Sponsored CME Lecture: Update on Opioid Management for Chronic Pain

Steven Stanos, DO

The Cosmopolitan of Las Vegas
March 12-15, 2015 | Las Vegas, Nevada
39.5 Category 1-A CME credits anticipated - Includes 15 pre-con credits beginning on March 11
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Please check where applicable and sign below. Provide additional pages as necessary.

Name of CME Activity: ACOFP 52nd Annual Convention and Scientific Seminars

Dates and Location of CME Activity: March 12-15, 2015, The Cosmopolitan Las Vegas, Nevada
Sponsored CME Lecture: Update on Opioid Management for Chronic Pain

Saturday, March 14, 2015 8:00-9:00 am

Name of Faculty/Moderator: Steven Stanos, DO

DISCLOSURE OF FINANCIAL RELATIONSHIPS WITHIN 12 MONTHS OF DATE OF THIS FORM

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B. I have, or an immediate family member has, a financial relationship or interest with a proprietary entity producing health care goods or services. Please check the relationship(s) that applies.

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- Stock/Bond Holdings (excluding mutual funds)
- Speakers' Bureaus*
- Employment
- Ownership
- Partnership
- Consultant for Fee
- Others, please list:

Please indicate the name(s) of the organization(s) with which you have a financial relationship or interest, and the specific clinical area(s) that correspond to the relationship(s). If more than four relationships, please list on separate piece of paper:

<table>
<thead>
<tr>
<th>Organization With Which Relationship Exists</th>
<th>Clinical Area Involved</th>
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<tbody>
<tr>
<td>1. MyMatrixx</td>
<td>1. Consultant for pain mgmt</td>
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<td>2. Pacer Colloquium</td>
<td>2. Consultant for pain mgmt</td>
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*If you checked “Speakers' Bureaus” in item B, please continue:

- Did you participate in company-provided speaker training related to your proposed Topic?
- Did you travel to participate in this training?
- Did the company provide you with slides of the presentation in which you were trained as a speaker?
- Did the company pay the travel/lodging/other expenses?
- Did you receive an honorarium or consulting fee for participating in this training?
- Have you received any other type of compensation from the company? Please specify:
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Steven Stanos, DO

Please fax this form to ACOFP at 866-328-1835 or email to joank@acofp.org as soon as possible

Deadline: Monday, January 12, 2015
Update on opioid management

Steven Stanos, DO
Medical Director, Pain and Headache Center
Swedish Medical Center
Medical Director, Occupational Medicine Services
Swedish Spine, Sports, and Musculoskeletal Medicine
Seattle, Washington

Steven.stanos@swedish.org
Treasurer, American Academy of Pain Medicine

Disclosures

Consulting:

Astra Zeneca, Collegium, MyMatrixx, Pfizer
Overview: Opioid Management

- Institute of Medicine Report: *Relieving Pain In America*
- Opioid abuse epidemic
- Assessment of patients
- FDA’s response for change
- Risk Management Principles
- Office Based Practices
- Update on long-acting opioid formulations
Institute of Medicine (IOM)

- 2011 Briefing
- Chronic pain affects 116 million Americans
- Annual cost: $635 billion/year
- Foster cultural transformation
- Individualizing care, focus on self-management
- Incentivize at primary care and foster collaboration
- Research and educational focus


"The Secretary of the Department of Health and Human Services should develop a comprehensive, population health-level strategy for pain prevention, treatment, management, education, reimbursement, and research that includes specific goals, actions, time frames, and resources."

Opioid Crisis

Opioid Misuse/Abuse/Diversion: A Major Public Health Problem

- Overdose deaths from prescription painkillers increasing
  - 16,651 in 2010; >3x # in 1999
  - 43% of all fatal overdoses
- Almost 1 million people >12 years old reported non-medical opioid use > 200 days in 2009-2010; 4.6 million people reported such use for 30 days or more
  - Highest prescription painkiller overdose rates in middle-aged adults
  - Highest rates in rural counties
  - Highest rates in Whites and American Indian or Alaska Natives
  - Many more Rx opioid overdose deaths in men than women
- Direct health care costs of nonmedical prescription painkiller use: $72.5 billion annually
- 2013 IMS Data
  - ER/LA opioids: $5.8 billion
  - Oxycontin® = $2.6 billion

2. Institute of Medicine 2011. Relieving Pain in America: A blueprint for Transforming Prevention, Care, Education and Research.
3. IMS Data 2013. ER/LA opioids market defined as OxyContin, OXYANA ER, Exalgo, Fentanyl, Butrans ER, Kadian ER, Morphine ER, Methadone, Nucynta ER and Tramadol ER.

Doctor Shoppers (2008)
• 1 in 143 patients received opioid scripts from multiple providers
• 0.7% of all patients
• Purchased 4% of opioids (cash only)
• “Extreme group”: 135,000 doctor shoppers with average of 32 opioid scripts from 10 docs in 10 month

McDonald D, Carlson K, PLOS ONE 2013;8 (7).
CDC: 38,329 overdose deaths in 2010
Drug overdose: leading cause of death, > traffic fatalities or gun homicides and suicides
16,849 prescription opioid overdose deaths in 2010
Heroin

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
You can identify a “problem patients” easily, if you know what to look for.

Opioid Effects

General
- Analgesia
- Altered mood
- Decreased anxiety
- Respiratory depression
- Inhibition central reflexes
- (-) GI motility
- Cough suppression
- (-) CRF, ACH
- Miosis
- Pruritus, nausea, vomiting

Reinforcing effects
- Reduce anxiety
- Decrease boredom
- Decrease aggression
- Increase self-esteem

TOLERANCE and ADDICTION

DEPENDENCE


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>Pre-adolescent 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, bipolar 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>

Reasons for Opioid-Related 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
  - Pharmacogenetics and methadone metabolism
  - Sleep disordered breathing

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)

RISK Management

Risk Management: An Evolving Process

1970
Controlled Substance Act

1976
Patient Package Inserts (PPIs)

1990
CNR’s “no blood, no drug” Restricted Access Program

1999
Medication Guides

2002
Prescription Drug User Fee Act Reauthorization III (PDUFA III)

2005
Risk Minimization Action Plans (RiskMAPs)

2007
FDAAA, PDUFA IV and Risk Evaluation and Mitigation Strategies (REMS)
FDA Blueprint for Prescriber Education: REMS for LA/ER opioids

Core Content

- Why prescriber education is important
- Assessing patients for treatment
- Initiating therapy, modifying dosing & discontinuing use
- Managing therapy
- Counseling patients & caregivers about safe use
- General Drug Information about ER/LA opioid products
- Tables of specific drug information on ER/LA opioid analgesics

Introduction for the FDA Blueprint for Prescriber Education, 2012

Factors Contributing to Abuse and Likability

• Extrinsic
  - Media attention
  - Pharmaceutical promotion
  - Peer preference
  - Cost and availability
  - Tamperability and Formulation
  - Open economy of drug abuse
  - Patient’s subjective reports, motivations

Factors Contributing to Attractiveness for Abuse

Preferred drug of abuse

Positive subjective effects
Media attention
Peer preferences
Drug formulation
Availability
Cost


Progression of Prescription Opioid Misuse and Abuse¹

Initial Route of Administration (n=112)

- 83% Oral
- 1% IV
- 16% Snorting

Route of Administration at Admission for Treatment (n=133)

- 62.4% Snorting
- 14.3% Oral
- 25.6% IV

IV, intravenous.
N=187 subjects admitted for treatment of OxyContin abuse or dependence.

Comparison of tapentadol tamper-resistant formulations (TRF) and Oxycontin in prescription opioid abusers


Abuse Rates and Routes of Administration of Reformulated ER Oxycodone

• FDA Chief Defends Zohydro as Criticism Intensifies
  March 14, 2014

• FDA pressed to rescind approval of Zohydro painkiller
  March 17, 2014

• Call for head of Health and Humans Services (HHS) to resign
  Sept 20, 2014

PROP
PHYSICIANS FOR RESPONSIBLE OPIOID PRESCRIBING
2012 JUL 25 1:148

July 25, 2012

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville MD 20852

The undersigned clinicians, researchers and health officials from fields that include Pain, Addiction,
Primary Care, Internal Medicine, Anesthesiology, Psychiatry, Neurology, Emergency Medicine,
Family Medicine, and Addictive Medicine have joined in support of STOP. MD addiction.

SWEDISH
Statements of scientific basis for petition

- “Over the past decade, a 4-fold increase in prescribing of opioids has been associated with a 4-fold increase in opioid related overdose deaths and 6-fold increase in individuals seeking addiction treatment.”
- “Prescribing of opioids increased over 15 years in response to a campaign that minimized risk for long-term use for CNCP.”
- “Long-term safety and effectiveness of managing CNCP with opioids has not been established.”
- “Recent surveys suggest patients receiving COT have shown many continue to experience significant chronic pain and dysfunction.”
- “Three large observational studies published in 2010 and 2011 found dose-related overdose risk in CNCP patients on COT.”

PROP Actions requested for label change

1. Strike the term “moderate” from the indication for non-cancer pain
2. Add a maximum daily dose, equivalent to 100 mg of morphine for non-cancer pain
3. Add a maximum duration of 90-days for continuous daily use for non-cancer pain
FDA Response to PROP
(Sept 10, 2013)
Center for Drug Evaluation and Research

- FDA public hearings on Approved Drug Labeling on COT
- Agency reviewed input from various presenters
- 600 comments to open docket
- 1900 comments to PROP Petition
- Multiple professional societies
  - Opposed PROP
  - Not supported by scientific evidence
  - “one-size-fits-all” approach is problematic and inconsistent

FDA PROP Response
Sept 10, 2014

X Strike the term “moderate” from the indication for non-cancer pain
X Add a maximum daily dose, equivalent to 100 mg of morphine for non-cancer pain
X Add a maximum duration of 90-days for continuous daily use for non-cancer pain
INDICATION:

“ER/LA opioids are indicated 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.”


“Because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risk of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain: ER/LA opioid analgesics are not indicated for as-needed pain relief.”

LA/ER Opioids Box Warning

- Addiction, abuse, and Misuse
- Life-threatening Respiratory Depression
- Accidental Exposure
- Neonatal Opioid Withdrawal Syndrome
- Interaction With Alcohol

Monitoring Patient Adherence

- Level of monitoring depends on risk stratification level determined during initial screening
  - State PDMPs (Prescription Drug Monitoring Programs)
  - Urine drug testing (UDT)
  - Behavioral assessment at each visit
  - Patient Counseling Document (PCD) use

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/Comorbid psychological disorder

**High Risk**
- Active substance abuse
- Active addiction
- Major untreated psychological disorder
- Significant risk to self and practitioner
Risk Assessment Tools (examples)

- Screener and Opioid Assessment for Patients with Pain
  - SOAPP-R validated
- Current Opioid Misuse Measure (COMM)
  - Current aberrant drug-related behavior
- Drug Abuse Screening Test (DAST-10)
  - Screen for probable 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


Opioid Risk Tool (ORT)

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 | 3
2 | 3
4 | 4

- 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

0-3: low risk (6%)
4-7: moderate risk (28%)
≥8: high risk (>90%)

N = 185
ADD, attention deficit disorder; OCD, obsessive-compulsive disorder.
**Patient Counseling Document**

- PCD should be provided to and reviewed with patient and/or the caregiver at time of prescribing.
- PCD is available at no charge at [www.er-la-opioidrems.com/lgwUI/remS/pcd.action](http://www.er-la-opioidrems.com/lgwUI/remS/pcd.action).

**Post Marketing Requirement (PMR)**

Public meeting (May 2014)

1: Risks associated with long-term use
   - Incidence of misuse, abuse, addiction, overdose, and death
   - Quantify other risk factors in this association
2: Outcome Validation
   - Measures for misuse, abuse, addiction, overdose, and death
3: Medical Code Validation Outcomes
4: Doctor/Pharmacy Shopping Validation

*Opioid Induced Hyperalgesia studies*
Opioid Hyperalgesia Consortium

- **Theory:** High dose opioid therapy leads to poor responders
- Poor responders caused by opioid-induced hyperalgesia (OIH)
- Some patients on long term opioid therapy develop a paradoxical hypersensitivity to pain caused by opioid treatment leading to higher doses and higher pain scores
- Multi-center studies across US to assess if hyperalgesia exists in patients on chronic high dose opioids

### Current Formulations Update

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Tamper-Resistance Mechanisms &amp; Notes</th>
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</thead>
<tbody>
<tr>
<td>OxyContin® (oxycodone CR)</td>
<td>- Matrix resists crushing with intention to prevent snorting</td>
</tr>
<tr>
<td></td>
<td>- Forms a viscous gel on dissolution with intention to prevent injection</td>
</tr>
<tr>
<td>Opana® ER (oxymorphone ER)</td>
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<tr>
<td>Nucynta® ER (tapentadol ER)</td>
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<tr>
<td>Targiniq ER (Nalaxone and Oxycodone ER)</td>
<td>- FDA approved July 23, 2014</td>
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<tr>
<td></td>
<td>- Not available</td>
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<tr>
<td>Hysingla ER (Hydrocodone Bitartrate)</td>
<td>- FDA approved November 20, 2014</td>
</tr>
<tr>
<td></td>
<td>- Available January 2015</td>
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<tr>
<td>Embeda® (Morphine ER/ Naltrexone)</td>
<td>- Morphine ER beads with sequestered naltrexone</td>
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<tr>
<td></td>
<td>- Deters injecting and snorting</td>
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<td></td>
<td>- FDA new labeling October 17, 2014</td>
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</tbody>
</table>
Conclusions

• The Opioid “epidemic” continues to be a significant problem in the US
• FDA’s response focuses on an evidence-based approach and is looking at critical questions
• Opioid management should be based on appropriate risk management and stratification
• Prescribers need to recognize opioid use can lead to death by accidental or intentional misuse
• Management includes awareness and integration of specific counseling, monitoring, and re-assessment of response
• www.ER-LA-opioidREMS.com