The Prescription Drug Abuse Epidemic: Finding Solutions with New Technologies in Formulation & Delivery Science

Tuesday December 13, 2016
The Prescription Drug Abuse Epidemic

Speakers:

• Bertha K Madras, PhD, Professor of Psychobiology, Department of Psychiatry, Harvard Medical School
• Beatriz Rocha, MD, PhD, Executive Director, Head Regulatory Affairs Clinical Strategy, Covance
• Alexander Kraus, PhD, VP Product Development, Technical and Government Affairs, Grunenthal USA
• Anita Gupta, DO, PharmD, Vice Chair, and Associate Professor, Drexel University College of Medicine, Division of Pain Medicine, Department of Anesthesiology

Moderator:

• Michael G. Palfreyman, PhD, DSc, President, Palfreyman BioPharma Consulting
MassBio Forum

The Prescription Drug Abuse Epidemic: Finding Solutions with New Technologies in Formulation & Delivery Science
The Prescription Drug Abuse Epidemic
MassBio Forum Panel Discussion

Drug Formulations:

▪ Can opiates be formulated to be 'tamper resistant' and/or 'abuse resistant'?

▪ Can opiates be formulated with other compounds (e.g. opiate antagonists) to mitigate, or reduce abuse and overdose?

▪ What are the limitations of formulations such as Embeda (Pfizer)?

▪ What are the FDA requirements to demonstrate ‘tamper resistance’ and ‘abuse deterrence’?
The Prescription Drug Abuse Epidemic
MassBio Forum Panel Discussion

Drug Formulations for Overdose and Abuse Treatments:

▪ Is 'Narcan' (naltrexone) in best formulation for ease of use and how can it be made more available?

▪ Should 'Narcan' be 'co-prescribed' with opiates?

▪ Is buprenorphine available to enough prescribers (e.g. Nurses as well as Doctors) and in easy to administer formulations?
Safer alternatives available, or in development for pain relief:

- Are selective opiates safer?
- Is ketamine an alternative?
- Other safer approaches to pain relief?
- Are combinations of non opiates with lower doses of opiates safer?
- Is an opiate vaccine possible?
Impact of Legislation:

- What impact has current, or impending legislation had on the opiate crisis and how does the legislation impact new formulations?

- Have opiate restrictions increased heroin use and overdose deaths?

- What other technical, therapeutic, or legislative approaches should be considered to address the opiate crisis?
Opioid Crisis: Origins and Solutions

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Made in America: Fade in America

Deaths
2012: 170
2015: 84
Estonia

To the Editor:

• we examined...incidence of narcotic addiction...
• 11,882 patients who received at least one narcotic preparation.
• only four cases of documented addiction...no history of addiction.
• ...addiction considered major in only one instance
• ...meperidine, Percodan, hydromorphone

We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

1989
Shift blame to provider if patient has pain

1990
Tragedy needed pain

1995
Pain as the fifth vital sign
Medical societies champion opioid use for pain control

1999
VA adopts “Pain: the 5th vital sign”
Mandates pain evaluation treatment

2000
Pain management for accreditation
Joint Commission (JCAHO) includes Pain management

Campaign: Opioids Safe to Treat Chronic Pain
1999: Oregon Medical Board disciplines a physician for failure to prescribe adequate pain relief medication.

2001: California jury awards $1.5 million to surviving children of W. B. after they sue father's physician, Dr. W. C., for undertreating his cancer pain before death.
And Yet...

Good evidence of dose-dependent risk for serious harms.


Insufficient evidence for long-term use of opioids to improve chronic pain and function.
Prescriptions for Opioids Escalated

Aftermath

Use and Addiction
- Use disorder: ~1.9 million people Rx opioids
- Users > cocaine, heroin, meth., MDMA, PCP combined

Neonatal Abstinence Syndrome
- 500% rise

Infectious diseases
- Conversion to heroin
- HIV, hepatitis C

Overdose Deaths
- ~ 28,000
In 2014, ~129 people died every day of drug poisoning
- 61% (79) are pharmaceutical opioid or heroin related.
Doctors Continue Prescribing Opioids for 91% of Overdose Patients!
33-39% also prescribed benzodiazepines

17% of high dose patients overdosed again within 2 years (n=2848; 2000-2012)
The Positives: Declining

- Opioid Rx availability
- Rx opioid abuse (12th graders)
- Admissions for treatment declining
- Workplace positive tests for Rx opioids
- Rate of increase in deaths related to Rx opioids

Tamper-proof medications have shown efficacy

Source: DEA 2016 National Drug Threat Assessment Summary
Top 5 Schedule II and III CPDs Distributed Nationwide 2006-2014

Source: DEA 2016 National Drug Threat Assessment Summary
Opioids remain remarkably effective pain-killers!

- Physician Education
- Patient Education
- Patient monitoring
- Take back programs
- Screen and Intervene
- Treat (MAT)
- Rescue (Narcan)
- Alternative analgesics
- Improved Opioids
Thank you

Questions?
ABUSE DETERRENT OPIOIDS
REGULATORY HISTORY

Beatriz Rocha, MD, PhD
Head, Clinical Regulatory Strategy
Covance
Regulatory Responses to the Growing Epidemic of Opioid Abuse

► FDA Opioids Action Plan
► Regulatory Guidance

Image - Covance
FDA Opioids Action Plan

September 2016

► Overall Objective: encourage drug companies to develop products that can mitigate abuse, while maintaining availability of opioid analgesics for the millions of pain patients

► [http://www.fda.gov/newsevents/newsroom/factsheets/ucm484714.htm](http://www.fda.gov/newsevents/newsroom/factsheets/ucm484714.htm)
FDA Opioids Action Plan

► Expand use of advisory committees
► Develop warnings and safety information for immediate-release (IR) opioid labeling
► Strengthen post market requirements
► Update Risk Evaluation and Mitigation Strategy (REMS) Program
► Expand access to abuse-deterrent formulations (ADFs) to discourage abuse
► Support better treatment
► Reassess the risk-benefit approval framework for opioid use
New Safety Measures Announced for Opioid Analgesics, Prescription Opioid Cough Products, and Benzodiazepines

August 2016

► Requirement of class-wide changes to drug labeling, including patient information, to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and a class of central nervous system (CNS) depressant drugs called benzodiazepines

- Boxed warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines – nearly 400 products in total – with information about the serious risks associated with using these medications at the same time

- Risks include extreme sleepiness, respiratory depression, coma and death

- This is part of the agency’s Opioids Action Plan, which focuses on policies aimed at reversing the prescription opioid abuse epidemic, while still providing patients in pain access to effective and appropriate pain management

► http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm518110.htm
Improving Product Labeling Opioid Analgesics

April 2014

Class-wide safety labeling changes (SLC) for all extended-release and long-acting (ERLA) opioid analgesics with and without abuse deterrent properties:

- Harmonized indication: the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate

- A new warning for Neonatal Opioid Withdrawal Syndrome (NOWS)

- Updated language in the Warnings and Precautions section of the label regarding addiction, abuse, and misuse, life-threatening respiratory depression, accidental ingestion, and drug interactions
Improving Product Labeling Opioid Analgesics

March 2016

► Class-wide SLC for immediate-release opioid analgesics similar to the 2014 SLC for ERLA opioid analgesics
  • Boxed warning with information about the risks of misuse, abuse, addiction, overdose and death
  • Potential for neonatal opioid withdrawal syndrome (NOWS) with prolonged maternal use of opioids during pregnancy
  • Updated indication stating that IR opioids should be reserved to manage pain severe enough to require opioid treatment and for which alternative treatment options are inadequate or not tolerated
  • Clearer information regarding patient monitoring and drug administration
  • New warnings for all opioids regarding serotonin syndrome and endocrine effects
Regulatory Guidance

► March 2016 – draft - Abuse Deterrence of Generic Solid Oral Opioid Drug Products
  • Comparative nonclinical studies to demonstrate that a generic (solid oral) opioid drug is no less abuse-deterrent than the innovator drug with respect to all potential routes of abuse.

► April 2015 - final – Abuse Deterrent Opioids
  • Studies to be conducted to demonstrate that a given formulation has abuse-deterrent properties
  • Recommendations about how those studies should be performed and evaluated
  • Discusses how to describe those studies and their implications in product labeling
  • Flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products
Approved Abuse Deterrent ERLA Opioid Analgesic Products

► **Embeda®** (Alpharma Pharmaceuticals LLC) approved in 2009, is an extended-release formulation of morphine sulfate with a sequestered opioid antagonist, naltrexone

- Embeda has properties that are expected to reduce abuse by the oral (chewing) and intranasal routes
- A human abuse potential study of IV morphine and naltrexone to simulate injection of crushed Embeda demonstrated evidence of abuse deterrence; however it is unknown whether the results from simulated crushed Embeda can predict a reduction in abuse by the IV route until additional post marketing data are available

► The first formulation of extended-release oxycodone was **OxyContin®** (Purdue Pharma L.P.) approved in 1995; reformulation approved in 2010

- Designed with physicochemical properties intended to deter abuse by being more difficult to prepare for intravenous abuse by syringe, and to resist breaking or crushing for intranasal abuse
- Original OxyContin no longer manufactured or marketed in the US
- In 2012, language was added to the label describing OxyContin’s abuse-deterrent properties based on the Agency’s review of in vitro and in vivo studies
Approved Abuse Deterrent ERLA Opioid Analgesic Products (cont)

➤ **Targiniq® ER** (Purdue Pharma, L.P.)

- Second extended-release oxycodone product with abuse-deterrent properties, of oxycodone and naloxone, an opioid antagonist
- Naloxone has low oral bioavailability due to high first pass metabolism, and is not intended to reach adequate levels to have an effect in patients taking the medication as prescribed
- If Targiniq ER is manipulated for abuse by injection or nasal insufflation, the naloxone levels are high enough to antagonize the reinforcing opioid effects
- Language in the label includes findings of in vitro studies and human abuse potential studies that indicate that Targiniq ER has pharmacologic properties that are expected to reduce abuse via the intranasal and IV routes of administration
Hysingla® ER (Purdue Pharma L.P.), approved in 2014, is the first extended-release formulation of hydrocodone with properties intended to deter abuse

- In vitro data demonstrate that Hysingla ER’s physicochemical properties can be expected to deter intranasal and intravenous abuse
- Data from human abuse potential studies, also support that these properties can be expected to deter intranasal abuse and oral abuse when chewed
Approved Abuse Deterrent ERLA Opioid Analgesic Products (cont)

- **Morphabond®** (Inspirion Delivery Technologies LLC), an extended-release formulation of morphine sulfate, approved in 2015, is the second extended-release morphine product with abuse-deterrent labeling
  - Physicochemical properties expected to make abuse via injection difficult
  - Data from human abuse potential studies as well as in vitro data also support that these properties are expected to reduce abuse by the intranasal route of administration
Approved Abuse Deterrent ERLA Opioid Analgesic Products (cont)

- **Xtampza® ER** (Collegium Pharmaceuticals, Inc.), the third extended-release oxycodone product with abuse-deterrent properties, was approved on April 26, 2016
  - In vitro data demonstrate physicochemical properties expected to make abuse by injection difficult
  - Data from pharmacokinetic and human abuse potential studies, along with support from the in vitro data, also indicate that physicochemical properties are expected to reduce abuse via the intranasal route

- **Troxyca® ER** (Pfizer, Inc.), the forth extended-release oxycodone product with abuse-deterrent properties, was approved on August 31, 2016
  - First extended-release combination analgesic drug product containing oxycodone hydrochloride and naltrexone hydrochloride that is released with manipulation by crushing.
  - Human abuse potential studies support that Troxyca ER has properties that can be expected to deter abuse by the oral and intranasal routes of administration
Post-Marketing Epidemiology Studies

► To all Sponsors of ERLA opioid analgesics with approved AD language in the label

► Whether the properties of their products result in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting
To all Sponsors of ERLA opioid analgesics with or without approved AD language in the label

Part of the ERLA Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risks associated with this class of drugs
THANK YOU

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Public
The Prescription Drug Abuse Epidemic: Finding Solutions with New Technologies in Formulation & Delivery Science

Formulation technologies to deter abuse
Alexander Kraus, PhD, Grunenthal USA, Inc. – Morristown, New Jersey
Disclosures and Disclaimer notice

- I am a full-time employee of Grünenthal USA, Inc.
- Grünenthal develops and markets abuse-deterrent formulation technology and products.
- The opinions expressed in the following are my own and not necessarily those of Grünenthal.
FDA Guidance on ADF Opioid Development and Labeling

- Draft guidance issued in 2013; final document released in April 2015
- FDA has since approved 7 extended release opioid products with abuse-deterrent labeling according to the concepts laid out in the guidance.
Important background provided by FDA in the guidance

- FDA considers the development of abuse-deterrent products a high public health priority.

- Abuse-deterrent technologies developed to date are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding.

- Current technologies do not address the most common form of abuse and misuse which is taking the product orally for non-medical purpose.

- A product that has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties.

- Abuse-deterrent properties are defined as properties shown to meaningfully **deter** abuse, even if they do not fully **prevent** abuse.
Technical approaches applied to create abuse-deterrence

1. Physical/Chemical barriers (crush-resistance, gelling, specific excipients)
   ⇒ OxyContin®, Hysingla® ER, MorphaBond®, Xtampza® ER

2. Agonist/Antagonist combinations (naloxone, naltrexone)
   ⇒ Embeda®, Targiniq® ER, Troxyca® ER

3. Aversion (SLS, capsaicin, niacin)

4. Delivery systems (depots, injectables, implants)

5. New molecular entities and pro-drugs (esters, PEGs, bioactivated cleavage)

6. Combination approaches (two or more of the above approaches)

7. Novel mechanisms (not yet known)
<table>
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<tr>
<th>PRO</th>
<th>CON</th>
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<tr>
<td>Different approaches have demonstrated reduction in liking and</td>
<td>Current technologies not able to address oral abuse/overuse.</td>
</tr>
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<td>euphoria in clinical abuse liability studies.</td>
<td>FDA requirements for AD labeling require significant additional</td>
</tr>
<tr>
<td>Epidemiological evidence is building up for certain products to</td>
<td>development efforts.</td>
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<tr>
<td>have sustainable reduction in real-world abuse.</td>
<td>Abuse deterrent products currently not competitive with generic</td>
</tr>
<tr>
<td>Products/approaches typically do not have negative impact on</td>
<td>opioids on pricing/manufacturing cost.</td>
</tr>
<tr>
<td>patients when used as intended.</td>
<td>Limited penetration of abuse-deterrent products in the market due to</td>
</tr>
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<td>imposed access barriers.</td>
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Backup
Drug Formulations

- Can opiates be formulated to be 'tamper resistant' and/or 'abuse resistant'?
- Can opiates be formulated with other compounds (e.g. opiate antagonists) to mitigate, or reduce abuse and overdose?
- What are the limitations of formulations such as Embeda (Pfizer)?
- What are the FDA requirements to demonstrate ‘tamper resistance’ and 'abuse deterrence'?
Prescription Opioid Crises
Physician and Pharmacist Perspective

ANITA GUPTA, DO, PHARM.D
VICE CHAIR, ASSOCIATE PROFESSOR
DREXEL UNIVERSITY COLLEGE OF MEDICINE
PHILADELPHIA PA
What is Multimodal Pain Treatment?
Multimodal Approach Addresses the Complex Nature of Pain Transmission

Peripheral nociceptors → Ascending input via Spinothalamic tract → Dorsal horn → Descending modulation → Pain


NE = norepinephrine
NSAIDs = nonsteroidal anti-inflammatory drugs

Opioids,
Alpha-2 agonists
Acetaminophen,
some NSAIDs
NE-reuptake inhibitors

Local anesthetics (epidural), Opioids,
Alpha-2 agonists

Local anesthetics (peripheral nerve block)

Local anesthetics (field block), NSAIDs, Coxibs
What is the Problem?
Opioid Misuse
Adverse Events
Drug Cost
Drug-Drug Interactions
Medication Adherence
In the United States, chronic pain affects more people than diabetes, heart disease, and cancer combined.
To muddle this further....
Depression and Pain

Chicken and Egg Phenomena

Chronic pain patients typically have psychiatric comorbidities

- Depression
- Anxiety
- Substance abuse
- Somatization
- Personality disorders

Which comes first?

Psychopathology may influence chronicity rather than onset of pain
<table>
<thead>
<tr>
<th>Condition</th>
<th>Preparedness</th>
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<tr>
<td>Hypertension</td>
<td>82.8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>82.3%</td>
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<tr>
<td>Depression</td>
<td>44.1%</td>
</tr>
<tr>
<td>Prescription Drug Use</td>
<td>30.2%</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>19.9%</td>
</tr>
<tr>
<td>Illegal Drug Use</td>
<td>16.9%</td>
</tr>
</tbody>
</table>
Why Does Opioid Addiction Develop?
Like
Euphoric and hedonic response

Want
Incentive-driven and motivated

Both are mediated by dopamine
Like
Euphoric and hedonic response

Want
Incentive-driven and motivated

Both are mediated by dopamine
The Dilemma
Promote Responsible Pain Management and Resource Utilization

- Patients using opioids are perceived to be especially difficult to manage, costly and complicated
- There are no standard, national best practices for coordinated care between providers or even pain management treatments
- Large multidisciplinary pain practices are a particularly challenging arena as they must work within a capitated environment while endeavoring to improve the quality of care but at lowering reimbursements
What is Causing High Prevalence of Prescription Drug Abuse?
What is Causing High Prevalence of Prescription Drug Abuse?

- **Misperceptions about their safety.** Because these medications are prescribed by doctors, many assume that they are safe to take under any circumstances.

- **Increasing environmental availability.** Between 1991 and 2010, prescriptions for stimulants increased from 5 million to 45 million, a 9-fold increase, and opioid analgesics increased from about 30 million to 180 million, a 6-fold increase.

- **Varied motivations for use of opioids.** Underlying reasons include: to get high; to counter anxiety, pain, or sleep problems; or to enhance cognition (although they may, in fact, impair certain types of cognitive performance).
Physicians Asking if the Pendulum Has Swung Too Far? What Can Be Done?
What Can Be Done?

- Development of benchmarking data, standardization of chronic pain care and systematic evidence based protocol development via using robust data.
- Emphasis on multimodal, interdisciplinary and biopsychosocial approaches to chronic pain.
- Integration of innovative technology and new platforms to engage patients.
- Shared responsibility models of chronic pain care for physicians and patients.
- Robust health education programs on safe and responsible opioid use for patients and providers.
- Preventing the transition from acute to chronic pain while hospitalized.
- Developing safeguards when on opioid therapy for chronic pain for both patients and providers such as naloxone availability.
Upcoming 2017 MassBio Forums

Jan 11: Security & Protection – The Premises, the Technology, the People; SEF

Jan 19: 2017 JP Morgan Recap: An Insider’s View; BD/Fin & EU

Jan 26: Best Practices in Developing a Regulatory Affairs Pipeline; HR & MassBioED