
Please see Important Safety Information on slide 55.. Full Prescribing Information is available at EXPAREL.com.
Disclosures

- The presenter has a consulting relationship with Pacira Pharmaceuticals, Inc. and Medtronic Inc.
The Opioid Epidemic

Where we are now.

How did we get here?

What can we do about it?
Where we are now

According to AAOS
Daily: 650,000 opioid prescriptions written
3900 People initiate non-medical use
78 people die opioid related deaths

According to HHS
Since 1999 opioid-related deaths have quadrupled

For every 1 death, there are:

10 treatment admissions for abuse
32 ER visits for misuse or abuse
130 who abuse or are dependent
825 non-medical users

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In 2016

Richard M. Fairbanks Foundation:

- 5% of Hoosiers had abused drugs in the past month
- 1000 Hoosiers had used heroin in the past month

With the opioid epidemic going back more than 25 years,

... we’ve influenced 2 generations of Americans to feel that they are entitled to drugs in order to live without pain,

... and 2 generations of doctors who, until just recently, felt they had the power/responsibility to eliminate pain.

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>U.S. (%)</th>
<th>Netherlands (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fractures</td>
<td>77%</td>
<td>0%</td>
</tr>
<tr>
<td>Ankle fractures</td>
<td>82%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Geographic Variation in the Prescription of Opioid Analgesics

Some states have more painkiller prescriptions per person than others.

Number of painkiller prescriptions per 100 people

- 52-71
- 72-82.1
- 82.2-95
- 96-143

SOURCE: IMS, National Prescription Audit (NPA™), 2012.

How did we get here?
CDC Issues Opioid Guidelines for 'Doctor Driven' Epidemic

Medscape Medical News

Read Now »
In the 1990s, doctors were encouraged to take pain more seriously

JCAHO – “The 5th Vital Sign”

- Heart rate
- Respiratory rate
- Blood pressure
- Temperature
- PAIN!!!
106th Congress passed HR3244 and President Clinton signed it into law. It declared the “Decade of Pain Control and Research”.

This was only the 2nd congressionally declared medical decade, the 1st being the “Decade of the Brain” in the 1990s.
There was a market and pharmaceutical companies took advantage.

Research showed growing numbers of Americans experiencing some form of chronic pain, estimated to be 1 in 3 by 2011.

Purdue Pharma L.P. (1991)

- Focuses on pain management
- Brands itself a “pioneer in developing medications for reducing pain, a principal cause of human suffering”
- MS contin (1987), hydromorphone, oxycodone, fentanyl, codeine, hydrocodone, Oxycontin (1996)
- But the evidence for use of these drugs for chronic pain treatment was dubious.

Health Care Policy Decisions in the New Millennium

- Reimbursement tied to patient satisfaction surveys
  - Press Ganey
  - ACA
  - CMS Pay for Performance
- Neutering of certain medical specialties
  - e.g. physiatry

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Health Care Policy Decisions in the New Millennium

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Now a perfect storm and an exponential increase in:
- prescription medication
- deaths
- substance abuse and hospitalizations
Over-Prescription Leads to a High Potential for Diversion

- Jeffrey Rodgers, M.D.
- Journal of Hand Surgery 2012
- 250 patients
- Average prescription 30 pills
- Average # consumed 10 pills
- Resulting in 4639 leftover pills
- “I know where ... ”
And, my wife’s experience ...
SPECIAL REPORT

SMACK EPIDEMIC

HOW PAINKILLERS ARE TURNING YOUNG ATHLETES INTO HEROIN ADDICTS

BY L. JON WERTHEIM AND KEN RODRIGUEZ

Photograph by Teruaki Nabekura
For Sports Illustrated

Background by Karen Rubin
For Sports Illustrated

Photo Illustration by El Pressano

Mitros Orthopaedics
Hard to believe!

- US population grew 10% between 2000-2010

But in the US

- In 1991 there were 76,000,000 opioid prescriptions written
- In 1998 there were 105,000,000 opioid prescriptions written
- In 2011 there were 219,000,000 opioid prescriptions written
- In 1999 there were 4,030 opioid-related deaths
- In 2010 there were 16,651 opioid-related deaths
- In 2015, 90% of the world’s opioids were consumed in North America
- In 2011 the U.S. had 5% of the world’s population but consumed 80% of the world’s narcotics

In 2008 …
Drug deaths overtook MVA deaths in Indiana

In 2014 …
1,100 Hoosiers died opioid-related deaths
Indiana rose to 15th nationally in drug-overdose deaths
$1.4 billion cost to state

Clair Fiddian-Green
South Bend Tribune, 01/21/2017
In 2015

- 52,000 American deaths from drug overdoses
- 33,000 secondary to opioids

Compare:
- 38,000 MVA deaths
- 36,000 deaths from gun violence
- 50,000 AIDS/HIV (1995)
What can we do about it?
In my training, I was taught the judicious use of narcotics

- William Smith, M.D,
  - University of Michigan, 1976

- Reasonable post-op dosing
Setting the Stage

Pain after TJR is a bad thing – especially with knees.

It makes it hard to mobilize the patient, likely increasing the risk of VTE.

It slows the pace of recovery and increases rate of needing further procedures, especially manipulations.

It decreases patient satisfaction – and this is now a factor in hospital reimbursement.

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It leads to increased infection rates.

“An increase in sympathetic tone leads to downregulation of immune function.”

It can lead to chronic pain syndromes.

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What’s Bad about Opioids?

Depressed vital signs – 
  respiratory rate and blood pressure
CNS depression – 
  sedation and confusion
GI side effects – 
  nausea, vomiting, constipation
Itching – 
  need for Benadryl (sedation)
Genitourinary – 
  urinary retention (catheters and infection)

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Acute high dose-fentanyl exposure produces hyperalgesia and tactile allodynia after coronary artery bypass surgery

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2Department of Cardiovascular Surgery, Gulhane Military Academy of Medicine, Ankara, Turkey
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Abstract. - OBJECTIVE: Opioid-induced hyperalgesia is well known complication of acute high dose and chronic opioid therapy. In this study, we evaluated development of opioid-induced hyperalgesia following intraoperative short-term use of μ-opioid agonist fentanyl after coronary artery bypass surgery.

PATIENTS AND METHODS: 100 patients undergoing elective coronary artery bypass graft surgery is divided into two groups. In group I (low dose), anesthesia was induced with propofol 1-2.5 mg/kg and fentanyl 2 mcg/kg, in group II (high dose) fentanyl 40-70 mcg/kg was used. In group I propofol 5-10 mg/kg/h, fentanyl 1-3 mcg/kg/h, in group II fentanyl 5-10 mcg/kg/h was used for maintenance of anesthesia. The tactile and thermal thresholds were measured before surgery and in 1st, 3rd and 7th postoperative days by using Von Frey filaments and a thermal source, respectively.

RESULTS: Tactile thresholds were significantly decreased at the first (6.08 ± 0.21 and 3.76 ± 0.13 g; p < 0.001) and third (6.76 ± 0.24 and 4.96 ± 0.16 g; p < 0.001) postoperative days compared to baseline preoperative values (7.72 ± 0.28, and 7.60 ± 0.21 g; p = 816) in two groups. Postoperative 1st(13.45 ± 0.33 and 10.05 ± 0.24 sec; p < 0.001) and 3rd day (14.77 ± 0.28 and 13.17 ± 0.26 sec; p < 0.001) assessments showed a statistically significant thermal hyperalgesia compared to the preoperative baseline values (16.67 ± 0.51 and 16.45 ± 0.42 sec; p = 0.987) in two groups. This decrease in both tactile and thermal thresholds returned to baseline control values at the 7th day of measurement.

CONCLUSIONS: Our results showed that patients undergoing coronary artery bypass surgery receiving fentanyl anesthesia developed postoperative tactile allodynia and thermal hyperalgesia and this was more prominent in high dose group.

Introduction

Opiates such as morphine and fentanyl are the primary agents used for conditions ranging from acute pain, postoperative pain to chronic pain112. Clinical use of this group of drugs is sometimes hindered by two opioid related phenomena. The first is antinociceptive tolerance that is defined as the decrease in the analgesic activity of a drug after a previous exposure to the same or a similar drug1. Thus, higher doses of the drug are required to elicit the same amount of pain relief. A second problem is a more recently recognized phenomenon of opioid-induced hyperalgesia. In this situation, prolonged or acute administration of opioids results in a paradoxical decrease of pain threshold and increase of atypical pain that appears to be unrelated to the original noxious stimulus53.

It is known that opioid-induced paradoxical pain may be seen in animal models and in humans5. Animal studies show that acute and chronic opioid exposure cause hyperalgesia and tactile allodynia16. A similar hyperalgesia phenomenon has been described in human in former opioid addicts and postoperative patients who exposed to opioids during the surgery1113. Indeed, it has been previously reported that the higher intraoperative opioid fentanyl or remifentanil doses, the greater postoperative pain level and morphine requirement14.

Postoperative pain is still a serious problem although a variety of strong analgesics are available. Dolin et al15 have reported that about 40% of all surgical patients experience different degree of pain after the surgery and among these patients, 24% were still experienced inadequate pain control. It has been suggested that the presence of
Chronic Opioid Use Prior to Total Knee Arthroplasty

Michael G. Zywiel, MD, D. Alex Stohl, BS, Seung Yong Lee, MD, Peter M. Bowhill, MD, Michael A. Mont, MD

II Abstract

**Background:** Chronic use of opioid medications may lead to dependence or hyperalgesia, both of which might adversely affect perioperative and postoperative pain management, rehabilitation, and clinical outcomes after total knee arthroplasty. The purpose of this study was to evaluate patients who underwent total knee arthroplasty following six or more weeks of chronic opioid use for pain control and to compare them with a matched group who did not use opioids preoperatively.

**Methods:** Forty-nine knees in patients who had a mean age of fifty-six years (range, thirty-seven to seventy-eight years) and who had regularly used opioid medications for pain control prior to total knee arthroplasty were compared with a group of patients who had not used them: Length of hospitalization, aseptic complications requiring reoperation, requirement for specialized pain management, and clinical outcomes were assessed for both groups.

**Results:** Knee Society scores were significantly lower in the patients who regularly used opioid medications at the time of final follow-up (mean, three years; range, two to seven years); the opioid group had a mean of 79 points (range, 45 to 100 points) as compared with a mean of 92 points (range, 59 to 100 points) in the non-opioid group. A significantly higher prevalence of complications was seen in the opioid group, with five arthroscopic evaluations and eight revisions for persistent stiffness and/or pain, compared with none in the matched group. Ten patients in the opioid group were referred for outpatient pain management, compared with one patient in the non-opioid group.

**Conclusions:** Patients who chronically use opioid medications prior to total knee arthroplasty may be at a substantially greater risk for complications and painful prolonged recoveries. Alternative non-opioid pain medications and/or earlier referral to an orthopaedic surgeon prior to habitual opioid use should be considered for patients with painful degenerative disease of the knee.
Many patients undergoing hip or knee replacement are still taking prescription opioid pain medications up to six months after surgery, reports a study in *PAIN®,* the official publication of the International Association for the Study of Pain® (IASP). The journal is published by Wolters Kluwer.

Led by Jenna Goesling, PhD, of the University of Michigan, the study identifies several "red flags" for persistent opioid use—particularly previous use of high-dose opioids. The results also suggest that some patients continue to use these potentially addictive pain medications despite improvement in their hip or knee pain.

**Concerns about Persistent Opioid Use after Joint Replacement**

Total knee and hip replacements are highly effective operations for patients with severe pain in these joints, and opioids are the main drugs used for acute pain management after such surgeries. However, little is known about long-term patterns of opioid use after joint-replacement surgery. This information is especially important as such surgeries become even more frequent as the US population ages and the "opioid epidemic" continues to produce dramatic increases in opioid use, misuse, and overdose.

Dr. Goesling and her team analyzed patterns of opioid use in 574 patients undergoing knee or hip replacement surgery (arthroplasty). Patients were followed up at one, three, and six months after surgery to assess rates of and risk factors for long-term opioid use.
The Journey Begins . . .

August 2013

- Entrepreneurial orthopaedic surgeon contacted me.
- A day in Decatur with Mike Berend

HELLO LIPOSOMAL BUPIVICAINÉ

Please see Important Safety Information on slide 57. Full Prescribing Information is available at EXPAREL.com.
Multimodal approach to acute surgical pain

- Anti-inflammatory medication
- Anti-convulsants
- Nerve blocks
- Local anesthetics
- Tylenol

Where I Came From

Total knees
General or epidural, followed by epidural overnight.

Total hips
General or spinal, followed by PCA overnight.
What is Liposomal Bupivicaine?

- Bupivicaine is packaged in a multivesicular liposomal structure (Depo Foam) that encapsulates the drug without altering its molecular structure. This liposomal structure breaks down, releasing the bupivicaine over a desired period of time.

- It is a slow release of a long acting local anesthetic. Bupivicaine typically lasts up to 8-12 hours.

Please see Important Safety Information on slide 57. Full Prescribing Information is available at EXPAREL.com.

Please see Important Safety Information on slide 55. Full Prescribing Information is available at EXPAREL.com.
Pharmacokinetics Demonstrate Plasma Levels of Bupivacaine That Can Persist for 96 Hours\(^1\)

- Other formulations of bupivacaine should not be administered within 96 hours following administration of EXPAREL\(^2\).
- Systemic plasma levels of bupivacaine following administration of EXPAREL are not correlated with local efficacy\(^2\).
- The rate of systemic absorption of bupivacaine is dependent on the total dose of drug administered, the route of administration, and the vascularity of the administration site\(^2\).


Please see Important Safety Information on slide 55. Full Prescribing Information is available at EXPAREL.com.
Late April 2014: Here we go

Adductor Canal Block
- Untrasound, in holding

Spinal
- In holding or in OR

Liposomal bupivicaine
- During the case


Please see Important Safety Information on slide 57. Full Prescribing Information is available at EXPAREL.com.
Earliest Memorial Data

2-day in hospital stay
Total knees only

Oral morphine equivalents
Prior to April – 484
June 2014 – 100

Where were the 100 OMEs coming from?

“There are three holes”

1) Me – pre-op cocktail
   (oxycontin or MS-contin)

2) Anesthesia
   (fentanyl)

3) Floor nurses – remember JCAHO?
   floats
   new grads
Dr. Mitros' patients

For a pain score of

0, 1, 2, 3  No narcotics - May be given 1-2 Tylenol

4, 5, 6  May be given one narcotic tablet

7, 8, 9, 10  May be given two narcotic tablets
ORAL MORPHINE EQUIVALENTS (OMEs)

484 → 100 → 34

June ’14       September ‘14

Would you publish?

Last 50 consecutive knees before LB (2014)  268  OMEs

First 50 consecutive knees with LB (2014)  102.5 OMEs ↓ 62%

50 consecutive knees with refined LB technique (2015)  45.6 OMEs ↓ 83%

Other benefits

Pain scores ↓ 75% on POD #1
↓ 50% on POD #2

PACU time ↓ by 35%

Reduced antiemetics dramatically
No falls

Catheter exposure

Before LB (50 cases) 30%
With LB (100 cases) 4%

Please see Important Safety Information on slide 57. Full Prescribing Information is available at EXPAREL.com.
Other benefits (cont.)

No epidurals or PCAs in over a year

Unit director: “Saves a minimum of one hour ($25) RN time per patient per day secondary to decreased narcotic use.” Giving few meds and dealing with fewer side effects. “Patients clearly mobilize faster, decreasing risk of VTE.”

Improved patient satisfaction: 35 out of 35 (both knees and hips) – “No Comparison”
So what do we have?

- Less narcotic, of course.
- Fewer narcotic related side effects
- Less predisposition to future narcotic problems
- Happier patients
- ↓ LOS – to the extreme . . . .
The Overall Cost of Opioid Abuse and Diversion

- Nationwide, the total economic burden of opioid abuse is estimated at approximately $78.5 billion annually, of which approximately billion represent increased health care costs and substance abuse treatment\(^1\)

- Among opioid-treated employees on workers’ compensation or short-term disability for a work-related injury, healthcare costs for addicts exceed those of non-addicts by about $10,000\(^2\)

\(^1\) Florence CS, et al. Med Care. 2016;54:901-8
Addressing the Opioid Epidemic
is the …

- Medical
- Moral
- Social
- Fiscal

… right thing to do!

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What can you do locally to deal with this public health issue?

- Meet with hospital officials and health system representatives.
  - Let them know that you have an understanding of what it means to have reimbursement tied to patient feedback.
  - Remind them that the health profession’s responsibility is to 1st do no harm – and that means minimizing narcotic use.
  - Express to them your understanding that reduced opioid programs might increase costs to them in the short term, but failing to undertake them increases the long-term costs to society.

NLC
What can you do locally to deal with this public health issue??

- Meet with community health officials to organize pill take-back dates and sites.
  - Make it easy!
- Give input to members of the US Congress.
  - Let them know of the ramifications of policies linking reimbursement to survey scores.
- Rethink pain and pain management in your own lives. Lead by example.
Increasing Interest in Opioid-Sparing Approach for Patient Care

Goal: Educate patients and physicians about their options when it comes to postsurgical pain control, promoting proactive discussions before surgery about non-opioid options.

“I want people to have the luxury of being able to feel like they can go back to their doctor and ask for something other than an opioid.”

-Gabby Reece, former star volleyball player

According to a recent national survey, 1 in 10 patients admit they’ve become addicted to or dependent on opioids after being exposed to these powerful medications following an operation.¹

These findings suggest that as many as 7 million patients could develop an opioid addiction or dependency this year after surgery.¹

Featured: U.S. News & World Report, USA TODAY, CNBC, Orthopedics Today, Sports Illustrated, SPRY Living

The national campaign has generated more than 250 social/traditional media placements and over 475 million media impressions. PlanAgainstPain.com has received 50K page views.³

3. As of October 20, 2016.
Questions?

steve@mitros.us
**Important Safety Information**

- **EXPAREL®** (bupivacaine liposome injectable suspension) is contraindicated in obstetrical paracervical block anesthesia
- In clinical trials, the most common adverse reactions (incidence ≥10%) following EXPAREL administration were nausea, constipation, and vomiting
- EXPAREL is not recommended to be used in the following patient population: patients <18 years old and/or pregnant patients
- Because amide-type local anesthetics, such as bupivacaine, are metabolized by the liver, EXPAREL should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at a greater risk of developing toxic plasma concentrations

**Warnings and Precautions Specific to EXPAREL**

- EXPAREL is not recommended for the following types or routes of administration: epidural, intrathecal, regional nerve blocks, or intravascular or intra-articular use
- Non-bupivacaine-based local anesthetics, including lidocaine, may cause an immediate release of bupivacaine from EXPAREL if administered together locally. The administration of EXPAREL may follow the administration of lidocaine after a delay of 20 minutes or more. Formulations of bupivacaine other than EXPAREL should not be administered within 96 hours following administration of EXPAREL

Full Prescribing Information is available at www.EXPAREL.com.
Important Safety Information (cont’d)

**Warnings and Precautions for Bupivacaine-Containing Products**

- **Central Nervous System (CNS) Reactions:** There have been reports of adverse neurologic reactions with the use of local anesthetics. These include persistent anesthesia and paresthesias. CNS reactions are characterized by excitation and/or depression.

- **Cardiovascular System Reactions:** Toxic blood concentrations depress cardiac conductivity and excitability which may lead to dysrhythmias sometimes leading to death.

- **Allergic Reactions:** Allergic-type reactions (e.g., anaphylaxis and angioedema) are rare and may occur as a result of hypersensitivity to the local anesthetic or to other formulation ingredients.

- **Chondrolysis:** There have been reports of chondrolysis (mostly in the shoulder joint) following intra-articular infusion of local anesthetics, which is an unapproved use.

Full Prescribing Information is available at www.EXPAREL.com.