Managing 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
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.

**Cancer Pain:**

Pain Assessment and Risk Screening

Intensity/Severity:
- Verbal Rating Scale (VRS)
- Numerical Rating Scale (NRS)
- Visual Analog Scale (VAS)
- Wong-Baker (Faces)
- FLACC
- Pain Assessment in Advanced Dementia Scale (PAINAD)

Quality:
- Descriptors
- Brief Pain Inventory
- McGill Pain Questionnaire

“Objective”
- fMRI
- Biological Pattern Algorithms

Psychological:
- Hospital Anxiety and Depression Scale
- Pain Catastrophization Scale
- Beck Depression Inventory

Substance Use/Misuse/Abuse:
- Opioid Risk Tool
- SOAPP-R
- COMM
- CAGE-AID
- Pasero Opioid Sedation Scale

Function:
- Oswestry Disability Index
- World Health Organization Disability Assessment Scale
- Timed Up and Go
- PROMIS, KOOS, WOMAC (location-specific)
Types of Acute Non-Cancer Pain

Surgery

Trauma
• Bone Fractures
• Burns
• Weapons

Acute Medical Illness
• Dental Caries
• Infectious Sequelae
• Lumbago
• Headache
• Abdominal Pain
Types of Chronic Non-Cancer Pain

- Lumbago
- Headaches
- Neck Pain/Cervicalgia
- Abdominal Pain
- Joint Pain
- Neuropathy
- Post-Surgical Pain Syndromes
- Pelvic Pain
- Psychological Syndromes
- Other Syndromes

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

Types of Cancer Pain

Tumor-Related
  Mass Effect, Swelling, Nerve Irritation, Bony Mets

Surgery
  Post-Surgical Pain Syndromes

Radiation
  Neuritis and Neuropathy

Chemotherapy
  Headache, Peripheral Neuropathy

Acute Pain

Non-Cancer Chronic Pain Conditions
Do we need to manage pain?

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

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?

Chronification... yes, it’s a word.

the process by which acute pain becomes chronic pain
A neologism ubiquitous in the pain literature; commonest use in regards to migraine.

## 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)

- **anxiety**
- **catastrophization**
- **depression**

**psychology**

**age**

**pre-operative pain**

**acute post-operative pain**

**genetics**

- **surgical technique**
- **anesthetic technique**

**nerve-sparing technique**

- **infection prevention**

**chronic or persistent post-operative pain**

- **adjuvant analgesics**
- **anti-hyperalgesics**
- **regional anesthesia**

Modified from Macrae
Analgesia vs Hyperalgesia

FROM:
Non-Nociceptive Environmental Stress Induces Hyperalgesia, Not Analgesia, in Pain and Opioid-Experienced Rats
Cyril Rivat, Emilie Laboureyras, Jean-Paul Lassè, Choé Le Roy, Philippe Richebé and Guy Simonet
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.

*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: Nociception

1662
RENÉ DESCARTES
TREATISE OF MAN
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

Biological Pharmacologics: Opioids
Biological Pharmacologics: Opioids

4,000 BCE - 1840

SUMERIAN CUNEIFORM
1500 BCE
HOMER THE ODYSSEY
0
1500
1809
MORPHINE ISOLATION

Biological Pharmacologic: Opioids

Biological Pharmacologics: Opioids

2000-2017

5th VITAL SIGN

CDC RAISES CONCERNS

DECLARATION OF MONTREAL

PURDUE LAWSUIT

DEA CHANGES ACETAMINOPHEN-CONTAINING OPIOIDS to SCHEDULE II from SCHEDULE III

CDC GUIDELINES

2000

2007

2010

2014

2016
Biological Pharmacologics: Opioids. America today.

- 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**

GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

DETERMINING WHEN TO INITIATE OR CONTINUE OPIOIDS FOR CHRONIC PAIN

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.

2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy.

CLINICAL REMINDERS
- Opioids are not first-line or routine therapy for chronic pain
- Establish and measure goals for pain and function
- Discuss benefits and risks and availability of nonopioid therapies with patient

GUIDELINE FOR PRESCRIBING OPIOIDS FOR CHRONIC PAIN

POCKET GUIDE: TAPERING OPIOIDS FOR CHRONIC PAIN

Follow up regularly with patients to determine whether opioids are meeting treatment goals and whether opioids can be reduced to lower dosage or discontinued.

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.

LEARN MORE  |  www.cdc.gov/drugoverdose/prescribing/guideline.html

CDC's Guideline for Prescribing Opioids for Chronic Pain is intended to improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder and overdose. The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care.

Recommendations focus on pain lasting longer than 3 months or past the time of normal tissue healing, outside of active cancer treatment, palliative care, and end-of-life care.

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### Biological Pharmacologic: Opioids. Remember, you have them within you.

<table>
<thead>
<tr>
<th></th>
<th><strong>u</strong></th>
<th><strong>d</strong></th>
<th><strong>k</strong></th>
<th><strong>nociceptin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endogenous Ligand</strong></td>
<td>Endorphin</td>
<td>Enkephalin</td>
<td>Dynorphin</td>
<td>Nociceptin</td>
</tr>
<tr>
<td><strong>Exogenous Agonist</strong></td>
<td>Morphine</td>
<td>Methadone</td>
<td>Fentanyl</td>
<td>Deltorphin</td>
</tr>
<tr>
<td><strong>Exogenous Antagonist</strong></td>
<td>Naloxone</td>
<td>Naltrexone</td>
<td>Naloxone</td>
<td>Naloxone</td>
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<table>
<thead>
<tr>
<th><strong>Effect</strong></th>
<th><strong>Receptors</strong></th>
<th><strong>Agonists</strong></th>
<th><strong>Antagonists</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia Supraspinal</td>
<td>u,d,k</td>
<td>analgesia</td>
<td>no effect</td>
</tr>
<tr>
<td>Analgesia Spinal</td>
<td>u,d,k</td>
<td>analgesia</td>
<td>no effect</td>
</tr>
<tr>
<td>Respiratory Function</td>
<td>u</td>
<td>decrease</td>
<td>no effect</td>
</tr>
<tr>
<td>Gastrointestinal Tract</td>
<td>u,k</td>
<td>decrease</td>
<td>no effect</td>
</tr>
<tr>
<td>Psychotomimesis</td>
<td>k</td>
<td>increase</td>
<td>no effect</td>
</tr>
<tr>
<td>Feeding</td>
<td>u,d,k</td>
<td>increase</td>
<td>decrease</td>
</tr>
<tr>
<td>Sedation</td>
<td>u,k</td>
<td>increase</td>
<td>no effect</td>
</tr>
<tr>
<td>Prolactin</td>
<td>u</td>
<td>increase</td>
<td>decrease</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>u/d</td>
<td>increase</td>
<td>decrease</td>
</tr>
</tbody>
</table>
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
- Abnormal Tone
- Impaired Feeding
- Impaired Growth
- Tolerance, Dependence, Addiction
- Impairment While Driving
- Hyperalgesia
- Impairment

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.

References:
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</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Morphine CR/ER (MS Contin) (Kadian) &amp; (Avinza) are Non-Formulary</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30</td>
<td>-</td>
</tr>
<tr>
<td>Hydrocodone ER (Zohydro)(Hyslinga)</td>
<td>30</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 (Lagilo)</td>
<td>7.5</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>200</td>
<td>-</td>
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<tr>
<td>Oxymorphone (Opana)</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Oxymorphone ER (Opana ER)</td>
<td>10</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 (Durasenic)</td>
<td>See Separate Recommendations</td>
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<tr>
<td>Tramadol (Ultrace)</td>
<td>120</td>
<td>10</td>
</tr>
<tr>
<td>Tramadol ER (Ultrace ER)</td>
<td>120</td>
<td>-</td>
</tr>
<tr>
<td>Tapentadol (Nucynta)</td>
<td>120</td>
<td>-</td>
</tr>
<tr>
<td>Tapentadol ER (Nucynta ER)</td>
<td>120</td>
<td>-</td>
</tr>
<tr>
<td>Buprenorphine (Subutex)</td>
<td>Non-Formulary</td>
<td>0.4 [sublingual]</td>
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<tr>
<td>Buprenorphine TTS (Butrans)</td>
<td>Non-Formulary</td>
<td>See Separate Recommendations</td>
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<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.

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

Acute can become chronic.

The unit is becoming part of regulation.

Biological Pharmacology: Opioids
Opioid Metabolism

CYP4502D6

**glucuronidation**
UDP-glucuronosyltransferase-2B7

**CODEINE**
- HYDROCODONE
- OXYCODONE
- TRAMADOL

**MORPHINE**
- HYDROMORPHONE
- OXYMORPHONE
- O-DESMETHYL-TRAMADOL

**MORPHINE-3-GLUCURONIDE**
**MORPHINE-6-GLUCURONIDE**

**HYDROMORPHONE**
- HYDROMORPHONE-3-GLUCURONIDE

**OXYMORPHONE**
- OXYMORPHONE-3-GLUCURONIDE
<table>
<thead>
<tr>
<th>PHENOTYPES</th>
<th>Celecoxib</th>
<th>Citalopram</th>
<th>Codeine, Hydrocodone, Oxycodone, Tramadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULTRA RAPID METABOLIZER</td>
<td>UM</td>
<td>N/A</td>
<td>30%</td>
</tr>
<tr>
<td>EXTENSIVE METABOLIZER</td>
<td>EM</td>
<td>60%</td>
<td>14-44%</td>
</tr>
<tr>
<td>INTERMEDIATE METABOLIZER</td>
<td>IM</td>
<td>&gt;35%</td>
<td>24-36%</td>
</tr>
<tr>
<td>POOR METABOLIZER</td>
<td>PM</td>
<td>2-4%</td>
<td>2-20%</td>
</tr>
</tbody>
</table>

Biological Pharmacologics: Opioids

Opioid Metabolism

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. Provide the CDC Guidelines as a reference.

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
   2) where controlled substances should be disposed
   3) 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.

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
## Biological Pharmacologics: Opioids
### Efficacy in Acute Pain

<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>
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<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>
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<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>
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<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>
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<td>83</td>
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<td>Piroxicam 20</td>
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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: 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)

Cardiovascular Adverse Events

Bleeding
Gastritis
Renal Injury

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 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

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

\[ \text{Mean Plasma Values} \]

\[ \text{Acetaminophen Concentration, mg/mL} \]

\[ \text{Time, h} \]

\[ 0 \quad 2 \quad 4 \quad 6 \]

\[ 0 \quad 5 \quad 10 \quad 15 \quad 20 \quad 25 \]

- IV acetaminophen 1,000 mg (n=6)
- Oral acetaminophen 1,000 mg (n=6)
- Rectal acetaminophen 1,000 mg (n=6)

\[ \text{Lachiewicz, P. F. The Role of Intravenous Acetaminophen in Multimodal Pain Protocols for Perioperative Orthopedic Patients. Orthopedics 36, 15–19 (2013)} \]
\[ \text{Toms, L. et al. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults (Review) Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. 4–6 (2012).} \]
\[ \text{Tzortzopoulou, A. et al. Single dose intravenous propacetamol or intravenous paracetamol for postoperative pain. Cochrane database Syst. Rev. CD007126 (2011).} \]
**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:**
(alpha-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-live 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.
Biological
Pharmacologics: NMDA-antagonists: Ketamine

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>
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<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>
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<tr>
<td></td>
<td>1-3 mcg/kg/min</td>
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Biological Pharmacologics: NMDA-antagonists: Ketamine

Nystagmus
Tremor
Psychomotor Agitation
Hallucinations
Hypersalivation
Dissociative State
Coma
Sympathomimetic Effects
17 studies, with variable timing and dosing, demonstrated statistically significant reductions in the development of persistent post-surgical pain at 3 and 6 months.

Comparisons of pain severity did not reach statistical significance.

39 clinical trials, 5 meta-analyses, were included. Variable timing and dosing, demonstrated statistically significant reductions in opioid consumption by 40%
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.
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

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
<table>
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<tr>
<th>RECEPTOR</th>
<th>MEDICATION EXAMPLES</th>
<th>ADVERSE EFFECTS</th>
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<tr>
<td>alpha-2</td>
<td>Dexmedetomidine, Clonidine</td>
<td>Bradycardia, Dry Mouth</td>
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<tr>
<td>COX-inhibition</td>
<td>Ketorolac, Ibuprofen, Celecoxib, APAP</td>
<td>GI Ulcers, Renal Dysn, Bleeding</td>
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<tr>
<td>Mu-Opioid</td>
<td>Morphine, Fentanyl</td>
<td>N/V, Constipation, Resp Depression, Pruritus, Urinary Ret, Delirium,</td>
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<td>Kappa-Opioid</td>
<td>Nalbuphine</td>
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<td>GABA-A</td>
<td>Diazepam, Lorazepam</td>
<td>Sedation, Delirium, Resp Dep c Op</td>
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<td>Na-Channel</td>
<td>Local Anesthetics</td>
<td>LAST</td>
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<td>Ca-Channel Neuropathic</td>
<td>Gabapentin, Pregabalin</td>
<td>Sedation, Impaired Cognition</td>
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<td>Na-Channel Neuropathic</td>
<td>Topiramate, Carbamazepine</td>
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<td>SNRI Antidepressant</td>
<td>Duloxetine, Venlafaxine</td>
<td>Insomnia, Malaise, Stomatitis,</td>
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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
Psychological

CATASTROPHIZATION: characterized by the tendency to magnify the threat value of pain stimulus and to feel helpless in the context of pain, by a relative inability to inhibit pain-related thoughts in anticipation of, during or following a painful encounter.

(Quartana, Expert Review Neurotherapeutics, 2009)

16/29 studies demonstrate a significant impact of catastrophization on the development of chronic post-surgical pain (CPSP). The rest are not significant. No study demonstrated improvement in CPSP. Estimated OR 1.55-2.1 with greater OR in MSK surgeries.

(Theunissen, Clin J of Pain, 2012)

Pain Catastrophization Scale (PCS)
Catastrophization Assessment Scale (CAS)
Hospital Anxiety & Depression Scale (HADS)
Cancer Pain Management (in 1 minute)

Cancer Pain Conditions
Prognosis
Function
Risks and Benefits
The Role of Opioids in Neoplasia

Opioids
COX-inhibitors
Gabapentinoids
Lidocaine Infusion
Ketamine Infusion
Magnesium Infusion
Steroids

External Beam Radiation
Radionuclide Therapy

Epidurals
Spinal Cord Stimulation
Intrathecal Drug Delivery
Neurolytic Blocks
Regional Anesthesia

Acupuncture & Traditional Chinese Medicine
Ayurvedic Medicine
Biofeedback

Pain Psychology
What are the median number of hours devoted to pain education in American medical schools over 4 years?

United States: 9 hours
Canada: 19.5 hours

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

QUALITY-Adjusted LIFE YEARS (QALYs)

100%

QUALITY OF LIFE

0%

AGE (YEARS) 20 40 60 80

Surgery

Trauma

QUALITY-ADJUSTED LIFE YEARS (QALYs)
Conclusion

It’s complicated.

Future efforts:
• Public health education
• Healthcare provider education
• Legislation/Regulation
• Non-pharm, Non-interventional resources
• Outcomes

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 so that it does not interfere with function and PREVENT CHRONIC PAIN

Thank You