New Options for Acute Pain Management

Raymond S. Sinatra MD, Ph.D
Opioids: The Cornerstone of Pain Control

- Bind to opioid receptors in spinal cord, brainstem and limbic cortex
- High Efficacy: dose dependent pain relief with no ceiling effect
- High Safety: No cardiovascular renal or hepatic effects
- Multiple agents: Morphine, hydromorphone, fentanyl, oxycodone, oxymorphone
  - Multiple delivery systems: oral, parenteral, transdermal, epidural
Opioid Analgesic Monotherapy Following Ambulatory Surgery

- Severe Pain: Even More Opioids
- Moderate Pain: More Opioids
- Mild Pain: Opioids
Opioid Monotherapy: Acute Pain

Improved Pain Control

Increased Ambulation, Improved Rehabilitation

Dose Dependent Adverse Events

Nausea/ vomiting
Pruritis
Urinary retention
Ileus
Sedation
Respiratory depression
Endocrine/Immune effects
Hyperalgesia
Intravenous Patient Controlled Analgesia (IV PCA)

“Allows patients to self-titrate analgesics in amounts proportional to the perceived pain stimulus”

1. Analgesic uniformity
2. Improved control
3. Improved satisfaction
4. Improved ambulation
IV PCA: 1985 to Present

“A delivery system that allows patients to self-titrate analgesics in response to the perceived pain stimulus”

- Rapid onset of effect (5-10 min)
- Minimizes the interval between analgesic request and pain relief
- Compensates for age related and genetic differences in opioid pharmacokinetics and pain processing
- High degree of patient acceptance, control, and satisfaction

Opioid Outliers

May represent 2-3% of post-surgical patients, hospital costs can be 3-10X higher than expected norms

Include:

• Patients at risk for life threatening respiratory depression or airway obstruction
• Patients with difficult to manage nausea and vomiting that is difficult to manage or resistant to treatment
• Patients with difficult to manage ileus and opioid induced bowel dysfunction
• Patients with poorly controlled pain as a result of high grade opioid tolerance or opioid hyperalgesia
IV PCA: Present-Day Application

- PCA should not be employed as monotherapy

- Avoid high opioid dose exposure and basal infusions

- Discontinue as soon as the patient tolerates oral diet

- PCA may be supplemented with non opioid adjuvants (30-50% reduction in morphine dose)

- PCA provides an effective adjunct to continuous regional blockade

- PCA opioids may be combined with ketamine, dexmedetomidine for patients with chronic pain/opioid dependency

COX-2=cyclooxygenase-2; NSAIDs=nonsteroidal antiinflammatory drugs.
Epidural PCA

“The Analgesic choice for high risk patients (ASA 3-4)
Recovering from extensive or very painful surgeries

1. Reduction in Opioid Dose
2. Allows use of Local Anesthetics
3. Provides “Pain Prevention”
4. Blunts Stress Responses
5. Reduces Cardiovascular and Pulmonary Complications
Central Neural Blockade: Epidural PCA

“The analgesic technique of choice for high risk patients (ASA 3-4), recovering from extensive/painful surgeries

- Catheter placed into the thoracic or lumbar epidural space
- Loading Dose: Hydromorphone 0.5-1mg with Bupivacaine 0.125-0.25% (6-12ml)
- Initiate Intraop Continuous Infusion: Hydromorphone 10-20 mcg/ml plus bupivacaine (0.0625-0.031%) at 6-12ml/hr
- PCA boluses added as the patient awakens in PACU
Incidence of Atelectasis Following Lung

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Ballantyne J. Anesth Analg 1998
IV-PCA

1. High Opioid Dose Requirement
2. Significant Side Effects
3. Overdosage Risks (programming errors and “proxy” dosing)
4. Does not Blunt Stress Responses
5. Not for Cognitively Impaired Patients

Epidural PCA

1. More Invasive
2. Requires Continuous Follow-up
3. Requires Optimal Catheter Positioning
4. Expensive
5. Not for Anti-coagulated Patients
Multimodal (Targeted) Analgesia

“Analgesic regimens that employ a variety of agents in small dose to block pain perception at different sites in the nervous system”

**Advantages**
- Reductions in pain intensity scores
- Reductions in opioid dose requirements
- Reductions in opioid side effects
- Improvements in surgical outcome?
Multimodal Analgesia Targets All Components
Postoperative Pain Is a Mixed Noxious Experience
Multimodal Pain Management

- Reductions in pain intensity
  - Increased Ambulation
  - Improved Rehabilitation

- Reductions in opioid dose
  - Decreased adverse effects
  - Decreased need to treat

- Increased patient satisfaction
- Reduced hospital and rehab unit stay
- Reduced overall medical costs

Increased Drug/Treatment cost?
Nociception and Multimodal Analgesia

1. Transduction
- NSAIDS, COX-2 Inhibitors, Anti-Histamines, Topical Local Anesthetics

2. Conduction
- Peripheral Nerve Block Local Anesthetics

3. Transmission
- Epidural Block Local Anesthetics

4. Modulation
- Opioids, Clonidine, COX-2 Inhibitors

5. Perception
- Muscle Relaxants, Beta Blockers

6. CNS Responses
- Muscle Relaxants, Beta Blockers

Opioids, Acetaminophen, Clonidine, Ketamine, Gabapentin, Tricyclics

PAIN
Mediators of Inflammation and Acute Pain

- The primary noxious mediator released from damaged tissue is PG
- PG is responsible for nociceptor activation and sensitization
- PG exacerbates peripheral inflammation

NSAIDS and Coxibs effectively block PG synthesis
Multimodal Analgesia

**Advantages:**
1. Reduction in pain intensity scores
2. Reduction in opioid dose requirements (opioid sparing effect)
3. Reduction in opioid side effects
4. Improvement in surgical outcome?

**Disadvantages:**
1. Requires knowledge of multiple drugs, their pharmacokinetics and pharmacodynamics
2. Every analgesic has its own unique adverse event profile
3. May increase drug-drug interactions
4. Requires skills in regional and
Continuous Peripheral Neural Blockade: A Major Component of Multimodal Analgesia

- Catheter Placement: Use of nerve stimulator or ultrasound guidance*
- Induction: Bupivacaine 0.5% (20-30ml), Ropivacaine 0.75% (30ml)
- Continuous Infusion: Bupivacaine 0.125%, Ropiv 0.2% at 8-12ml/hr

*ultrasound guidance has improved CPNB success rate to 90%, reduced loading dose requirements by 25% at Yale
Movement Pain (CPM) After Total Knee Replacement

### Rehabilitation Following Total Knee Replacement

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<th>CFB</th>
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<td>60*</td>
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<tr>
<td>1 Month</td>
<td>90**</td>
<td>95</td>
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Sustained Release Bupivacaine (Exparel™)

- Extended-release bupivacaine suspended within DepoFoam™ lipid microvessicles
- Catheter-free delivery, avoidance of external pump technology
- Single injection provides 72 hours of continuous pain relief
**Liposomal Bupivacaine (Exparel™)**

_Bupivacaine encapsulated into Liposomes (DepoFoam)_
Sustained release extends bupivacaine's duration of activity up to 72hrs, and improves tolerability and safety (Concentration 15mg/ml)

_Surgical Incision Size/ Dose of Liposomal Bupivacaine_
- Up to 3 cm in length 120 mg 8 mL;
- 3-6 cm in length 300 mg 20 mL;
- Major orthopedic/ reconstructive surgery 600 mg 40 mL
Liposomal Bupivacaine Hemorrhoidectomy Trial. Median Time to First Opioid

Data on File 2010, Pacria Pharma
Multimodal Analgesic Benefits With NSAIDs

- Large meta-analyses of randomized, double-blind studies found that NSAIDs, and COX-2 inhibitors significantly decreased:

1. Opioid dose requirements by 15%-55%
2. Postoperative nausea by 12%, vomiting 32%
3. Sedation scores by 29%

Mechanism of NSAID Activity

COX-1
“Constitutive”

COX-2
“Inducible”

Arachidonic acid

Prostaglandins

Protection of gastric mucosa

Hemostasis

Pain, inflammation, and fever

# Indications And Doses Of NSAIDS Approved for Acute Surgical Pain Management*

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<tr>
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<th>Celecoxib</th>
<th>Ibuprofen</th>
<th>Ketorolac</th>
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<td>Oral</td>
<td>Injectable/OTC Oral</td>
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<td><strong>Dose:</strong></td>
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<td>400-800mg IV IV Infusion QID</td>
<td>15-30mg slow IV Push QID</td>
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<td><strong>Fever Indication</strong></td>
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*Per Package Inserts
(Ibuprofen Injection (Caldolor ®))

• **Indications and usage in adults**
  - Management of mild to moderate pain
  - Management of moderate to severe pain as an adjunct to opioid analgesics

• **Dose 400-800mg q6hrs**

• **Clinical data support preoperative dosing**

• **No limitation on duration of use**

Caldolor Prescribing Information.
Full prescribing information can be accessed at www.caldolor.com.
Inhibition of COX-2 Relative to COX-1

- Ketorolac
- Naproxen
- Ibuprofen
- Celecoxib
- Diclofenac

Increasing Hemorrhagic Risk
Increasing Thrombotic Risk

Orthopedic Pain Study:
VAS Scores at Rest and With Movement

Reduction in Pain Intensity Scores After Orthopedic Surgery

Assessed at Rest

Assessed With Movement

VAS = visual analog scale
* Statistical significance was demonstrated at each assessment. Patients required 31% less morphine over the first 24 hrs.

Celecoxib for Acute Pain\textsuperscript{1*}

1. The only selective Cox-2 Inhibitor available in US
2. High platelet safety profile: allows peri-operative dosing
3. High GI safety: Reduced incidence of GI bleeding
4. Extended duration: 12-24 hrs
5. Cardiovascular Morbidity\textsuperscript{2}: Observed in long term trials, effects in acute pain?

Dosing for Acute Pain
400 mg loading dose, followed by 200 mg on day 1, Thereafter 200 mg BID

Injectable Acetaminophen (Ofirmev™)

- Injectable, central acting, non opioid, non-NSAID analgesic widely used in Europe for over 20 years

Approved for:
1. Mild pain (as monotherapy);
2. Severe pain (as a component of multimodal analgesia)

Provides analgesia comparable to ketorolac 30mg
No effects on platelet function, renal function, or bone remodeling.

Ready to use 100ml buffered solution. Solution infused over 15 min; Dose: 1mg every 6 hours

Injectable Acetaminophen Following Orthopedic Surgery

• Randomized, double blind, controlled evaluation performed in patients recovering from total hip and total knee replacement.

• Treatment groups:
  IV Acetaminophen 1gm (n= 51)
  IV Placebo (n= 50)

• 4 doses, 100 ml solution every 6 hr over 24 hr
• IV-PCA Morphine for rescue analgesia

IV Acetaminophen vs Placebo: Mean

IV-PCA Morphine Self-Administration At 6 Hr Intervals

28% Reduction over 24hrs

Value of IV-APAP in Acute Pain

- Intraoperative administration
- Postoperative multimodal analgesia for inpatient and outpatient surgery
- Post-trauma analgesia for ED
- High safety profile compared to NSAIDs (no renal, CV, or surgical site effects)
- Possible reduction in opioid adverse events
- Useful antipyretic effects
Tapentadol HCl- (Nucynta™)

Oral, centrally-acting analgesic1,2
- Dual mechanism of action in one chemical entity:1,2
  - mu-opioid receptor agonist
  - Norepinephrine (NE) reuptake inhibitor
- FDA approved for acute and chronic pain
- Immediate-release (IR) 50-, 75- and 100-mg tablets
- Continuous-release (CR) tablets available for chronic pain

Tapentadol (50-100mg) Comparable to Oxycodone 15 mg

Bunionectomy Study

Mean onset of pain relief within 32 minutes*

SPID = a higher score indicates more pain relief.

Oh C et al. Poster #229 presented May 8, 2008 at the APS Annual meeting.

*P< 0.001, tapentadol 75 mg vs placebo, 100 min. **P<0.001 vs. placebo.
Nonopioid Pain Modulators as Perioperative Analgesic Adjuncts

- Perioperative administration of ketamine, gabapentin and clonidine
- All provide measurable opioid-sparing effects,
- May also reduce pain intensity scores.\(^\text{1-5}\)
- May reduce wound site hyperalgesia and limit development of persistent pain.\(^\text{1,2}\)

Analgesic Adjuvants: The Key to Chronic Pain Prevention?

1. Classical Analgesics (Opioids and NSAIDS) reduce acute pain intensity, but have minimal to no effect on central sensitization and pain persistence.

2. Novel analgesic adjuncts and adjuvants such as the Gabapentioids, Ketamine, TRPV-1 antagonists (Capsacin), and NGF antagonists, have minimal effect on acute pain intensity but may suppress central sensitization and pain persistence.
Multimodal Analgesia With Ketamine:

Ketamine infusions are reserved for opioid tolerant and hyperalgesic patients as well as others with severe pain and opioid intolerance.

Hallucinations and other cognitive side effects are less commonly observed with low dose infusions.

Intraop: Ketamine loading dose of 0.1-0.2mg/kg, or infusion of 0.1mg/kg/hr.

Postop: ketamine infusion of 0.05-0.1mg/kg/hr.
Multimodal Analgesia With Ketamine: Efficacy Meta-analysis

Continuous Infusion of Ketamine + Opioid

VAS at Rest

- Edwards 10 mg Intra 24 hr post
- Edwards 20 mg Intra 24 hr post
- Edwards 5 mg Intra 24 hr post
- Jaksch 0.12 mg/kg/hr Intra 2 hr post
- Stubhaug 0.12 mg/kg/hr Intra 48 hr post
- Adriaennssens 0.15 mg/kg/hr Nil 48 hr post
- Guillou 0.12 mg/kg/hr Nil 48 hr post
- Heinke 0.6 mg/kg/hr Intra 0 post

Overall

Subramaniam K Anesth Analg 99;482-495:2004
Chronic Pain Prevention: Is there a place for Sub-anesthetic Doses of Ketamine?

1. RCT 100 patients scheduled for rectal cancer surgery under combined epidural/general anesthesia (bupivacaine/sufentanil/clonidine mixture).

2. Assigned to either:
   - Group 1: (No ketamine)
   - Group 2: (iv ketamine 0.25 mg/kg + infusion of 0.125 mg/kg per h)
   - Group 3: (iv ketamine 0.5 mg/kg + infusion of 0.25 mg/kg per h)
   - Group 4: (epidural ketamine (0.25 mg/kg) + 0.125 mg/kg per h)
   - Group 5: (epidural ketamine (0.5 mg/kg and 0.25 mg/kg per h)

4. All iv and epidural infusions were stopped at the end of surgery and IV-PCA morphine was initiated

5. Group 3 patients required less IV-PCA morphine and experienced significantly less wound mechanical hyperalgesia at 2 weeks, and 1, 6, and 12 months. Group 3 patients also reported significantly less residual pain at 1 and 6 months.

Wound Site Hyperalgesia: Relationship to Chronic Pain

Relationship between the area of wound site hyperalgesia* after abdominal colectomy surgery and residual pain 6 months later

Ketamine Based Analgesia

- Ketamine is a dissociative anesthetic
- It is a non-selective NMDA receptor antagonist that inhibits glutamate induced Ca++ and Na+ influx.
- When administered in low dose (0.05-0.2mg/kg/hr) ketamine provides measurable analgesia and opioid sparing effects
- Low doses also suppress central sensitization and hyperalgesia

Gabapentinoid Based Analgesia

Gabapentin and Pregabalin bind to the alpha-2-delta sub-unit of the N-type voltage gated calcium channel

Gabapentinoid binding diminishes Ca++ influx and the release of nociceptive compounds (Substance P, Calcitonin Gene-related peptide (CGRP) and Glutamate) in peripheral nerves, spinal and supraspinal neurons

Gabapentinoids decrease ectopic firing of sensitized nerve endings, and blunt the progression of central sensitization.

Approved for neuropathic pain conditions, increasingly advocated for acute pain management *

Pregabalin Reduces Chronic Pain Following Knee Arthroplasty

240 Patients recovering from TKA treated with an epidural infusion for 72hrs were randomized into two groups:

(1) Pregabalin 300 mg Preop + 150 mg BID for 14 days
(2) Placebo Preop + Placebo BID for 14 days.

Outcomes:

1. Follow-up telephone Interviews

2. S-LANSS scoring used to assess neuropathic pain complaints at 1, 3, and 6 months following surgery. (scores greater than 12 indicated neuropathic pain.)

Buvanendran etal  Anesthesia and Analgesia 2010;110:199-207
Leeds Assessment of Neuropathic Symptoms and Signs- Courtesy of Sir Norman Wisdom CEO/Founder. Admin@neurocenter.com
Neuropathic Pain Following TKA

- **Pregabalin**
- **Placebo**

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<tr>
<td>6 month</td>
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* indicates statistical significance.
Allodynia or Hyperalgesia of Knee

![Bar chart showing the comparison between Pregabalin and Placebo at 3-month and 6-month intervals.](chart.png)

- **3 month**
  - Pregabalin
  - Placebo

- **6 month**
  - Pregabalin
  - Placebo

*Significant difference
Neural, Humoral, and Sensitization Blockade - Target the Key Components of Acute Pain

Inflammatory Pain
- PGE

Nociceptive Pain
- Cytokines

NMDA Activation Sensitization

Humoral Blockade (NSAIDs & Coxibs)

Neural Blockade, Acetaminophen

Sensitization Blockade (Ketamine)

Decreased Pain Perception, Diminished Peripheral and Central Sensitization
Peripheral Kappa Opioid Receptors

- KORs are found on a variety of immune cells
- Activation of KORs results in decreased release of pronociceptive and pro-inflammatory mediators (e.g., CGRP, SP, TNF-α, IL-1β, IL-6)

From Walker 2003
Kappa Agonist CR845 Reduces Pain Intensity Following Lap Hysterectomy

* $p < 0.05$ vs. placebo, unpaired t-test (Mean ± SEM)
Kappa agonist CR845: Time Course of Opioid-Sparing Effect

*\( p < 0.05 \) vs. placebo, unpaired t-test (Mean ± SEM)
Opioid Monotherapy vs Multimodal Analgesia

- **Give More Opioids!**
  - Potent Opioids
  - Weak Opioids
- **Moderate to Severe Pain**
  - Neural Blockade
  - Acetaminophen, NSAIDs, Coxibs, Gabapentanoids
- **Mild to Moderate Pain**
  - Weak Opioids
- **Breakthrough Pain**
What Novel Analgesics are being Evaluated and may be Available in the Next 5 years

- TRPV-1 antagonists- ion channel blockers selective for c-fiber nerve endings (no effect on sensory motor fibers)
- ORL- Powerful anti-nociceptive and anti-neuropathic analgesics with no respiratory depression, tolerance or abuse potential
- Peripherally selective Canabinoid agonists (CB-2) Anti-nociceptive and anti-neuropathic analgesics with no respiratory depression, tolerance or abuse potential
- Anti-nerve growth factor- NGF Antibodies that destroy a primary mediator responsible for persistant pain
- LOX Inhibitors- Powerful anti-inflamatories that have less adverse effects than NSAIDS, Coxibs
# Future Multimodal Analgesics

2000-2010: “The Decade of Pain Management”, A number of novel analgesics and analgesic delivery systems are in development or about to be released.

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<td>Neurokinin inhibitors</td>
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<td>Exparel 2011</td>
<td>Selective NMDA inhibitors</td>
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<td>IV Acetaminophen (2010)</td>
<td>Selective ion channel blockers TRPV-1)</td>
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<td>Pregabalin (2005)</td>
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What Will Pain Management

- Multimodal
- Less reliance on central acting opioids
- Continuous delivery to avoid analgesic gaps
- Less invasive
- Decreased side effects
- Less cumbersome for patient and caregivers
- Enhanced satisfaction, improved outcomes