ASPMN: Taskforce on REMS
Risk Evaluation and Mitigation Strategy for Long-Acting/Extended-Release Opioids
A White Paper

Impact of REMS for both prescriber & non‐prescriber clinicians

Presenters
Laurie Jowers Ware
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Objectives
• Identify factors that led to the FDA Risk Evaluation and Mitigation Strategy (REMS) for opioid.
• Discuss the elements of the FDA REMS Program
• Describe potential impact of REMS on patients, prescribers and healthcare professionals.
• Address potential impact on decreased morbidity & mortality while assuring access to opioids when prescribed appropriately for pain
ASPMN REMS Taskforce

- **Purpose:** To educate colleagues and monitor impact on RNs (Expanded to include Physician Assistants)
- **Key stakeholders:** American Society for Pain Management Nursing, International Nurses Society on Addictions, American Academy of Physician Assistants, American Association of Nurse Anesthetists, American Academy of Nurse Practitioners, Hospice and Palliative Nurses Association, Oncology Nursing Society
- **Outcome:** Create White paper

ASPMN REMS Taskforce Members

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Food and Drug Administration and the “problem”
Growth in Opioid Prescribing
National Institute on Drug Abuse reports number of opiate prescriptions escalated from about 40 million in 1991 to 180 million in 2007

- 350% increase at a time when nation’s population increased by 19%


Impact on Federal Agencies
The US Food and Drug Administration (FDA) alerted
Overdose and deaths
1. Appropriate & inappropriate use
2. Sharing & selling
3. Growth in opioid prescribing
   Pill mills

The Science of Addiction: Implications for Nurses and Prescribers
Dana Murphy-Parker, MS, PMHNP-BC
Director: Psychiatric/Mental Health Nurse Practitioner Program
University of Wyoming Fay W Whitney School of Nursing
KEY TERMS

- Dependence
- Tolerance
- Addiction


Extent of the Problem

Nonmedical Use of opioids

- 2009, use 12 or older was greater than 2.2 million
  - 16 million 12 and older had taken a prescription pain reliever, tranquilizer, stimulant, or sedative for nonmedical purposes at least once in the year prior to being surveyed
  - 12.6 drug induced deaths per 100,000 in 2007


Initiates of Specific Illicit Drugs among Persons Aged 12 or Older: 2009

[Graph showing initiates of specific illicit drugs among persons aged 12 or older in 2009]

27,658 unintentional drug overdose deaths occurred in the U.S. in 2007. Drug overdose deaths were second only to motor vehicle crash deaths among leading causes of unintentional injury death in 2007 in the United States.

By 2006, opioids were involved in more overdose deaths than heroin and cocaine combined.


FACTORS THAT CAUSE HUMAN DISEASE: INTERACTION OF THE HOST, AGENT & ENVIRONMENT

HOST
  Person

AGENT
  (infectious or environmental hazard)
  Prescription Opioid Medication

Environment
  (that promotes exposure)
  Genetic and Environmental Are there known risk factors for Addiction?
Dr. Glen Hanson,  
Former Director Of NIDA  

- “No one is born an addict.”  
- “Addiction genes,” are biological differences that may make someone more or less vulnerable to addiction.”  
- “Environment makes up a large part of addiction risk.”  

Who’s At Risk?  
- Genetics  
- Neurobiology  
- Gender & ethnicity  
- Surrounding Environment; parental attitudes, use, peer pressure;  
- Mental Disorders  
- Type of drug and route used/availability, costs
Opioid Users Are a Heterogeneous Population

Nonmedical users

- Recreational user
- "Self-treater"
- Adherent
- Substance abuse disorder

Pain patients

- Adherent
- "Chemical cop"
- Substance abuse disorder

Opioid R, misuse and abuse is not limited to nonmedical users: patients who take opioids for legitimate pain may also be at risk


Opioid Users Are a Heterogeneous Population

Retrospective Accounts Of Initial Subjective Effects Of Opioids In Patients Treated For Pain Who Do Or Do Not Develop Opioid Addiction: A Pilot Case Control Study.

- Subjective differences experienced by patients prescribed opioids for pain
  - Aim: Compare those who ultimately developed addiction to opioids and those who did not over a period of years.
  - Measure ‘euphoria’ after drug administration.
  - Results: Investigational group experienced greater euphoria effects at initial exposure of opioid treatment for pain than controls (p<.001)

BIEBER, C; FERNANDEZ, K; BRENNAN, M; JAMISON, R; SHARPE-POTTER, J; WEISS, R; BORSOOK, D; BUTLER, S; OSGOOD, E; THOMSON, H & KATZ, N (2008). RETROSPECTIVE ACCOUNTS OF INITIAL SUBJECTIVE EFFECTS OF OPIOIDS IN PATIENTS TREATED FOR PAIN WHO DO OR DO NOT DEVELOP OPIOID ADDICTION: A PILOT CASE CONTROL STUDY. EXPERIMENTAL AND CLINICAL PSYCHOPHARMACOLOGY, 16 (5), 429 – 434.

Pilot Study results (cont)

- “I feared I would lose the contentment I had”.
  - 80% of investigational group members stated this was true compared to 10% of control group.
- “A thrill had gone through me”
  - revealed by 85& of the investigational group members in comparison to 10% of the control group members. (p<.001).
- Determining risk may impact traditional decision making in high risk. Possible protective factors
  - subjective experience of the patient,
  - genetic predisposition,
- Strategies may include increased patient education prior to initiation of therapy.
Risk Factors For Drug Dependence Among Out-patients On Opioid Therapy In A Large Us Health Care System.

- **AIM:** Sought to access the prevalence and risk factors for opioid drug dependence among outpatients on long-term opioid therapy in a large health care system.

- Four variables combined (age, depression, psychotropic medications & pain management) increased the risk of opioid dependence vs. those without these factors.

- Knowing that the patient had a history of opioid abuse or dependence increased the risk of current opioid dependence significantly (p<.001).


Increase in ED Visits Related to Opioid Use

- Estimated number of emergency department (ED) visits involving nonmedical use of opioid medication pain relievers rose from 144,644 in 2004 to 305,885 in 2008, an increase of 111 percent.

- ED visits involving oxycodone products, hydrocodone products, and methadone increased 152%, 123%, and 73% percent between 2004 and 2008

ED visits for the nonmedical use of prescription and over-the-counter drugs are now comparable to ED visits for use of illicit drugs like heroin and cocaine.

ABERRANT DRUG-TAKING BEHAVIORS Predictive of current substance use and mental health problems

- Focus on these behaviors may contribute to an adversarial relationship between physicians and patients receiving Chronic Opioid Therapy (COT).

- Programs that have used evidence of misuse or aberrant behavior to discontinue COT have led to substantial proportions of patients being lost to follow-up, with questionable clinical outcomes.

Clinicians (especially RNs) need to be educated about the disease of addiction

Partnership of ASPMN & IntNSA: A place to start!

Need:
- Treatment protocols
- Advocacy
- Research needed

FDA and REMS: Risk Evaluation Mitigation Strategy

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Acute Care Services
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Intent of REMS

- Ensure proper prescribing and safe use of products
- Limit misuse and abuse
- Decrease the deaths related to prescription drug use
Evolution Of Risk Management Related To Opioids

- Early 1990’s risk management plans – product labeling
- 2005 RiskMaps - education, reminders
- 2007
- 2009 Introduction of REMS
  - Elements to assure safe use
  - Effectiveness
  - Legally enforceable

Evolution of REMS

In 2007, Congress Gave FDA New Authority to Require REMS to Better Manage Drug Safety Problems

- Determines REMS necessary to ensure risk vs. benefits on new products
- Can impose if “new” safety information becomes evident

Now, even after drug has been approved

FDA and Risk Evaluation Mitigation Strategies (REMS)

- On February 6, 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a REMS
- Separate stakeholders & public meetings were held
- On April 19, 2011, FDA released REMS for long-acting and extended-release opioids

Responding to Prescription Abuse Crisis

- April 19, 2011 Office National Drug Control Policy collaborative plan released along with FDA REMS

- Key elements
  - Expansion of state-based prescription drug monitoring programs
  - Medication disposal
  - Education for providers and patients
  - Reduction of “pill mills” and doctor shopping through law enforcement


Affected Opioids

- Brand name and long-acting and extended-release products formulated with the following active ingredients:
  - Fentanyl
  - Hydromorphone
  - Methadone
  - Morphine
  - Oxycodone
  - Oxymorphone
  - Transdermal buprenorphine
Elements of REMS

Medication Guide
- Must be available for distribution by the pharmacy dispensing the medication

Elements of REMS

Elements to Assure Safe Use (ETASU)
- Pharmaceutical companies must
  - Notify prescribers of the existence of a REMS and need to complete a training
  - Ensure that training is provided to prescribers
  - Ensure that training is by accredited, independent Continuing Medical Education (CME) provider
  - Provide prescribers with information for patient education about safe use, storage and disposal of opioid

General Information For Safe Opioid Prescribing
- Patient selection and assessment: Goals of therapy, assessment of risk of abuse, determination of opioid tolerance when applicable
- Prescribing consideration: Pharmacokinetics, addiction/abuse, and misuse; non-medical use by others, medication interactions
- Ongoing management: Establishing goals, patient provider agreements, adherence, recognizing aberrant behavior, managing adverse events
Cont.....

• Patient education about safe use, storage and disposal of medications
• Initiating and modifying doses:
• Maintenance: Reassessment and continued management
• Monitoring for misuse and abuse
• Discontinuation of opioid therapy but not discontinuing care

Elements of REMS

• Timetable for Submission of Assessments
  • Assessments of the approved REMS for evaluation of goals
    • 6 months
    • 12 months
    • Annually
  • Results of these evaluations must be reported to the FDA
    • FDA decides if additional actions or modifications to the REMS program are required

Possible Future Element of REMS

• Efforts to link DEA certification to education
  • Would require legislative action
  • Rockefeller Bill has elements addressing this issue

• Implementation of National Prescription Monitoring Program
  • At present implemented on state level; inconsistencies, inability to track across state borders
  • Center for Lawful Access and Abuse Deterrence (CLAAD) recommendation
Pharmaceutical efforts:

- Active ingredient into a matrix
  - it cannot easily be extracted or that is not easily ground into powder
- An opioid antagonist is sequestered in inner core of tablet
  - designed to be released if the tablet is crushed or dissolved
- An irritant is sequestered in inner core of tablet
  - designed to be released if the tablet is crushed or dissolved

The FDA

- Goal: Educate Prescribers
  - Does prescriber education about interactions with patients prior to and during the use of opioids reduce their inappropriate use?
- Outcome: Reduction of “abuse, misuse, addiction and overdose deaths”
  - Outcomes measurements: Are they accurate?
  - What does the FDA plans to do if the rates of deaths increase or don’t change?

Challenges For Clinicians And Patients

Balloon Effect
1. Prescribers switch to CIII opioids and CII immediate release opioids which are currently not part of the REMS program

Decreased prescribing of opioids if certification becomes mandatory and linked to DEA
1. Perhaps return to more abuse of street illicit drugs
2. Unrelieved pain
3. Increase in hospitalizations/ED visits due to increased pain
**Challenges with Metrics**

Laurie Jowers Ware, PhD, RN  
Associate Dean and Professor  
School of Nursing  
University of West Georgia  
Carrollton, Georgia

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**FDA Assessment Requirements**

*Current Assessment Requirements*

- Completion of training program
- Independent audit of quality of educational materials
- Evaluation of providers’ understanding of risks and measures to be taken if lack of understanding demonstrated
- Evaluation of patients’ understanding of risk
- Plan for evaluating drug specific changes in abuse, misuse, overdose, and addiction
- Evaluation of changes in prescribing behavior

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**What are the Challenges With Metrics?**

Multiple databases (NSDUH, DAWN, and MTF) do not provide sufficient data to answer questions about prescription drug abuse  
Data not necessarily associated with legitimate prescribing  
Mortalities where more than one agent involved; challenges with ICD coding  
Difficulty in tracking prescription abuse across state lines  
Lack of empirical data
Other Challenges
Most adverse events related to medications “not prescribed” to person
   How do you control/monitor event?

How Can Success Be Measured?
Indirect Measures
   • Current data base information such as serious adverse events

How Can Success Be Measured?
Direct Measures
   • Provider education/certification
   • Pharmaceutical reporting of education and opioid prescribing and integration into national databases
   • Evidence of inappropriate prescribing
   • Frequency of adverse events
   • Data related to lower frequency adverse events against patient access
Recommendations

- Measure potential unintended consequences of REMS such as limiting patient access due to decreased prescribing.
- Measure outcomes such as serious adverse effects and patient access to care.
- Determine if the current REMS that applies only to long-acting and extended-release opioids will shift prescribing patterns and create future problems in terms of access and abuse.
- Determine if non-mandated education will be effective or should education be coordinated with state regulatory authorities and professional organizations.

The Future

- Initial REMS education will be implemented in early 2012.
- REMS is a system that will be implemented and evolve over time – may eventually include all opioids.
- No clear answers as to the appropriate metrics to measure the impact of REMS.
- FDA recommends a single shared system to measure efficacy.

Assuring Excellence Pain Care

- Manage pain appropriately through thorough evaluation and risk assessment.
- Participate in ongoing education.
- Provide ongoing education to patients about safe use of opioid therapy and the risks of unintended use.
- Become involved in outreach efforts to increase public awareness about the dangers of non-medical use of opioid therapy.
Consensus

The taskforce believes it is important for all healthcare professionals to stay abreast of policy changes and be involved in any future legislation that may affect access to pain management.

Acknowledgement

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