judicious use of short and long acting agents
  - Focus on persistent and breakthrough pain
  - Maintain standard of care
- Treatment goals
  - Improved level of independent function
  - Increase in activities of daily living
  - Decreased pain

Conclusion (cont)
- Pharmacovigilance
  - Functional outcomes
  - Standard medical practice
  - FSMB policy
- Open Issues
  - What is meant by pain management?
  - Who needs what treatment?
  - Do universal approaches work?
  - Does it improve outcomes?
    - For patients
    - For regulators
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