Managing Acute Non-Cancer Pain in the Hospital

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Disclosures of Financial Relationships

Ramana K. Naidu, MD

has disclosed relationships with an entity producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients.

Speaker’s Bureau
Halyard Health
Abbott
BLISSFUL INSENSATION?

CONGENITAL INSENSITIVITY TO PAIN

DENTAL ABSCESSES

CORNEAL ABRASIONS

BONE FRACTURES

INFECTIONS

BLISSFUL INSENSATION?
CONGENITAL INSENSITIVITY TO PAIN

DENTAL ABSCESS
CORNEAL ABRASIONS
BONE FRACTURES
INFECTIONS

The philosophical dichotomy of acute pain...
The philosophical dichotomy of acute pain...

Warning Signal
Avoidance Reminder
Healing

Suffering
Depression
Helplessness
Definitions

Pain: an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Acute Pain:
• Pain that is limited to the expected period of healing.
• Temporal definitions vary. <1 month. <3 months. <6 months.

Subacute Pain:
• A transitional period between acute and chronic pain where one is concerned the acute pain is becoming persistent.
• Temporal definitions vary. 1-6 months.

Chronic Pain:
• Pain that persists beyond the expected period of healing.
• Temporal definitions vary. >3 months. >6 months.

Types of Acute Non-Cancer Pain

Trauma
• Bone Fractures
• Burns
• Weapons

Surgery

Acute Medical Illness
• Dental Caries
• Infectious Sequelae
• Lumbago
• Headache
• Abdominal Pain

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Global burden of disease: Pain
4.3% of the world’s population is free of disease, injury, or sequelae.

Global prevalence of Dental Caries:
2.4 billion individuals

Global prevalence of Tension-Type Headaches:
1.6 billion individuals

Greatest cause of years lived with disability is:
Low back pain

Do we need to treat or manage or acute non-cancer pain?

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Consequences of untreated/unmanaged acute pain for the patient:
- Autonomic changes
- Endocrinological changes: increased cortisol, insulin resistance, etc.
- Psychological distress
- Development of chronic pain —> all of the above
Do we need to treat or manage or acute non-cancer pain?

Consequences of untreated/unmanaged acute pain for the patient:
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- Psychological distress
- Development of chronic pain —> all of the above

Consequences of untreated/unmanaged pain for the provider:
- Empathetic distress
- Ethical consequences
  - IASP Declaration of Montréal
- Legal Consequences
  - *James, 1991, North Carolina*
  - *Chin, 1998, California*  

* end-of-life cancer pain cases

• What is standard of care in pain management today?
• What is the goal of acute pain management?

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What is standard of care in pain management today?
What is the goal of acute pain management?

1. Manage pain
2. Prevent chronification
Surgery... predicted trauma... an impactful acute pain model
Surgery... predicted trauma... an impactful acute pain model

**Chronification**

**T R A N S I T I O N S  I N  C A R E  &  T R A N S I T I O N S  I N  P A I N**

- PRE
- INTRA
- POST
- POST-DISCHARGE
Surgery... predicted trauma... an impactful acute pain model

TRANSITIONS IN CARE & TRANSITIONS IN PAIN

PRE  INTRA  POST  POST-DISCHARGE
Surgery… predicted trauma… an impactful acute pain model
## Persistent Post-Surgical Pain (PPSP)

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>Approx Incidence PPSP</th>
<th>Approx Incidence of Severe PPSP</th>
<th>Approx Number of Cases Annually in USA</th>
<th>Approx Maximal Number of Patients at Risk for PPSP per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Limb Amputation</td>
<td>30-80%</td>
<td>5-10%</td>
<td>159,000</td>
<td>127,000</td>
</tr>
<tr>
<td>Sternotomy</td>
<td>30-50%</td>
<td>5-10%</td>
<td>598,000</td>
<td>299,000</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>30-40%</td>
<td>10%</td>
<td>280,000</td>
<td>112,000</td>
</tr>
<tr>
<td>Breast Surgery</td>
<td>20-30%</td>
<td>5-10%</td>
<td>479,000</td>
<td>144,000</td>
</tr>
<tr>
<td>Inguinal Herniorraphy</td>
<td>10-50%</td>
<td>2-4%</td>
<td>609,000</td>
<td>304,000</td>
</tr>
<tr>
<td>Total Hip Replacement</td>
<td>12-28%</td>
<td>5%</td>
<td>400,000</td>
<td>112,000</td>
</tr>
<tr>
<td>Total Knee Replacement</td>
<td>8-13%</td>
<td>5%</td>
<td>605,000</td>
<td>78,000</td>
</tr>
<tr>
<td>Cesarean Section</td>
<td>10%</td>
<td>4%</td>
<td>220,000</td>
<td>22,000</td>
</tr>
</tbody>
</table>

Persistent Post-Surgical Pain (PPSP)

- Post-operative pain
- Pre-operative pain
- Acute post-operative pain
- Chronic or persistent post-operative pain

Factors:
- Psychology
- Age
- Genetics
- Surgical technique
- Anesthetic technique
- Adjuvant analgesics
- Anti-hyperalgesics
- Regional anesthesia
- Nerve-sparing technique
- Infection prevention

Modified from Macrae
Analgesia vs Hyperalgesia

FROM:
Non-Nociceptive Environmental Stress Induces Hyperalgesia, Not Analgesia, in Pain and Opioid-Experienced Rats
Cyril Rivat, Emilie Laboureiras, Jean-Paul Laulin, Chloé Le Roy, Philippe Richebé and Guy Simonnet
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Analgesia vs Anti-Hyperalgesia

Analgesia
NO anti-hyperalgesia

COX-Inhibitors
Alpha-2 Agonists
Acetaminophen
Lidocaine

Analgesia BUT Hyperalgesia

Anti-Hyperalgesia
NO analgesia

Low-dose Ketamine
Magnesium

Analgesia and Anti-Hyperalgesia

Regional Anesthesia
Analgesia vs Anti-Hyperalgesia

Analgesia
- NO anti-hyperalgesia
  - COX-Inhibitors
  - Alpha-2 Agonists
  - Acetaminophen
  - Lidocaine

Analgesia BUT Hyperalgesia
- Opioids

Anti-Hyperalgesia
- NO analgesia
  - Low-dose Ketamine
  - Magnesium

Analgesia and Anti-Hyperalgesia
- Regional Anesthesia
The management of pain must involve both analgesia and anti-hyperalgesia.

**Pearl: Analgesia vs Anti-Hyperalgesia**

Analgesia will address acute physiological and psychological adverse effects.

Anti-hyperalgesia will address the chronification of pain and the resultant long duration of physiological and psychological adverse effects.
Overview of Anatomy: Pathological Nociception

Central sensitization
- Memory formation
- Emotional response
- Sympathetic response
- Hypothalamus-Pituitary-Adrenal response
- Attenuation of Descending Inhibition
- Descending facilitation
- Dorsal Horn: Rexed Laminae II, V

Peripheral sensitization
- Dorsal Root Ganglion (DRG) modulation
- Tissue Chemokines

• Americans constitute 4.6% of the world’s population and consume approximately 80% of the world’s opioids.

• Americans consume 99% of the world’s hydrocodone

• There are enough prescribed opioids for each American to take a prescription opioid every 4 hours for a month.

• Estimated 2.1 million Americans with prescription opioid substance use disorder in 2012

• Estimated 467,000 addicted to heroin in 2012.
Number of Deaths per year from Opioids in the United States: 2000-2016

Deaths


Natural and Semi-synthetic opioid analgesics
Methadone
Synthetic opioid analgesics excluding methadone
Heroin
All Opioids

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Deaths


ADVERSE EFFECTS WITH ACUTE USE

RESPIRATORY DEPRESSION
NAUSEA/VOMITING
PRURITUS
URTICARIA
CONSTIPATION
URINARY RETENTION
DELIRIUM
SEDATION
MYOCLONUS
SEIZURES

ADVERSE EFFECTS WITH CHRONIC USE

HYPOGONADISM
IMMUNOSUPPRESSION
INCREASED FEEDING
INCREASED GROWTH HORMONE
WITHDRAWAL
TOLERANCE, DEPENDENCE
ABUSE, ADDICTION
HYPERALGESIA
IMPAIRMENT WHILE DRIVING
Biological Pharmacologics: Opioid Adverse Effects

ADVERSE EFFECTS WITH ACUTE USE

- Respiratory Depression
- Nausea/Vomiting
- Pruritus
- Urticaria
- Constipation
- Urinary Retention
- Delirium
- Sedation
- Myoclonus
- Seizures

ADVERSE EFFECTS WITH CHRONIC USE

- Hypogonadism
- Immunosuppression
- Increased Feeding
- Increased Growth Hormone
- Withdrawal
- Tolerance, Dependence
- Abuse, Addiction
- Hyperalgesia
- Impairment While Driving
Biological Pharmacologics: Opioid Adverse Effects

ADVERSE EFFECTS WITH ACUTE USE

- Respiratory Depression
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- Urinary Retention
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- Sedation
- Myoclonus
- Seizures

- Hypogonadism
- Immunosuppression
- Increased feeding
- Increased growth
- Opioid withdrawal
- Impairment while driving
- Sedation
- Myoclonus
- Seizures
- Hyperalgesia
- Impairment while driving

ADVERSE EFFECTS WITH CHRONIC USE

- Track naloxone respiratory depression event data at your institution as a quality measure

- Hyperalgesia
- Impairment while driving

ACP
ADVERSE EFFECTS WITH ACUTE USE

RESPIRATORY DEPRESSION
NAUSEA/VOMITING
PRURITUS
URTICARIA
CONSTIPATION
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TOLERANCE, DEPENDENCE
ABUSE, ADDICTION
HYPERALGESIA
IMPAIRMENT WHILE DRIVING

Track naloxone respiratory depression event data at your institution as a quality measure.
**Biological Pharmacologics: Opioid-Induced Hyperalgesia (OIH)**

It is the very notion we should NOT use opioids in pain management as it leads to a paradoxical increase in pain.

The Health & Retirement longitudinal cohort saw an increase in severe, moderate, and mild pain from 1998-2010.

The odds of recovery from chronic pain were 4 times higher for non-opioid users than for chronic opioid users.

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A Population-based Cohort Study on Chronic Pain: The Role of Opioids
Per Sjögren, MD, DMSC, Morten Grønbæk, PhD, Vera Peuckmann, PhD, and Ola Ekholm, PhD

---

Follow up regularly with patients to determine whether opioids are meeting treatment goals and whether opioids can be reduced to lower dosage or discontinued.
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1. Limiting opioids dispensed for new acute prescriptions to 7 days.
2. Reducing the dispensation of stronger and long-release opioids.
3. Enhancing pharmacist counseling for new opioid patients.
4. Adding 750 new medication disposal kiosks (doubling the current footprint)
5. Contributing $2 million in additional funds to opioid abuse treatment charities.
The standard unit for opioid risk stratification: Oral Morphine Equivalents (OMEs, MEQs)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ORAL (mg)</th>
<th>PARENTERAL (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine CR/ER (MS Contin) (Kadian) &amp; (Avinza) are</td>
<td>Non-Formulary</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Hydrocodone ER (Zohydro)(Hyslinga)</td>
<td>Non-Formulary</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Oxycodone CR (Oxycontin)</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid)</td>
<td>7.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Hydromorphone ER (Exalgo)</td>
<td>Non-Formulary</td>
<td></td>
</tr>
<tr>
<td>Meperidine (Demerol)*</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>Codeine**</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td>Propoxyphene (Darvon)**</td>
<td>Non-Formulary</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone (Opana)</td>
<td>Non-Formulary</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone ER (Opana ER)</td>
<td>Non-Formulary</td>
<td></td>
</tr>
<tr>
<td>Levorphanol</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Fentanyl (Sublimaze)</td>
<td>-</td>
<td>0.1</td>
</tr>
<tr>
<td>Fentanyl TTS (Duragesic)</td>
<td></td>
<td>See Separate Recommendations</td>
</tr>
<tr>
<td>Tramadol (Ultrim)</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>Tramadol ER (Ultrim ER)</td>
<td>Non-Formulary</td>
<td></td>
</tr>
<tr>
<td>Tapentadol (Nucynta)</td>
<td>Non-Formulary</td>
<td></td>
</tr>
<tr>
<td>Tapentadol ER (Nucynta ER)</td>
<td>Non-Formulary</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine (Subutex)</td>
<td>Non-Formulary</td>
<td>0.4 (sublingual)</td>
</tr>
<tr>
<td>Buprenorphine TTS (Butrans)</td>
<td>Non-Formulary</td>
<td>See Separate Recommendations</td>
</tr>
<tr>
<td>Nalbuphine (Nubain)</td>
<td>Non-Formulary</td>
<td></td>
</tr>
<tr>
<td>Pentazocine (Talwin)</td>
<td>Non-Formulary</td>
<td></td>
</tr>
</tbody>
</table>

Calculate your patient’s OMEs prior to admission, daily during admission, and monitor trends.

Use a table, app, spreadsheet, EMR, etc.

Risk associated with outpatient use of opioids is directly related to daily dose.

Acute can become chronic.

The unit is becoming part of regulation.

Basic Principles of Patient-Controlled Analgesia

*Encourage use only when in severe pain, and oral route of administration early.*
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What are the best practices for transitions from inpatient to outpatient pain management?

1) Reiterate the message that the patient needs to get off of opioids sooner than later. If they are on them for longer than 7-10 days, there is something “awry,” and they should seek expert opinion.

2) Patients should understand how much they are on (OMEs) and monitor trends.

3) Provide patients with information on risks and benefits of use.

4) Patients should be given information about how controlled substances should be locked/secured
   1) how they may not be given to others and used only as prescribed
   3) where controlled substances should be disposed
   4) summary of the state’s laws with regards to driving or operating machinery

5) Provide patients and their primary care providers with outpatient pain and addiction clinic information in case they are concerned about the development of chronic pain, or addiction.

Biological Pharmacologics: Opioids
Opioid Metabolism

CYP4502D6

Opioid Metabolism

HYDROCODONE

HYDROMORPHONE

HYDROMORPHONE-3-GLUCURONIDE

HYDROMORPHONE-3-GLUCURONIDE

HYDROMORPHONE-3-GLUCURONIDE

HYDROMORPHONE-3-GLUCURONIDE

CODEINE

MORPHINE

MORPHINE-3-GLUCURONIDE

MORPHINE-6-GLUCURONIDE

MORPHINE-6-GLUCURONIDE

MORPHINE-6-GLUCURONIDE

MORPHINE-6-GLUCURONIDE

OXYCODONE

OXYMORPHONE

OXYMORPHONE-3-GLUCURONIDE

OXYMORPHONE-3-GLUCURONIDE

OXYMORPHONE-3-GLUCURONIDE

OXYMORPHONE-3-GLUCURONIDE

TRAMADOL

O-DESMETHYL-TRAMADOL

UDP-glucuronosyltransferase-2B7

glucuronidation
## Biological Pharmacologic: Opioids
### Opioid Metabolism

<table>
<thead>
<tr>
<th>PHENOTYPES</th>
<th>Celecoxib</th>
<th>Citalopram</th>
<th>Codeine, Hydrocodone, Oxycodone, Tramadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>% POPULATION 2C9</td>
<td>% POPULATION 2C19</td>
<td>% POPULATION 2D6</td>
<td></td>
</tr>
<tr>
<td>ULTRA RAPID METABOLIZER UM</td>
<td>N/A</td>
<td>30%</td>
<td>7%</td>
</tr>
<tr>
<td>EXTENSIVE METABOLIZER EM</td>
<td>60%</td>
<td>14-44%</td>
<td>48%</td>
</tr>
<tr>
<td>INTERMEDIATE METABOLIZER IM</td>
<td>&gt;35%</td>
<td>24-36%</td>
<td>35%</td>
</tr>
<tr>
<td>POOR METABOLIZER PM</td>
<td>2-4%</td>
<td>2-20%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Opioids are... “powerful” “strong”

“painkillers”
Opioids can be effective for **static** pain, but are **that** not effective for **dynamic** pain. Most acute pain is dynamic pain - pain associated with movement.

Consider the importance of dynamic pain management for:

- DVT/PE prophylaxis
- Atelectasis/pneumonia prophylaxis
- Urinary catheterization removal

<table>
<thead>
<tr>
<th>Analgesic and dose</th>
<th>People in comparison (n)</th>
<th>Proportion with 50% pain relief (%)</th>
<th>NNT</th>
<th>Lower CI</th>
<th>Higher CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoricoxib 180/240</td>
<td>248</td>
<td>77</td>
<td>1.5</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Etoricoxib 100/120</td>
<td>500</td>
<td>70</td>
<td>1.6</td>
<td>1.5</td>
<td>1.8</td>
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<tr>
<td>Valdecoxib 40</td>
<td>473</td>
<td>73</td>
<td>1.6</td>
<td>1.4</td>
<td>1.8</td>
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<tr>
<td>Dipyrone</td>
<td>113</td>
<td>79</td>
<td>1.6</td>
<td>1.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Ibuprofen 800</td>
<td>76</td>
<td>100</td>
<td>1.6</td>
<td>1.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Ketorolac 20</td>
<td>69</td>
<td>57</td>
<td>1.8</td>
<td>1.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Ketorolac 60 (intramuscular)</td>
<td>116</td>
<td>56</td>
<td>1.8</td>
<td>1.5</td>
<td>2.3</td>
</tr>
<tr>
<td>Diclofenac 100</td>
<td>411</td>
<td>67</td>
<td>1.9</td>
<td>1.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Piroxicam 40</td>
<td>30</td>
<td>80</td>
<td>1.9</td>
<td>1.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Paracetamol 1000 + codeine 60</td>
<td>197</td>
<td>57</td>
<td>2.2</td>
<td>1.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Oxycodone IR 5 + paracetamol 500</td>
<td>150</td>
<td>60</td>
<td>2.2</td>
<td>1.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Bromfenac 25</td>
<td>370</td>
<td>51</td>
<td>2.2</td>
<td>1.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Rofecoxib 50</td>
<td>675</td>
<td>54</td>
<td>2.3</td>
<td>2.0</td>
<td>2.6</td>
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<tr>
<td>Diclofenac 50</td>
<td>738</td>
<td>63</td>
<td>2.3</td>
<td>2.0</td>
<td>2.7</td>
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<tr>
<td>Naproxen 440</td>
<td>257</td>
<td>50</td>
<td>2.3</td>
<td>2.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Oxycodone IR 15</td>
<td>60</td>
<td>73</td>
<td>2.3</td>
<td>1.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Ibuprofen 600</td>
<td>203</td>
<td>79</td>
<td>2.4</td>
<td>2.0</td>
<td>4.2</td>
</tr>
<tr>
<td>Ibuprofen 400</td>
<td>4703</td>
<td>56</td>
<td>2.4</td>
<td>2.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Aspirin 1200</td>
<td>279</td>
<td>61</td>
<td>2.4</td>
<td>1.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Oxycodone IR 10 + paracetamol 650</td>
<td>315</td>
<td>66</td>
<td>2.6</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Ketorolac 10</td>
<td>790</td>
<td>50</td>
<td>2.6</td>
<td>2.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Ibuprofen 200</td>
<td>1414</td>
<td>45</td>
<td>2.7</td>
<td>2.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Oxycodone IR 10 + paracetamol 1000</td>
<td>83</td>
<td>67</td>
<td>2.7</td>
<td>1.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Piroxicam 20</td>
<td>280</td>
<td>63</td>
<td>2.7</td>
<td>2.1</td>
<td>3.8</td>
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<tr>
<td>Diclofenac 25</td>
<td>204</td>
<td>54</td>
<td>2.8</td>
<td>2.1</td>
<td>4.3</td>
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<tr>
<td>Morphine 10 (IM)</td>
<td>946</td>
<td>50</td>
<td>2.9</td>
<td>2.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Biological Pharmacologics: Cyclo-Oxygenase Inhibitors (COX-inhibitors) (historically known as NSAIDs)

**ARACHIDONIC ACID**

- **COX-1**
  - Decreased Stomach Acid
  - Increased Mucous
  - Vasodilator
  - Hyperalgesic
  - Inhibits Platelet Aggregation
  - Sleep/Wake Cycle
  - Vasodilator
  - Inhibits Platelet Aggregation

- **COX-2**
  - Decreased Stomach Acid
  - Increased Mucous
  - Vasodilator
  - Hyperalgesic
  - Inhibits Platelet Aggregation

- **TXA2**
  - Platelet Aggregation
  - Vasoconstrictor

- **PGE2**
  - Vasodilator
  - Hyperalgesic
  - Inhibits Platelet Aggregation

- **PGI2**
  - Vasodilator
  - Hyperalgesic
  - Inhibits Platelet Aggregation

- **PGD2**
  - Vasodilator
  - Hyperalgesic
  - Inhibits Platelet Aggregation

- **PGF2**
  - Bronchoconstrictor
  - Myometrial Contraction

**COX-1**
- Constitutive. Found in all tissues esp GI tract

**COX-2**
- Inducible. Kidney, GI tract, CNS, endothelium
Biological Pharmacologics: Cyclo-Oxygenase Inhibitors (COX-inhibitors) (historically known as NSAIDs)

ARACHIDONIC ACID

**COX-1**
- Constitutive. Found in all tissues esp GI tract
- TXA2: Platelet Aggregation Vasoconstrictor
- PGE2: Decreased Stomach Acid, Increased Mucous, Vasodilator, Hyperalgesic
- PGI2: Vasodilator, Hyperalgesic, Inhibits Platelet Aggregation
- PGD2: Sleep/Wake Cycle, Vasodilator, Inhibits Platelet Aggregation
- PGF2: Bronchoconstrictor, Myometrial Contraction

**COX-2**
- Inducible. Kidney, GI tract, CNS, endothelium
- PGE2: Decreased Stomach Acid, Increased Mucous, Vasodilator, Hyperalgesic
- PGI2: Vasodilator, Hyperalgesic, Inhibits Platelet Aggregation
Biological Pharmacologics: Cyclo-Oxygenase Inhibitors (COX-inhibitors) (historically known as NSAIDs)

Biological Pharmacologics: Cyclo-Oxygenase Inhibitors (COX-inhibitors) (historically known as NSAIDs)

Out-of-Hospital Cardiac Arrest (OHCA) associated with NSAID use in the prior 30 days.

Statistically significant:
- Use of diclofenac OR 1.5
- Use of ibuprofen OR 1.3

Not statistically significant:
- Use of naproxen OR 1.29
- Use of celecoxib OR 1.13
- Use of rofecoxib OR 1.28
Steroids (glucocorticoids) reduce pain by reducing prostaglandin synthesis. However, their side effect profile is significant and should not be used for non-surgical, acute non-cancer pain unless other options are not effective or possible. They should not be used chronically.

Dexamethasone is routinely used in the peri-operative arena for post-operative nausea and vomiting. It is associated with a reduction in NRS/VAS and opioid consumption, 8mg > 4 mg.

Side effects:
• Increased weight gain
• Proximal muscle weakness
• Insomnia
• Gastrointestinal side effects
• Gastrointestinal bleeding
• Psychiatric side effects
• Osteoporoses with long-term use
• Infections
• Hyperglycemia
• Cushing Syndrome
• Thromboembolism
Biological Pharmacologics: Acetaminophen/Paracetamol

Biological Pharmacologic: Acetaminophen/Paracetamol

Aniline analgesic.
Mechanism of action remains unknown. The proposed COX-3 mechanism is controversial.

Safety:
4 grams/day limit is safe in adults. Lean-body weight based: 60mg/kg/day
Prospective trials involving central pain related to stroke shows safety up to 6g/day

- Hepatitis: if indolent, 4 g/day ok
- Alcoholism: if not drinking >2 drinks/day, 4g/day ok
- Combination Hepatitis and Alcoholism: depends. 2g/day limit or avoid?

Caution in combination with CYP450 3A4 /2E1 inhibitors:
consider effect of coumadin, anticonvulsants, and antipsychotics
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Efficacy:
Single dose oral paracetamol/acetaminophen provides effective pain relief for about half of patients after surgery. (Cochrane, 2008).
Intravenous paracetamol provided pain relief for 36% of patients after surgery. (Cochrane, 2016).

Cost:
Oral acetaminophen is OTC and costs pennies.
Intravenous acetaminophen, depending on your contract, $100s/day

Cochrane database Syst. Rev. CD007126

• Toms, L. et al. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults (Review) Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. 4–6 (2012).
• Tzortzopoulou, A. et al. Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. Cochrane database Syst. Rev. CD007126
Clonidine
Effective in animal model analgesic trials. While it can be effective in reducing pain and opioid consumption, it is limited by its side effect of bradycardia and hypotension.

Dexmedetomidine:
(alph-2 agonist) 1620: 1 (alpha-1 agonist) can be used for both analgesic and sedative properties. It is particularly useful in patients with heroin abuse because it helps with withdrawal symptoms, provides analgesia, and calms/sedates. The drug crosses the BBB and has been studied via several routes of administration: IM/IV/IN/Regional though not PO.

It is expensive, and can only be used intravenously in monitored settings due to the same concerns regarding bradycardia and hypotension.

Still early in our experience as far as the literature. We have support for its use, particularly in the ICU or in pediatrics. Its benefit remains during the infusion, and does not seem to provide longer-term benefit due to an elimination half-life of 2 hours.
Gabapentinoids (Gabapentin and Pregabalin): MOA: alpha-2-delta ligand antagonists (calcium channel membrane stabilizer). Useful in peri-operative pain management resulting in reduce opioid consumption and potentially in reducing the development of chronic pain after surgery.

Use is limited with side effects which include sedation, cognitive impairment, tremor, hallucinations, swelling, visual changes, dry mouth, etc. Use particular caution in the geriatric population and in patients with renal impairment.

More benefit and adverse effects seen with higher dosing.

SNRI/SSRI Antidepressants (Duloxetine, Venlafaxine, Desvenlafaxine, Milancipran, etc.) Have not been proven to be useful in acute pain.


Ketamine is an anesthetic drug (Controlled Substance III). It exerts various effects depending on the dose and has many mechanisms of action:

- NMDA antagonist
- Kappa opioid agonist
- Potentiates antinociception of mu-opioid effect
- Inhibits alpha-6 nicotinic receptors

In addition to its impact on anti-hyperalgesia, it is also being widely studied for anti-depression and may play a role in the affective component of pain perception.

Do not use, or exercise caution in individuals with schizophrenia, schizoaffective disorder, post-traumatic stress disorder, Cluster A personality disorders.

<table>
<thead>
<tr>
<th>USE</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANESTHETIC</td>
<td>2-5 mg/kg</td>
</tr>
<tr>
<td>DISSOCIATIVE (PEDI)</td>
<td>1-2 mg/kg</td>
</tr>
<tr>
<td>CHRONIC PAIN INFUSION</td>
<td>0.5 - 1 mg/kg/hr</td>
</tr>
<tr>
<td>LOW-DOSE INFUSION for OIH</td>
<td>0.1-0.2 mg/kg/hr</td>
</tr>
<tr>
<td></td>
<td>1-3 mcg/kg/min</td>
</tr>
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</table>
Biological Pharmacologics: NMDA-antagonists: Ketamine

Nystagmus
Tremor
Psychomotor Agitation
Hallucinations
Hypersalivation
Dissociative State
Coma
Sympathomimetic Effects
A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain

E. D. McNicol¹, R. Schumann² and S. Haroutounian³

¹Department of Anesthesiology and Pharmacy, Tufts Medical Center, Boston, MA, USA; ²Department of Anesthesiology, Tufts Medical Center, Boston, MA, USA; and ³Department of Anesthesiology, Washington University in St. Louis, St. Louis, MO, USA

17 studies, with variable timing and dosing, demonstrated statistically significant reductions in the development of PPSP at 3 and 6 months.

Comparisons of pain severity did not reach statistical significance.
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Comparisons of pain severity did not reach statistical significance.
Biological Pharmacologics: Voltage-Gated Sodium Channel Blockade: Lidocaine Infusion.

Lidocaine is an anti-arrhythmic and local anesthetic drug. It relieves pain at doses from 1-2 mg/kg/hr.

It has been widely studied in colectomy, laparoscopic surgery, and reduces opioid consumption. In chronic pain, it has been studied for CRPS, headache, and other neuropathic pain conditions such as erythromelalgia, where it can be the “cure” for sodium channelopathy.

Its effect lasts during the infusion and shortly wears off.

Do not use, or exercise caution in individuals where sodium channel cardiac blockade would be problematic, e.g. sinoatrial block or 2nd or 3rd degree block.
<table>
<thead>
<tr>
<th>Biological &amp; Multi-Modal Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
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<tr>
<td>Resp Depression</td>
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<tr>
<td>Sedation</td>
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<tr>
<td>Delirium</td>
</tr>
<tr>
<td>N/V</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Gastritis</td>
</tr>
<tr>
<td>Renal Dysfunction</td>
</tr>
<tr>
<td>Platelet Inhib</td>
</tr>
<tr>
<td>LAST</td>
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</table>
Biological Multi-Modal Analgesia

Analgesia
Resp Depression
Sedation
Delirium
N/V
Constipation
Pruritus
Gastritis
Renal Dysfunction
Platelet Inhib
LAST
Biological Multi-Modal Analgesia

De Oliveira, 2012. Anesth Analg
Biological Multi-Modal Analgesia

Analgesia
Resp Depression
Sedation
Delirium
N/V
Constipation
Pruritus
Gastritis
Renal Dysfunction
Platelet Inhib
LAST

Biological Multi-Modal Analgesia

Blaudszun, 2012. Anesthesiology
Biological Multi-Modal Analgesia

Kehlet, 2005. Anesthesiology
Biological Multi-Modal Analgesia

- Analgesia
- Resp Depression
- Sedation
- Delirium
- N/V
- Constipation
- Pruritus
- Gastritis
- Renal Dysfunction
- Platelet Inhib
- LAST
<table>
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<tr>
<th>RECEPTOR</th>
<th>MEDICATION EXAMPLES</th>
<th>ADVERSE EFFECTS</th>
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<tbody>
<tr>
<td>alpha-2</td>
<td>Dexmedetomidine, Clonidine</td>
<td>Bradycardia, Dry Mouth</td>
</tr>
<tr>
<td>COX-inhibition</td>
<td>Ketorolac, Ibuprofen, Celecoxib, APAP</td>
<td>GI Ulcers, Renal Dysn, Bleeding</td>
</tr>
<tr>
<td>Mu-Opioid</td>
<td>Morphine, Fentanyl</td>
<td>N/V, Constipation, Resp Depression, Pruritus, Urinary Ret, Delirium,</td>
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<tr>
<td>Kappa-Opioid</td>
<td>Nalbuphine</td>
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</tr>
<tr>
<td>GABA-A</td>
<td>Diazepam, Lorazepam</td>
<td>Sedation, Delirium, Resp Dep c Op</td>
</tr>
<tr>
<td>Na-Channel</td>
<td>Local Anesthetics</td>
<td>LAST</td>
</tr>
<tr>
<td>NMDA-Antagonism</td>
<td>Ketamine, Memantine</td>
<td>Depends. Psychomimetic FX</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>Dexamethasone</td>
<td>Hyperglycemia, Acute Angle Glaucoma, Perineal Dysesthesia</td>
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<tr>
<td>Ca-Channel Neuropathic</td>
<td>Gabapentin, Pregabalin</td>
<td>Sedation, Impaired Cognition</td>
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<tr>
<td>Na-Channel Neuropathic</td>
<td>Topiramate, Carbamazepine</td>
<td>Sedation, Nephrolithias</td>
</tr>
<tr>
<td>SNRI Antidepressant</td>
<td>Duloxetine, Venlafaxine</td>
<td>Insomnia, Malaise, Stomatitis,</td>
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</tbody>
</table>
Biological
Regional Anesthesia

NEURAXIAL
Intrathecal
Epidural, Caudal

PARA-NEURAXIAL
Paravertebral
Lumbar Plexus

PROXIMAL PERIPHERAL NERVE
Interscalene, Supraclavicular, Infraclavicular
Intercostal
Transversus Abdominis Plane (TAP)

DISTAL PERIPHERAL NERVE
Median, Radial, Ulnar
Femoral, Saphenous
Sciatic, Tibial, Common Peroneal
Regional anesthesia is the most impactful modality of acute pain management. It can eliminate acute pain.

Regional anesthesia can significantly reduce opioid consumption

Regional anesthesia reduces the development of chronic pain after surgery.

Epidural analgesia reduces persistent post-surgical pain after thoracotomy
Paravertebral analgesia reduces persistent post-surgical pain after mastectomy

Risks include nerve injury, hematoma, infectious complications, local anesthetic systemic toxicity, cardiovascular collapse, anaphylaxis
Biological Complementary and Integrative Medicine

- MUSIC
- TOUCH
- MASSAGE
- ACUPUNCTURE
- ACUPRESSURE
- HYPNOSIS
- BIOFEEDBACK
- GUIDED IMAGERY
- DISTRACTION
- CREATIVE ARTS
- HERBAL THERAPY
- HOMEOPATHY
The Acute Pain Service

The first Acute Pain Service started at the University of Washington in 1986 and they published their development of an anesthesiology-based postoperative pain management service in 1988.

An Acute Pain Service (APS) can be directed by:
- Anesthesiologists
- Internal Medicine
- Family Practice
- Emergency Medicine
- Psychiatry
- Neurology
- Physiatrists
- Nurse Practitioners

Goals:
- Patient safety: Reduce complications
- Reduce length of stay
- Improve patient satisfaction

Economics:
Will not be profitable with direct billing. It will reduce very expensive complications, and therefore, would need to be supported by the hospital/medical center.
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What are the median number of hours devoted to pain education in American medical schools over 4 years?
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United States: 9 hours
Canada: 19.5 hours
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IT IS A CONTRIBUTING COMPONENT TO OUR OPIOID EPIDEMIC THIS MUST CHANGE.

ACGME Fellowship in Acute Pain Medicine and Regional Anesthesia Starting in July 2017. 1 year duration after a residency in anesthesiology.
ICD-11 will have a **persistent post-surgical** and **persistent post-trauma** pain code. This will have an impact in the recognition and management of chronified pain.

We have no outcome parameters from CMS, the Joint Commission, or insurers that look specifically at chronic pain after surgery or trauma.

Europe does because of single payer systems and this is where most of the literature regarding PPSP or chronification comes from.
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The Future of Acute Pain Medicine
The need for long-term outcomes. Morbidity vs Mortality.

QUALITY-ADJUSTED LIFE YEARS (QALYs)

QUALITY OF LIFE

0% 100%

QUALITY OF LIFE

AGE (YEARS) 20 40 60 80

Surgery

Trauma

ACP
The Future of Acute Pain Medicine
The need for long-term outcomes. Morbidity vs Mortality.

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QUALITY OF LIFE

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QUALITY-ADJUSTED LIFE YEARS (QALYs)

QUALITY OF LIFE

TRAUMA

Surgery

AGE (YEARS) 20 40 60 80

100% 0%
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AGE (YEARS)

QUALITY OF LIFE

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100%

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Surgery

Trauma
Conclusion

Future efforts should go into:
• Public health education, eg smoking cessation
• Healthcare provider education
• Legislation/Regulation
• Non-pharm, Non-interventional resources
• Outcomes
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Understand the differences between analgesia and anti-hyperalgesia.

- Opioids have a role in acute pain medicine, but... they are not the solution to pain. They, in fact, can make pain worse over time.
- Multimodal Analgesia is important to reduce consequential side effects
- Non-Pharm and Non-Interventional modalities should always be used.
- Regional anesthesia can be impactful, though must weigh risks.
- Goals are to MANAGE PAIN and PREVENT CHRONIC PAIN
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• Goals are to MANAGE PAIN and PREVENT CHRONIC PAIN

Thank You
Clinical Vignette

An 64 y/o gentleman with h/o rheumatoid arthritis, CKD (eGFR=43 ml/min/1.73m²), CAD, tripped over a cord at night in trying to go to the bathroom at home. In the ED, he has found to have a femoral neck fracture and orthopedic surgery is determining whether he is a surgical candidate. You are called to evaluate and manage his acute pain.

He is supine in the gurney, crying, stating he has 10/10 pain. He is able to converse and is alert, aware, and oriented x3. Already, he has received morphine 10mg IV approximately 10 minutes before you arrive.

PMH:
Inflammatory Bowel Disease
CKD (Stage 3B)
CAD, had drug-eluting stent in 2013.
Chronic inflammatory and osteoarthritis of shoulders, hips, and knees.

PSH:
s/p colectomy when he was 38 years old. Has been on chronic opioid therapy since.

Current Meds:
Aspirin 162mg PO daily
Valsartan 80mg PO BID
Metoprolol 50mg PO BID
Acetaminophen 650mg PO every 6 hours as needed for pain
Morphine IR 15mg PO every 6 hours as needed pain
Naloxegol 12.5mg PO daily

Allergies:
Codeine

Social
Quit smoking 10 years ago
Consumes <2 alcoholic beverages per week
Lives alone.
Clinical Vignette

What is your next step for managing his acute pain?
Clinical Vignette

What is your next step for managing his acute pain?

Possible questions:
1) Ask him on average how much morphine or any other opioid he consumes?
Answer: “I take the morphine 15mg 4 times a day. But I used to be OxyContin 40mg PO 3 times a day like a month ago.”
What are his OMEs? Is that high risk? What is the OME of what he received, morphine 10mg IV?

2) Where is your pain?
Answer: “My hip and thigh and shoulder…”

3) Can you describe these three pains? Which one is the worst?
Answer: “The shoulder feels achy, it’s not bad though. The hip is a sharp stabbing pain and the thigh is a strong ache. It’s 10/10, can you get me something?”

4) Why do you take morphine on a daily basis?
Answer: “Shoulder pain I’ve had for years.”

5) Are you taking any blood thinners besides the aspirin?
Answer: No

6) Do you have anyone who lives with you or supports you?
Answer: “My ex-wife. They already called her and she is coming in.”

6) Consider: Regional anesthesia, low-dose ketamine infusion, acetaminophen, oral opioid therapy that must be at least what he was taking at home. Would you give a COX-inhibitor? Would you give a gabapentinoid?
You can consider lidocaine, dexmedetomidine as well, but these should only be used in the ICU, and are not warranted unless pain was too difficult to manage with the current regimen.
Ice/heat, music, guided imagery, therapy dog, possibly acupuncture/acupressure, psychological evaluation and social worker evaluation.
Clinical Vignette

He has a fascia iliaca catheter placed and the next morning he has a femoral intramedullary nail placed by orthopedic surgery. Post-operatively, the fascia iliaca catheter is re-inserted. He has been maintained on low-dose ketamine and is taking morphine IR 15mg every 4 hours as needed.

He is doing well with PT/function, satisfaction, POD 0, 1, and is told he can go home on POD2 with home health.

The anesthesiologist removes the regional anesthesia catheter, you stop the ketamine infusion, and he states the pain has returned to 7/10.

What do you do?
Clinical Vignette

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What do you do?
You increase the morphine IR to 15-30mg PO q4h PRN.

What do you tell him on discharge?
Opioid consumption reduction, Opioid-induced hyperalgesia, Discuss opioid weaning with your surgeon and PCP
Is he addicted? Screening tools (COMM) can be used by his PCP
Would you give him COX-inhibitors now? What about taking them with his aspirin?
Would you give him anything else besides acetaminophen and morphine? Gabapentin?
What would you do for his chronic shoulder pain?