Managing Pain in the Hospital
Post-Operative Pain... Acute Pain, Chronic Pain, Cancer Pain

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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 Honoraria
Halyard Health
Abbott

The philosophical dichotomy of acute pain...

Warning Signal
Avoidance Reminder
Healing
Suffering
Depression
Helplessness

Heckert J.
The Hazards of Growing Up Painlessly

BLISSFUL INSENSATION?

CONGENITAL INSENSITIVITY TO PAIN

DENTAL ABSCESSES
CORNEAL ABRASIONS
BONE FRACTURES
INFECTIONS
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

End Of Life 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”
    • PMRI
    • Biological Pattern Algorithms

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

Substance Use/Misuse/Abuse:
• Opioid Risk Tool
• SOAPP
• COMM
• EAGLE
• Pareso 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:
1.8 billion individuals

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

References:

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

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

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

Chronication... 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>
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<tr>
<td>Thoracotomy</td>
<td>30-40%</td>
<td>10%</td>
<td>280,000</td>
<td>112,000</td>
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<tr>
<td>Breast Surgery</td>
<td>20-30%</td>
<td>5-10%</td>
<td>479,000</td>
<td>144,000</td>
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<tr>
<td>Ileal Herniorrhaphy</td>
<td>10-50%</td>
<td>2-4%</td>
<td>608,000</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>76,000</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)

- pre-operative pain
- nerve-sparing technique
- infection prevention
- age
- genetics
- surgical technique
- anesthetic technique
- adjuvant analgesics
- and hyperalgesics
- regional anesthesia

Acute post-operative pain

Psychology

Chronic or persistent post-operative pain

Analgesia vs Hyperalgesia

- COX-Inhibitors
- Acetaminophen
- Alpha-2 Agonists
- Lidocaine

Analgesia BUT Hyperalgesia

Opioids

Analgesia and Anti-Hyperalgesia

Pearl: Analgesia vs Anti-Hyperalgesia

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

Peripheral sensitization
Dorsal Root Ganglion (DRG) modulation
Dorsal Horn: Rexed Laminae II, V
Descending facilitation
Attenuation of Descending Inhibition
Sympathetic response
Emotional response
Memory formation

Overview of Anatomy: Pathological Nociception

Central sensitization
Memory formation
Emotional response
Sympathetic response
Hypothalumus-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 Pharmacology: Opioids

4,000 BCE - 1840

SAMARUAN CLUNE/FORM
HOMER THE ODYSSEY
MORPHINE ISOLATION

4000-3000 BCE 1500 BCE 0 1500 1800
Biological Pharmacologic: Opioids


1840-1975
- 1844: Codeine Isolation
- 1898: Heroin Synthesis
- 1906: Morphine Isolation
- 1914: Hydromorphone Synthesis
- 1939: Semisynthetic Synthesis
- 1973: Synthetic Radiolabeled Opioid Ligands
- 1970: U.S. Controlled Substances Act (CSA)

1970-2007
- 1973: U.S. Pure Food and Drug Act International Opium Convention
- 1986: WHO Cancer Pain
- 1996: Hospice Care
- 1997: Pain Vitals Sign
- 2000: Veterans Affairs
- 2007: Purdue Pharma Law Suit

2000-2017
- 2000: CDC Guidelines
- 2007: 5th Vital Sign
- 2010: Declaration of Montreal
- 2014: DEA Changes Acetaminophen Containing Opioids to Schedule II from Schedule III
- 2016: CDC Guidelines

Biological Pharmacologic: Opioids, America today.

- Americans constitute 4.6% of the world’s population and consume approximately 80% of the world’s opioids.
- Americans consume 95% 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 2.5 million Americans with prescription opioid substance use disorder in 2012
- Estimated 467,000 addicted to heroin in 2012.
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.

| Biological Pharmacology: Opioids. Remember, you have them within you. |
|---|---|---|---|
| | u | d | k | nociceptin |
| Endogenous Ligand | Endorphin | Enkephalin | Dynorphin | Nociceptin |
| Exogenous Agonist | Methadone | Methadone | Methadone | Methadone |
| Exogenous Antagonist | Naloxone | Naltrexone | Nalbuphine | Nalorphine |

<table>
<thead>
<tr>
<th>Effects</th>
<th>U</th>
<th>D</th>
<th>K</th>
<th>Nociceptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia Spinal</td>
<td>u,d,k</td>
<td>analgesia</td>
<td>no effect</td>
<td></td>
</tr>
<tr>
<td>Analgesia Supraspinal</td>
<td>u,d,k</td>
<td>analgesia</td>
<td>no effect</td>
<td></td>
</tr>
<tr>
<td>Respiratory Function</td>
<td>u</td>
<td>decrease</td>
<td>no effect</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Tract</td>
<td>u,k</td>
<td>decrease</td>
<td>no effect</td>
<td></td>
</tr>
<tr>
<td>Psychotomimesis</td>
<td>u,d,k</td>
<td>increase</td>
<td>decrease</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>u,k</td>
<td>increase</td>
<td>decrease</td>
<td></td>
</tr>
<tr>
<td>Feeding</td>
<td>u,d,k</td>
<td>increase</td>
<td>decrease</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>u</td>
<td>increase</td>
<td>decrease</td>
<td></td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>u</td>
<td>increase</td>
<td>decrease</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse Effects with Acute Use**
- Hypogonadism
- Immunosuppression
- Increased feeding
- Increased growth
- Withdrawal
- Dependence, dependence
- Delirium
- SEDATION
- MOYCLONUS
- SEIZURES

**Adverse Effects with Chronic Use**
- Respiratory Depression
- Nausea/Vomiting
- Pruritus
- Urticaria
- Constipation
- Urinary Retention
- Delirium
- Sedation
- Myoclonus
- Seizures

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

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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.

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.

Pharmacogenomics: Opioid Metabolism

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>% Population</th>
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<tbody>
<tr>
<td>Ultra Rapid Metabolizer</td>
<td>7%</td>
</tr>
<tr>
<td>Extensive Metabolizer</td>
<td>48%</td>
</tr>
<tr>
<td>Intermediate Metabolizer</td>
<td>35%</td>
</tr>
<tr>
<td>Poor Metabolizer</td>
<td>10%</td>
</tr>
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</table>

CYP4502D6

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Glucuronidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>O-Desmethyl-Tramadol</td>
</tr>
</tbody>
</table>

Celecoxib, Citalopram, Codeine, Hydrocodone, Oxycodone, Tramadol
**Biological Transitions in Care**

**Pharmacologics: Opioids**

**Biological**

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 rather 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 (Oxycodone HCL) and monitor trends.

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

4) Patients should be given information about how controlled substances
   1) should be locked/secured
   2) 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.

**Pharmacologic: Opioids**

**Efficacy in Acute Pain**

**Opioids are...**

“powerful” “strong”

Opioids can be effective for static pain, but are frail not effective for dynamic pain. Most acute pain is dynamic—pain associated with movement.

Consider the importance of dynamic pain management for:

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

**Pharmacologic: Cyclo-Oxygenase Inhibitors (COX-inhibitors) (historically known as NSAIDs)**

**ARACHIDONIC ACID**

- Constitutive. Found in all tissues esp GI tract
- Inducible. Kidney, GI tract, CNS, endothelium

**COX-1**

Inhibits Platelet Aggregation

- Vasodilator
- Hyperalgesic

**COX-2**

Induces Various Prostanes

- Vasodilator
- Hyperalgesic

<table>
<thead>
<tr>
<th>COX-1 Activity</th>
<th>COX-2 Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TXA2</td>
<td>PGI2</td>
</tr>
<tr>
<td>Inhibits Platelet Aggregation</td>
<td>Vasodilator</td>
</tr>
<tr>
<td>Hyperalgesic</td>
<td>Hyperalgesic</td>
</tr>
<tr>
<td>Decreased Stomach Acid</td>
<td>Increased Stomach Protection</td>
</tr>
<tr>
<td>Decreased Stomach Acid</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Increased Stomach Protection</td>
<td>Vasodilator</td>
</tr>
</tbody>
</table>
Biological Pharmacologics: Cyclo-Oxygenase Inhibitors (COX-inhibitors) (historically known as NSAIDs)

Cardiovascular Adverse Events

- Increasing COX-1 selectivity
- Increasing COX-2 selectivity

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

Biological Pharmacologics: Steroids

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
- Gastrointestinal side effects
- Gastrointestinal bleeding
- Psychiatric side effects
- Osteoporosis with long-term use
- Infections
- Hyperglycemia
- Cushing Syndrome
- Thromboembolism

Biological Pharmacologics: Acetaminophen/Paracetamol

Analagic. 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
- 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 CYP3A4 /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
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:
Dexmedetomidine is an alpha-2 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/agitates. 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 perioperative pain management resulting in reduced 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.

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 antihyperalgesia, it is also being widely studied for antidepressant 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>0.5-2 mg/kg</td>
</tr>
<tr>
<td>DISOCIATIVE (PEDI)</td>
<td>0.1-2 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>0.3 mcg/kg/min</td>
</tr>
</tbody>
</table>

Nystagmus, Tremor, Psychomotor Agitation, Hallucinations, Hyperalization, Dissociative State, Coma

Sympathomimetic Effects

**Biological**
Pharmacology: Alpha-2 Agonists

**Biological**
Pharmacology: Neuropathic Analgesics

**Biological**
Pharmacology: NMDA-antagonists: Ketamine

**Biological**
Pharmacology: Anti-Epileptic Drugs (AEDs)

**Biological**
Pharmacology: Anti-Epileptic Drugs (AEDs)
17 studies, with variable timing and dosing, demonstrated statistically significant reductions in the development of persistent postsurgical pain at 3 and 6 months. Comparisons of pain severity did not reach statistical significance.

Biological
Pharmacologic: NMDA-antagonists: Ketamine

Biological
Pharmacologic: 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 by 40%

Variable timing and dosing, demonstrated statistically significant reductions in opioid consumption by 40%

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.
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.
Catastrophization: characterized by the tendency to magnify the threat value of pain stimuli 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
Goals & Expectations
Risks and Benefits
The Role of Opioids in Neoplasia

Cancer Pain Relief

Qualitied Adjusted Life Years (QALYs)

The Future of Pain Medicine

General Medical Education in Pain Medicine

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.
Conclusion

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