Multimodal Perioperative Analgesia: A Pharmacologic Review

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Disclosure
I have no personal or professional financial relationships or interests with any proprietary entity producing healthcare goods/or services

Yet...
But I’m working on it!
Learning Objectives

• Review the classes of non-opioid medications utilized perioperatively
• Understand how each pharmacologic option contributes to managing pain and reducing opioid consumption
• Discuss the differences between perioperative opioid options (specifically oral)

Brief Recap of Shortage Protocol

Pre-operative phase

• Non-opioid cocktail:
  – Celecoxib (NSAID)
  – Acetaminophen
  – Gabapentin
• ERAS*:
  – Intrathecal Duramorph

• Opioid options:
  – Short Acting:
    • Hydromorphone
    • Oxycodone
  – Long Acting:
    • Methadone
    • MS Contin
    • Oxycontin
Brief Recap of Shortage Protocol

**Intra-operative phase**

- Non-opioid options:
  - Lidocaine
  - Ketamine
  - Dexmedetomidine
  - Esmolol
  - Volatile Anesthetics
  - IV Acetaminophen (redose)
  - Rectal Acetaminophen (redose)

- Opioid options:
  - Rectal Morphine
  - Rectal Hydromorphone

**Post-operative phase**

- Non-opioid options:
  - IV/Rectal Acetaminophen
  - Ketamine Rescue
  - Lidocaine gtt continuation
  - Ketamine gtt continuation
  - Redose NSAID where appropriate

- Opioid options:
  - Rectal Morphine
  - Rectal Hydromorphone
  - Oral Oxycodone
  - Oral Hydromorphone
Brief Recap of Shortage Protocol

Miscellaneous

• Neuraxial:
  – Epidural
  – Local anesthetic spinal

• Surgeon:
  – Intercostal blocks
  – Local infiltration

• Regional:
  – Significantly increased the number of TAP blocks
  – Consideration of regional approach in operative cases where not routine

NSAIDs
NSAIDs- Mechanism

So why not COX2 selective all the time?
So why not COX2 selective all the time?

NSAIDs

<table>
<thead>
<tr>
<th>Table 1. NSAID Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>More COX-1 Selective</strong></td>
</tr>
<tr>
<td>Ketorolac (Spir, others)</td>
</tr>
<tr>
<td>Flurbiprofen</td>
</tr>
<tr>
<td>Ketoprofen</td>
</tr>
<tr>
<td>Indomethacin (Indocin, others)</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
</tbody>
</table>
NSAIDs

• Multiple studies that demonstrate opioid sparing effect of both mixed and COX2 selective.
• Must balance benefit with potential risks:
  – GI injury
  – Renal injury
  – Hepatic injury
  – Increased risk of CVA/MI higher with greater COX2 activity (maybe)
  – Can worsen bleeding or can inhibit blood thinning effect of ASA
PRECISION TRIAL

- Randomized, double blinded, prospective evaluating Celecoxib, Ibuprofen, Naproxen in patients at “increased cardiovascular risk”.
- Compared 600mg TID Ibuprofen, 375 mg BID Naproxen, and 100mg BID Celecoxib
- Found Celecoxib to be non-inferior from a CV event perspective
- Caveats- company sponsored, lower dose of Celebrex than in previous studies, consideration of time with ASA
Acetaminophen (NSAID?)

Acetaminophen—Mechanism

- NSAID?
  Only very weak (if any) peripheral COX inhibition. Older studies demonstrated reduction in swelling post injury when compared with placebo.

- Central COX inhibitor?
  Thought until recently to exert primary effect through some degree of central COX inhibition.

- Maybe modulation of serotonin?

- More recently: Indirect activation of Cannabinoid (CB1) receptor

- Probably some combination
Acetaminophen

- Multiple studies demonstrate either opioid reduction, or decreased pain scores without change in opioid consumption.
- Hepatic toxicity in overdose.
- Can cause elevation of liver enzymes in patients if taken 4000mg per day chronically. Grain of salt...
- Can cause renal injury in overdose.

Acetaminophen

- Rarely effective as monotherapy (not never though...)
- However... primary role to be used as an adjunct and has shown synergism.
Acetaminophen

• Bet you didn’t know (or maybe you did)...
  – More than 25 billion doses used per year in the United States alone
  – Increases risk of GI bleed in combination with NSAIDs therapy (higher risk than NSAIDs administered alone)
  – Can cause GI irritation even as monotherapy
  – Safe in patients with chronic stable liver disease... probably
  – Safe in patients with hepatitis (without cirrhosis)
  – Median lethal dose of 400mg/kg, 1977 panel determined hepatotoxic dose to be 15000mg

Gabapentinoids

NOT SURE IF THE PAIN MEDS AREN'T WORKING
OR IF THEY ARE AND THE PAIN I WOULD BE IN WOULD HAVE KILLED ME ALREADY
What are the Gabapentinoids?

- Class within anticonvulsants which are structural analogs of GABA
- Two drugs within the class are:
  - Gabapentin (Neurontin)
  - Pregabalin (Lyrica)
- Likely the most commonly prescribed anticonvulsants for treating pain
Gabapentin (Neurontin)

- Synthesized in 1977 as drug for treatment of spasticity and in mid 1990s for treatment of epilepsy
- Primarily used in the U.S. for neuropathic pain
- Non-linear kinetics and absorption is dose dependent
- Absorption is 80% at 100 mg and 27% at 1600 mg
- Excreted unchanged in the urine

Gabapentin (Neurontin)

- Side effects:
  - Dizziness (27-46%)
  - Somnolence (15-25%)
  - Peripheral edema
  - Indigestion
  - Dry mouth
  - Itching
  - Impotence
  - Tingling in hands/feet
  - Weight gain
  - Tremor
Pregabalin

• Studies demonstrate anticonvulsant, analgesic, and anxiolytic activity
• 98% excreted unchanged in urine
• Linear absorption kinetics (absorbed throughout small intestine) >90% over dose range of 10-300 mg

Pregabalin (Lyrica)
Pregabalin (Lyrica)

• Side Effects:
  – Dizziness (22-38%)
  – Somnolence (15-28%)
  – Peripheral edema (10-15%)
  – Weight gain 2-3 kg (4-14%)
  – Euphoria (5%) led to Schedule V listing

Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance, ml/min</th>
<th>Maximum Daily Pregabalin Dose, mg</th>
<th>Maximum Daily Gabapentin Dose, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60</td>
<td>600</td>
<td>3,600</td>
</tr>
<tr>
<td>30–60</td>
<td>300</td>
<td>1,400</td>
</tr>
<tr>
<td>15–30</td>
<td>150</td>
<td>700</td>
</tr>
<tr>
<td>15</td>
<td>75</td>
<td>300</td>
</tr>
</tbody>
</table>
Current indications

• Gabapentin-
  – FDA approved only for postherpetic neuralgia and treatment of partial seizures
  – Used off label for diabetic neuropathy, CRPS, phantom limb pain, spinal stenosis, MS related pain, migraine prophylaxis, as an adjuvant for cancer related pain, fibromyalgia

Current indications

• Pregabalin-
  – FDA approved for diabetic neuropathy, post herpetic neuralgia, seizures, and more recently fibromyalgia.
  – Used off label for generalized anxiety disorder, CRPS, phantom limb pain, migraine prophylaxis, spinal stenosis, panic disorders
Mechanism of Action

- Modulate the α-2δ subunit of presynaptic P/Q-type voltage-gated calcium channels
- Which is thought to effect the subsequent release of excitatory neurotransmitters from activated nociceptors, such as glutamate
- Other mechanisms may include activation of noradrenergic pathways
What’s the Difference?

• The principal difference is in their bioavailability...

What’s the Difference?

• Both drugs are absorbed by amino acid carriers, but absorption of gabapentin is limited to a small part of the duodenum.
• Conversely, Pregabalin is absorbed throughout the entire small intestine.
• Thus differences in theoretical side effects, saturation, etc.
Perioperative Use?

"The other way is less invasive, but I kind of already promised the interns."

Perioperative Utility

- Over 100 trials evaluating the use of perioperative Gabapentin to reduce post operative pain.
- Smaller but still growing number of trials evaluating the efficacy of Pregabalin to this same end.
- The consensus appears to be that the perioperative use of gabapentinoids does reduce post operative pain and opioid use.
Perioperative Utility

• In a meta-analysis that included 12 RCTs of high quality (6-7/7 Cochrane Quality Score) indicated statistically significant reduction in pain at 20-24 hours

Perioperative Utility

• Same analysis indicated a statistically significant reduction of post operative analgesic consumption but also a statistically significant increase in sedation
Perioperative Utility

- Another meta-analysis with more liberal inclusion criteria demonstrated a 35% reduction in total opioid consumption over the first 24 h following surgery, a significant reduction in postoperative pain at rest (in the first 24 h) and with movement (at 2 h, 4 h and 12 h).

We removed your spinal column... it appeared to be the source of your pain...
How to dose? Timing...

- Studies comparing timing of dosing are somewhat limited. Two studies in particular compared administration of Gabapentin 2 hours preoperatively and immediately post incision via NG tube- with no statistically significant difference in total opioid consumption or pain scores.
How to dose? Timing...

- Another small study involving two stage molar surgery utilizing post op and pre op Pregabalin showed a small advantage for post op dosing... but only for pain at rest in the first twenty four hours.
- A study examining preoperative gabapentin versus a combination regimen of preoperative and postoperative dosing found less PCA morphine use at 24, 36, and 48 h in the combination regimen.

How to dose? Timing...

- A Cochrane review utilizing data from unpublished studies indicated that post operative first dose administration of Gabapentin showed efficacy in treatment of acute post operative pain.
Studies are too few with number of patients enrolled also too few to make a definitive recommendation... However there are solid trends...

Optimal Dosing

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Surgery</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et al.</td>
<td>175</td>
<td>Laminectomy</td>
<td>Placebo, 600mg, 900mg, or 1,200mg of gabapentin given preoperatively or postincision</td>
<td>Patients receiving either 900 or 1,200mg had lower pain scores during the first 24h compared with the 600mg and placebo groups</td>
</tr>
<tr>
<td>Pandey et al.</td>
<td>100</td>
<td>Discectomy</td>
<td>Placebo, 300mg, 600mg, 900mg, or 1,200mg of gabapentin given 2h preoperatively</td>
<td>Patients receiving 2600mg had lower visual analog scores at all time points compared with placebo or 300mg groups</td>
</tr>
<tr>
<td>Van Elbraete et al.</td>
<td>67</td>
<td>Lumbar spinal fusion</td>
<td>Determination of optimal gabapentin dose for 30% reduction in morphine use by an up-and-down sequential allocation technique</td>
<td>Optimal dose for 30-50% reduction in morphine use calculated at 21.7mg/kg (1,500mg per 70kg)</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>84</td>
<td>Lumbar spinal fusion</td>
<td>Placebo, 75mg, or 150mg of pregabalin preoperatively</td>
<td>Patient-controlled analgesia and adjuvant angesic use were lower in the 150mg group but not in the 75mg group compared with placebo</td>
</tr>
<tr>
<td>Jokela et al.</td>
<td>90</td>
<td>Laparoscopic gynecological surgery</td>
<td>Active placebo, 75mg of pregabalin, or 150mg of pregabalin preoperatively</td>
<td>Pain scores at rest and in motion were lower in the 150mg group but not the 75mg group compared with placebo</td>
</tr>
</tbody>
</table>
Gabapentin versus Pregabalin

• Level of evidence for Gabapentin far outweights that of Pregabalin...
• But appears to be primarily a function of the fact that Gabapentin has been studied to a much greater degree as opposed to a true performance difference.
• Indeed it appears as though their performance is comparable.
• Gabapentin is generic, and thus less expensive.

What about Chronic Postsurgical Pain?

<table>
<thead>
<tr>
<th>Authors</th>
<th>N</th>
<th>Surgery</th>
<th>Gabapentinoid Dose</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Fassoulaki et al.</td>
<td>60</td>
<td>Abdominal hysterectomy</td>
<td>Gabapentin 400 mg every 6h beginning preoperatively and continuing for 5 days</td>
<td>Decreased incidence and intensity of pain at 1 month</td>
</tr>
<tr>
<td>Sen et al.</td>
<td>60</td>
<td>Herniorrhaphy</td>
<td>Gabapentin 1,200 mg 1h before surgery</td>
<td>Decreased pain scores at 1, 3, and 6 months</td>
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<td>Sen et al.</td>
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<td>Decreased incidence of incisional pain at 1, 3, and 6 months</td>
</tr>
<tr>
<td>Brogly et al.</td>
<td>50</td>
<td>Thyroidectomy</td>
<td>Gabapentin 1,200 mg 2h before surgery</td>
<td>Decreased incidence of neuropathic pain at 6 months</td>
</tr>
<tr>
<td>Amr and Youse</td>
<td>150</td>
<td>Mastectomy</td>
<td>Gabapentin 300 mg/day starting the night before surgery and continuing for 10 days</td>
<td>Decreased incidence of burning pain at 6 months</td>
</tr>
<tr>
<td>Fassoulaki et al.</td>
<td>75</td>
<td>Breast surgery for cancer</td>
<td>Gabapentin 1,200 mg/day for 10 days after surgery</td>
<td>Decreased incidence of burning pain at 3 months</td>
</tr>
<tr>
<td>Buvanendran et al.</td>
<td>240</td>
<td>Total knee arthroplasty</td>
<td>Pregabalin 300 mg 1–2h before surgery and a 14-day taper after surgery</td>
<td>Decreased incidence of neuropathic pain at 3 and 6 months</td>
</tr>
<tr>
<td>Personen et al.</td>
<td>70</td>
<td>Cardiac surgery</td>
<td>Pregabalin 150 mg 1h before surgery and 150 mg daily for 5 days</td>
<td>Decreased incidence of pain with movement at 3 months</td>
</tr>
<tr>
<td>Burke and Shorten</td>
<td>40</td>
<td>Lumbar discectomy</td>
<td>Pregabalin 300 mg 90 min before surgery and 150 mg at 12 and 24 h after surgery</td>
<td>Decreased pain scores and improved function at 3 months</td>
</tr>
</tbody>
</table>
What about Chronic Postsurgical Pain?

- Meta analysis combining trials evaluating the effect of gabapentin and pregabalin on chronic post surgical pain determined that though better designed and more appropriately powered trials were necessary, both gabapentin and pregabalin were effective in reducing chronic postsurgical pain.
Lidocaine infusion

• Thought to reduce pain scores, opioid consumption, PONV, time to flatus, time to bowel movement.
• Moderate evidence for open abdominal surgery.
• Cumulatively, very low evidence: 2018 cochrane update.
• Total joint (hip specifically)- found to offer no benefit
Lidocaine infusion

- Local anesthetic mechanism of action via blockade of fast voltage gated Na+ Channels—preventing generation of an action potential.
- However this mechanism does not explain benefit with levels achieved during systemic administration
- It is therefore thought that the benefit is via anti-inflammatory properties.

Lidocaine infusion

- Local anesthetics have been found:
  - to reduce polymorphonuclear granulocyte (PMN) adherance, migration, and accumulation at the site of inflammation.
  - to interfere with macrophage and monocyte function.
Lidocaine infusion

• Concern therefore becomes- what about infection?
  – Local anesthetics have inherent antibiotic and antiviral properties (e coli, s aureus)
  – However this is at higher concentrations- what about systemic use?
  – Hasn’t been an issue so far.

Lidocaine infusion

• MAC sparing
  – As high as 60% in certain animal models
  – Between 10 and 30% reduction in humans
  – Does have a reduced hemodynamic response and reduction in BIS increase, but only when exposed to surgical stimulus
  – Would need to be an anti-nociceptive mechanism? Possibly due to blockade of spinal cord WDR neurons?
Exparel

- 1.3% Bupivacaine in multivesicular liposomes.
- 285 dollars wholesale price- now even higher per 20 ml vial (previously 14 dollars)
- Traditional bupivacaine hcl 1 to 3 dollars for similar dose.
- Cost is higher yes- but can it save money by minimizing other resources? Reduce LOS?
Exparel

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Exparel

• Meta-analysis comprised of 17 studies that met strict inclusion criteria involving 779 patients
• Compared with local anesthetic infiltration (of the long acting variety...)
• No effect on pain at rest 24h after surgery
• No effect on opioid consumption 24h following surgery
Exparel

- No effect on pain at rest 48h after surgery
- No effect on opioid consumption 48h after surgery
- No effect on post operative opioid consumption 72 hours after surgery
- No effect on LOS
- No difference between ortho vs non ortho surgery

BUT....

Did show a decrease in post-operative nausea. Mechanism??
Exparel

Caveat-
Thoracic data not included (studies did not meet inclusion criteria), but infiltration technique does generate interesting discussion...

Ketamine

Did someone in here say Ketamine?
Ketamine

- Reduces opioid consumption perioperatively—particularly with thoracic, upper abdominal, and major orthopedic surgical patients
- Particularly useful in patients who are opioid tolerant
- Unique in that it is an analgesic, anesthetic, and amnestic in one drug
- Does not cause respiratory depression as monotherapy

Ketamine

- Primary mechanism is via NMDA antagonism (non-competitive), though full mechanism is not fully understood.
- Multiple additional sites of action being studied:
  - Opioid activity
  - Voltage gated Na and Ca activity
  - SNRI and SSRI effect
  - Several more...
Ketamine

• Causes increase in sympathetic tone- which makes it an ideal drug from a hemodynamic standpoint- with the caveat that it is a direct cardiac depressant...

• Can cause reversal of opioid tolerance... caution respiratory depression in patients on high dose opioid medications.

Ketamine

• Most well known adverse effect is agitation and hallucinations
• Most common side effect likely nausea/vomiting
• Can prolong QT, elevate BP, elevate liver enzymes, cause nystagmus, predispose to arrhythmias (likely catecholamine related), increase secretions, etc.
Ketamine

Meta-analysis suggested a modest but statistically significant reduction in the incidence of chronic pain after surgery following treatment with ketamine. However, small trials.

Ketamine

No more ketamine for me, I'm just going to stick to good old acid.
Esmolol

- Often used to rapidly blunt physiologic response to surgery or laryngoscopy or for rapid reduction in heart rate
- Beta1 receptor blocker
- Rapid onset- short acting with elimination half time of 9 minutes
Esmolol

- May have pain relieving properties as well
- Meta-analysis showed patients treated with an perioperative esmolol infusion had lower pain scores, reduced opioid rescue requirement, and less PONV. Esmolol also had a MAC sparing effect. There was no impact on the emergence time.
- Caveat is that the studies were small, low powered, and heterogeneous. Currently 79 registered trials looking at further study, however.

Esmolol

- Difficult to say whether the anti-nociceptive trend is due to the opioid sparing effect (and thus reduced hyperalgesia) or frank analgesic properties.
- Proposed analgesic mechanisms include:
  - by blocking β-adrenoceptors within the brainstem and decrease neuronal inflow traffic into the central nervous system rather than acting within the brain directly
  - Decreased hepatic blood flow prolonging the duration of other anesthetic/analgesic medications?
  - Anti-inflammatory?
Dexmedetomidine

- Sedative and analgesic
- α2 receptor agonist, with 8 times greater receptor affinity than clonidine
- Does not cause respiratory depression as monotherapy
- Biphasic effect on blood pressure - lower BP with lower doses (central activation) and higher BP with higher doses (peripheral activation)
Dexmedetomidine

- Other reported side effects include: nausea, vomiting, dry mouth, bradycardia, atrial fibrillation, pyrexia, chills, pleural effusion, atelectasis, pulmonary edema, hyperglycemia, hypocalcaemia, acidosis...
- However, no absolute contraindication to its use

Dexmedetomidine

- As with all other adjuvant drugs...

Cochran Review for abdominal pain-
“compared with no treatment - seemed to reduce the need for opioids without worsening the experience of postoperative pain after abdominal surgery in adults. However, the quality of evidence was very low because studies were poorly conducted and because results were not similar across studies”
Dexmedetomidine

• And our very own Dr. Naik:

*The Effect of Dexmedetomidine on Postoperative Opioid Consumption and Pain After Major Spine Surgery*

Airton L. Abreu, Edward C. Carriquiry, Rhodiane M. Loureiro Fernandes, Geovani K. Cadenaboy, Timothy L. McHugh, Marcel C. Durante

Conclusion:

No difference in post operative opioid consumption and pain scores (24, 48, and 72 hours).

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Dexmedetomidine

The question becomes whether the method of usage bears an impact (probably yes).
Long acting and Sustained release Opioids

- Rule of thumb (true in MOST cases- but not all):
  Any “Contin” or “ER” opioid dose can be determined by the following method:

Expected daily equivalent dose of the short acting = Total daily dose of long acting

Example: 10mg of Oxycodone (IR) q4hours = 60mg of Oxycodone (IR) a day

Therefore this patient would get 60mg of Oxycontin a day, BUT split over 2 (sometimes 3) doses.

Thus 30mg BID Oxycontin = 10mg q4hours Oxycodone

Long acting and Sustained release Opioids

- So what does this mean? In theory...

![Diagram showing pharmacokinetics of different opioid formulations]
Long acting and Sustained release Opioids

• So what does this mean? In theory...

Long acting and Sustained release Opioids

• However in a study for osteoarthritis pain...
  Patients receiving short- and long acting opioids reported no significantly different scores for pain levels ($P = .201$ and $P = .296$, respectively). Though patients taking short-acting opioids had numerically higher average pain scores than patients receiving combination or extended release therapies (5.67 vs 5.35, respectively), the analgesic effects between short- and long-acting opioids were not considered significant ($P = .201$).
Long acting and Sustained release Opioids

With that said...

– Shorter acting, quicker onset opioids have a stronger association with hyperalgesia... (though occurs with all opioids with prolonged exposure...)
– Shorter acting, quicker onset opioids tend to have a greater dopamine surge...
– Utilization as single dose “priming” method as opposed to repeated dosing requires further study...

Methadone
Methadone

- Exists in a racemic mixture where one enantiomer (Levomethadone) binds to the \( \mu \) receptor and the other enantiomer (Dextromethadone) binds to the NMDA receptor.
- Single dose lasts 4-8 hours (analgesic time), which is extended with larger dosing or repeated dosing.
- Elimination half-life ranges widely but generally 15-55 hours. (traditionally taught as 24 hour half-life)
Methadone

- Only opioid shown to reduce post operative opioid consumption (complex spine surgery)
- Advantages:
  - Less Tolerance
  - Less Hyperalgesia
  - Neuropathic properties
  - Less addictive?

Methadone

- Disadvantages:
  - Management gets dicey at higher doses
  - In untrained hands- potentially higher risk of respiratory depression
  - Can prolong QT at higher doses
  - Repeated dosing significantly prolongs duration (maybe not a bad thing)
Methadone

<table>
<thead>
<tr>
<th>24 Hour Oral Morphine Equivalent</th>
<th>Morphine:Methadone Ratio per 24 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 mg/24 hrs</td>
<td>2:1</td>
</tr>
<tr>
<td>30 – 99 mg/24 hrs</td>
<td>4:1</td>
</tr>
<tr>
<td>100-299 mg/24 hrs</td>
<td>8:1</td>
</tr>
<tr>
<td>300-499 mg/24 hrs</td>
<td>10:1</td>
</tr>
<tr>
<td>500-999 mg/24 hrs</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1000 mg/24 hrs</td>
<td>20:1</td>
</tr>
</tbody>
</table>

Methadone

Minimal Peaks and Troughs in Absorption of Zohydro Compared With IR Hydrocodone
Oral? But this is surgery...

JAMA Internal Medicine study demonstrated a 31% reduction in total opioid consumption with no change in pain scores by transitioning from IV use to oral/subcutaneous use where possible on an inpatient unit.

20mcg of Fentanyl IV = 0.4mg hydromorphone IV = 2mg oral hydromorphone or 5mg oral oxycodone

Think about the analgesic impact per MME when choosing your opioid...

Our Outcomes

To reiterate: goal was to generate an analgesic bridge to PACU while minimizing IV consumption...
Opioid consumption in MMEs

Opioid MME per patient by phase of care
Future

- Endocannabinoid system
- Resiniferatoxin- champion of Scoville Scale
- MAGNETS!! How do they work?? (Transcranial Magnetic Stimulation)
- Peripheral Stimulator
- Detox? We’ll find out....
References


