Alternatives to Opioids in Pain Management

Presenters:

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Regional Physician Lead, Opioid Management & Pain Programming

DCHA Opioid Response Symposium 2021
Learning Objectives

- Explain the use of Multimodal Analgesia in pain management
- Describe opioid-sparing approaches in pain management
- Discuss important considerations in pain management for patients with Opioid Use Disorder
Multimodal Analgesia

- Channels-Enzymes-Receptors-Targeted Analgesia (CERTA) described in 2015
- A patient-centered, combined analgesic regimen designed to address specific pain syndromes.
- Mechanistic framework to target physiologic pathways involved in pain signal transmission and integration.
- Can involve medications, interventions, and practices.
- Current evidence-based approaches in practice include:
  - Alternatives to Opioids Programs in ED (ALTO)
  - Postoperative pain management in Enhanced Recovery After Surgery Programs (ERAS)

- Various mechanisms targeted in pain analgesia
  - COX inhibition
  - Trp-V1 antagonism
  - Sodium channel blockade
  - Dopamine receptor antagonism
  - Calcium channel blockade
  - NMDA-glutamate receptor antagonism
  - GABA receptor antagonism
  - 5HT-1 receptor agonism
  - Central Alpha 1,2 receptor agonism
  - Opioid receptor agonism
<table>
<thead>
<tr>
<th>CERTA CLASS</th>
<th>ANALGESIC</th>
<th>Musculoskeletal (Joint)</th>
<th>Arthritis (OA/RA)</th>
<th>Headache</th>
<th>Upper Respiratory</th>
<th>Nausea/Emesis</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Shock</th>
<th>Anaphylaxis/Severe Reactions</th>
<th>Hypertensive Crisis</th>
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<td>COX-1, COX-2 Inhibitors</td>
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Adapted from:

Review Article

Essential pharmacologic options for acute pain management in the emergency setting

David H. Glauser¹, Sergey M. Mores³

¹Johns Hopkins Medicine in Maryland, Baltimore, Maryland, USA
²Brigham and Woman's Hospital, Boston, MA, USA
³Mid-Atlantic Permanente Medical Group, Brooklyn, NY, USA
The Case for NSAIDS

- Especially useful in early injury or during periods of re-injury.
- Helpful for preventing chronic pain by preventing peripheral sensitization.
- “Controlled substances” carry a false perception of being more potent than non-controlled analgesics.


Figure 2. Demonstration of analgesic efficacy for the NSAID ketorolac approximately equivalent to that of therapeutic doses of morphine (upper panel) but with a lower incidence of side effects (lower panel).

Acetaminophen

- Inhibits prostaglandin hydperoxidase
- Evidence of COX-2 inhibition in humans
- COX-3 inhibition described in canines
- Metabolites are active
  - TRPA1 receptor activity to suppress transduction at the dorsal horn
  - Inhibition of Na channels to prevent the re-uptake of endogenous cannabinoids
- Risks: Hepatotoxicity at high/persistent dosing.

Graph adapted from Washington DC Dept of health
http://www.doh.dc.gov/dcrx
Examples of Multimodal Analgesia from ALTO Protocols

(Adapted from St. Joseph Regional Medical Center, 2015)

**Acute on Chronic Radicular Low Back Pain**
- Acetaminophen 1000 mg PO
- Ibuprofen 600 mg PO, or Ketorolac 30-60 mg IV/IM
- Muscle relaxant (eg. cyclobenzaprine)
- Gabapentin 300 – 400 mg PO
- Dexamethasone 8 mg IV
- Lidoderm patches
- Ketamine IV 0.1 – 0.3 mg/kg in 50 mL NS over 10 min
  - 0.1 mg/kg/h until pain tolerable
- Procedures: TPI, dry needling, acupuncture

**Extremity Fracture or Joint Dislocation**
- Ketamine IN 0.5 mg/kg (50mg/mL concentration)
- Nitrous Oxide up to 70%
- Acetaminophen 1000 mg PO
- Procedures: Reduction, Ultrasound-guided regional anesthesia

**Renal Colic**
- Ketorolac 30 mg IV
- Lidocaine infusion 1.5 mg/kg IV in 100 mL NS over 10 min. MAX 200 mg
- Acetaminophen 1000 mg PO
- 1 L 0.9% NS bolus + Tamsulosin PO
Regional Blocks and bed-side procedures can be leveraged for management of acute pain, and some forms of chronic pain.

Many ALTO protocols include a suite of procedures identified to be especially useful in acute management. Procedures can offer > 6-12 hours of analgesia without motor dysfunction, allowing safe discharge.

Point-of-Care Ultrasound (PoCUS) has been revolutionizing the feasibility of these modalities.

The Mid-Atlantic Permanente Medical Group is currently implementing PoCUS across the region in various disciplines, which will include CDUs, Pain, and Cardiology. Meanwhile, SonoSite Cart ultrasounds are currently available in most departments.

Examples of ALTO Procedural analgesia:
- Dental blocks
- Occipital nerve blocks
- Sphenopalatine blocks (nasal approach)
- Trigger Point Injections
- Joint Injections (knee, carpal tunnel, shoulder)
- Truncal blocks
- Manual manipulation, myofascial release
- Posterior tibial nerve block
- Anterior femoral cutaneous nerve block
- And many more…
Considerations in Substance Use Disorder

Patients on Methadone Maintenance Therapy for OUD

- *Daily dosed* methadone in MAT does not confer analgesia beyond 6-8 hours. Pain dosing frequency is every 12 to 8 hours (NEVER “prn”)

- Relapse risk higher with inadequate pain management than with use of opioids for acute pain

- Clinical recommendations:
  - Screen for prolonged QTc > 480 ms
  - Use [multimodal analgesia](#), paying attention to potential interactions (especially QTc-prolonging meds and CNS depressants)
  - Discuss “split dosing” q12h or q8h if patient is on “take homes”
  - If opioids required, will require higher doses (x1.5) and/or more frequent dosing
  - Avoid mixed agonist/antagonist opioids and combination products with acetaminophen
Considerations in Substance Use Disorder

Patients on Buprenorphine for OUD

- **NEW:** Recent changes to “X-waiver” requirement
- Available in outpatient pharmacies
- μ-receptor agonist with very high affinity
- Antagonism at κ-receptor (+mood effects)

- Buprenorphine products labelled for OUD:
  - SL Buprenorphine-naloxone (Suboxone, Zubzolv, Bunavail)
  - SL Buprenorphine (Subutex)
  - Buprenorphine implant (Sublocade)

- Clinical considerations:
  - Split dosing q8h to better cover pain while on OUD maintenance

Considerations in Substance Use Disorder

Buprenorphine for pain

- No ceiling effect for analgesia
- Plateau of respiratory depression
- μ-receptor agonist with very high affinity
- Antagonism at κ-receptor (+mood effects)
- Favorable safety profile with medical comorbidities
- Buprenorphine products labelled for pain:
  - Transdermal buprenorphine (Butrans)
  - Buccal buprenorphine (Belbuca)
  - IV buprenorphine (Buprenex)

Naltrexone Maintenance Therapy

- Multimodal analgesia is essential.
- Discontinue the naltrexone if opioids required.
- Analgesic blockade can be overcome with very high doses of opioids (6 to 20 X).
- Dedicated specialty consultation and readiness to provide respiratory support recommended at the point of care.
References and Additional Reading

- Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD006146. (Opioids in Neuropathic Pain)
- Daitch et al Conversion from high Dose Full opioid Agonists to SL Buprenorphine Reduces Pain Scores and Improves QOL for CP Patients. Pain Med 15:2087
- Falcon et al (2016) Antidepressant like effects of buprenorphine are mediated by kappa opioid receptors. Neuropsychopharmacology 41(9):2344

Additional citations are annotated within the presentation slides, as updated.
Thank you!
Multimodal Analgesia in the Time of an Epidemic

Palak Turakhia, MD MPH
The Epidemic
The Epidemic

Sources of Prescription Opioids Among Past-Year Non-Medical Users

- Given by a friend or relative for free
- Prescribed by ≥1 physicians
- Stolen from a friend or relative
- Bought from a friend or relative
- Bought from a drug dealer or other stranger
- Other

Number of Days of Past-Year Non-Medical Use

Percent of Users

As an anesthesiologist

- Perioperative period may be source of initial exposure for some patients
- Persistent (greater than 90 days) opioid use after major or minor surgery is approximately 6%
- Patients often prescribed more than they need – 40-70% of opioids prescribed postoperatively go unused
Other Side Effects of Opioids

- Postoperative Nausea & Vomiting
- Respiratory Depression
- Constipation/ileus
- Urinary Retention
- Wound Complications/Delayed Healing
Opioid Sparing Adjuvants

- Non-steroidal Anti-inflammatory Drugs
- Acetaminophen
- Alpha 2 Adrenergic Agents
- Anti-convulsants
- Ketamine
- Intravenous Lidocaine
Non-Steroidal Anti-inflammatory Drugs – Mechanism of Action

Injury to cell membrane causes release of phospholipids

Phospholipase A

Arachidonic Acid

Inhibited by NSAIDS

Cyclooxygenase 1 or 2

Prostaglandins

Central and Peripheral Sensitization
NSAIDs: Side Effects

- Surgical Bleeding
- Gastrointestinal Bleeding
- Oliguria
- Renal Failure
Non-Steroidal Anti-Inflammatory Drugs

- In certain surgeries preoperative celecoxib offers similar pain relief to ketorolac
- Perioperative NSAID use has been shown to decrease opioid usage and side effects, including nausea and vomiting
Acetaminophen – Mechanism of Action

- Exact mechanism of action is unknown.
- Thought to rapidly enter central nervous system and centrally inhibit prostaglandins via the COX pathway
- It may reinforce the descending serotonergic inhibitory pathway
- It has weak peripheral anti-inflammatory activity and insignificant impact on platelet function
Acetaminophen

- Opioid sparing effects in different types of moderate to major surgery
- Some reduction in postoperative nausea and vomiting
- Acetaminophen comes in three forms, oral, rectal and intravenous
- Very little evidence supporting intravenous over oral form for
NSAIDS + Acetaminophen

• Thought is that combining the two classes of drugs provides improved pain relief over either drug alone

• Most commonly studied NSAID has been ibuprofen
Alpha-2 agonists

Analgesic and sedative effects

**Locus ceruleus**

**Dorsal horn of the spinal cord**
# Alpha 2 agonists

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<thead>
<tr>
<th>Clonidine</th>
<th>Dexmedetomidine</th>
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<tbody>
<tr>
<td>• Analgesic effects equivocal</td>
<td>• More selective, shorter duration of action than clonidine</td>
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<td>• Use is limited by side effects including bradycardia, hypotension</td>
<td>• Has been shown to decrease postoperative morphine consumption, PONV, length of stay in certain populations</td>
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# Anti-convulsants

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<tr>
<th>Gabapentin</th>
<th>Pregabalin</th>
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<td>Binds to the alpha-1 delta subunit of the presynaptic calcium channel</td>
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<td>Dose-independent absorption</td>
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Anti-convulsants – Mechanism of Action

- Voltage gated calcium channels are upregulated in spinal cord and dorsal root ganglia after surgical trauma.
- Gabapentinoids may produce antinociception by inhibiting release of excitatory neurotransmitters
- Also reduces excitability of dorsal horn neurons
- In patients given preoperative gabapentinoids, patients had better pain relief, decrease in opioid requirements and adverse effects such as postoperative nausea, vomiting, ad urinary retention.
- Side effects include respiratory depression, sedation
Ketamine – Mechanism of Action

• Reversible antagonist at the N-methyl-D-aspartate (NMDA) receptor found
  • On peripheral afferent nociceptive neurons that synapse at the dorsal horn of the spinal cord,
  • In the cortex, which contributes to decreased arousal and antinociceptive effects

• Also exerts effects on mu-opioid receptors, muscarinic receptors, monoaminergic receptors, GABA receptors and several others

• Has been show to have an opioid sparing effect, but impact on postoperative pain scores is ambiguous.
# Ketamine – Side Effects

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<th>CNS side effects</th>
<th>Other side effects</th>
<th>Long Term Use (Potential)</th>
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<tbody>
<tr>
<td>• Dizziness</td>
<td>• Hepatotoxicity</td>
<td>• Impaired cognition</td>
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<td>• Dysphoria</td>
<td>• Uropathy</td>
<td>• Impaired Memory</td>
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<td>• Headaches</td>
<td>• Increase in ICP/IOP</td>
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<td>• Dreams</td>
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<td>• Hallucinations</td>
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Intravenous Lidocaine

**Intraoperative Benefits**
- Decrease in anesthetic requirements
- Decrease in airway reactivity in smokers
- Blunting of hemodynamic response to airway manipulation

**Analgesic Benefits**
- Decrease in PONV/ileus
- Small decrease in length of stay
- Decrease in pain scores and opioid consumption
Intravenous Lidocaine – Mechanism of Action

• The mechanism of action is not sodium and calcium channel blockade but the decrease in pro-inflammatory cytokines including inter-leukin 6 and inter-leukin 8.

• May also inhibit NMDA receptors

• Most benefit is seen in patients undergoing laparoscopic or open abdominal surgery
Intravenous Lidocaine – Side effects

• Toxicity is rare but can present with tinnitus, perioral numbness and cardiac arrhythmias

• Could consider monitoring levels in higher risk patients with renal or hepatic dysfunction
References

• E.Y. Chen, A. Marcantonio, P. Tornetta 3rd Correlation between 24-hour predischarge opioid use and amount of opioids prescribed at hospital discharge JAMA Surg, 153 (2018), p. e174859


• Lauren K. Dunn, Marcel E. Durieux; Perioperative Use of Intravenous Lidocaine. Anesthesiology 2017;126(4):729-737