Objectives

• 1. Develop a multimodal and evidenced based approach to treating acute pain in an opioid naïve/opioid intolerant patient

• 2. Develop a pragmatic approach to treating acute pain in the opioid tolerant patient

• 3. Utilize non-opioid strategies to optimize patient satisfaction and safety
Case Scenario #1

- A 48 yo female with adenocarcinoma of the colon presents for an open sigmoid colectomy

- Past medical history is unremarkable

- Takes acetaminophen and NSAIDs at home for pain

- NKDA

- Patient would like to avoid epidural analgesia as they were one sided during her pregnancies and she wants to walk P.O.D #1

- Perioperative Pain Plan???
Techniques of Perioperative Pain Control

- “Multimodal”

- Peripheral Nerve Blocks
- Neuraxial (Epidural, spinal opioids)
- Oral (opioid and nonopioid)
- Continuous non-opioid infusions
  - Ketamine and Dexmedetomidine (Precedex)
- Intravenous opioids
Multimodal Pain Control

- Defined as the continuous use of more than one method for controlling acute pain
- Takes advantage of additive or synergistic effects through combining multiple agents
- Reduced side effects (enhanced safety) due to lower doses of drugs and differences in SE profiles
Mechanistic Approach to Multimodal Analgesia

Perception: opioids, NMDA antagonists, APAP Anticonvulsants, COX-2 inhibitors, α2-agonists

Modulation: Neuraxial opioids, NMDA antagonists

Transmission: Local anesthetics, opioids, α2-agonists

Transduction: Local anesthetics, anticonvulsants, NSAIDs, COX-2 inhibitors,

Adapted with permission from Kehlet H, Dahl JB. Anesth Analg. 1993;77:1048-1056.
Perioperative Pain Control

- Options for this patient include:
  - IV PCA
  - Neuraxial Opioids
  - Surgeon Infiltration
  - Truncal Blocks
    - Transversis Abdominal Plane (TAP) Blocks, Rectus Sheath Blocks
  - Paravertebral Blocks
Perioperative Pain Control cont.

- You recommend a single shot preservative free morphine spinal and a postoperative PCA
  - As well, you recommend perioperative NSAIDs, acetaminophen, scheduled oral opioids and a preop antinociceptive (multimodal)
Single Dose Spinal Morphine

- Any thoracic, abdominal, LE procedures
- Onset of action 30-45 minutes
- Duration of effective analgesia: 12-24 h (Depodur??)
- Duration of risk of side effects: up to 24 h
  - Pruritis, Nausea/vomiting, Respiratory Depression
- Increased monitoring postoperatively
  - Includes continuous pulse oximetry
- Provide PCA medicine for break through pain
- Do not put basal on PCA in first 24 h
Single Dose Spinal Morphine

• Numerous studies indicate that preservative free single shot morphine spinals:
  – Reduce pain scores for 12 hours
  – Reduce morphine consumption by 50-75% for the first 24 hours
Case #1 cont.

- Unfortunately, the patient refuses all neuraxial analgesia…
Surgeon Infiltration

• A large metaanalysis looking at the efficacy of wound catheters
  – 32 studies over 40 years
  – *Showed no improvement in analgesia at rest or with activity except in one small subgroup*
    • Women undergoing gynecologic and obstetric surgery at 48 hours

• Intraperitoneal instillation of bupivacaine during laparoscopic cholecystectomy yielded *inferior postoperative pain* control when compared to intramuscular tramadol

• Intraperitoneal nebulization of ropivacaine during laparoscopic cholecystectomy yielded reduced shoulder pain and unassisted walking time but increased nausea and vomiting
Truncal Blocks

- Transversis Abdominis Plane (TAP) and Rectus Sheath blocks achieve analgesia by blocking the nerves of the abdominal wall

- 52 Patients undergoing umbilical hernia repair received either local infiltration by the surgeon or rectus sheath blocks
  - Improved pain and decreased opioid consumption in the rectus sheath block group (44)

- Metaanalysis of TAP blocks from 1990-2009 shows improved postoperative pain
  - Improved pain scores for 6 hours
  - Decreased postoperative opioid consumption and side effects
  - Case and provider dependent (46)
TAP Block
Paravertebral Blocks

• Blocking individual nerve roots as they leave the spinal cord in the paravertebral space

• Continuous paravertebral catheters resulted in comparable analgesia when compared to thoracic epidurals in patients undergoing thoracotomies. Better hemodynamic stability and less pressor requirements

• Continuous paravertebral catheters comparable to thoracic epidurals in patients undergoing thoracotomies/lung resections
  – Postoperative complications and analgesia comparable between the two groups
  – PVB group left hospital one day sooner (six v. seven days)
Paravertebral Blocks cont.

• Metaanalysis revealed that single shot paravertebral blocks are superior to general anesthesia for breast surgery
  – Decreased pain, nausea, vomiting, hospital length of stay

• In outpatient inguinal hernia repair, PVB with 0.5% levobupivacaine provided improved recovery, long-lasting analgesia, shorter recovery room stays, and earlier home readiness time than fast-track GA via LMA.
Case Scenario #1 cont.

- Pt. elects for the multimodal plan including TAP Blocks. Pt. does quite well using minimal opioids and is discharged on P.O.D. #3. Due to minimal opioid consumption, patient has minimal side effects.
Case Scenario #2

• A 32 yo female with a history of chronic pain secondary to chronic pancreatitis/sphincter of Oddi dysfunction presents for a biliary bypass surgery

• Past medical history is unremarkable except for chronic pain

• Medications include oral dilaudid 4-8mg every 4-6 hours and oxycodone 5-10mg as needed for breakthrough pain.

• NKDA

• Perioperative Pain plan?????
Opioid-dependent Patients and Perioperative Management Issues

• Only a small number of published reviews exist that address the treatment of acute pain in patients with opioid dependence and substance abuse disorders

• Few controlled studies or scientifically rigorous sources of data available to guide the anesthesiologist in optimizing anesthetic and analgesic care, despite the increasing prevalence of opioid-dependency
Who is Tolerant?

• Patients taking $\geq 50$ mg of oral morphine equivalent per day for over 2 weeks should be considered opioid tolerant

• What is 50 mg of oral morphine equivalent?
  – Duragesic 25 mcg patch
  – 10 Vicodin 5mg pills
  – 7 Percocet 5mg pills
  – MS Contin 30 mg bid
  – Oxycontin 20 mg bid
  – Dilaudid 12.5 mg/day orally
  – Morphine IV 17 mg; Dilaudid IV 2.5 mg; Fentanyl IV 175 mcg

  – With tolerance and higher doses of opioids, withdrawal must always be considered
Case Scenario #2

- You recommend to this patient a general anesthetic, a patient controlled thoracic epidural (PCEA), conversion to a long acting opioid agent when tolerating oral medications, and a multimodal approach to her perioperative pain.

- The patient asks why epidurals are better than intravenous medications.
Clinical Outcomes Related To Epidural Analgesia in Patients Undergoing Thoracic and Large Abdominal Surgeries

- Better pain control
- Decreased incidence of cardiovascular and pulmonary complications
- Decreased duration of mechanical ventilation
- Decreased incidence of major infections
- Decreased cancer recurrence
- Less morbidity and mortality in high risk groups
- Decreased stress response
- Decreased deep venous thrombosis
- Decreased blood loss
Benefits Of Epidural Analgesia

• Provides intense, prolonged analgesia limiting the total amount of systemic opioids and decreasing the potential for opioid-related side effects.

• Prevention/improvement of phantom limb pain
  – In patients undergoing lower limb amputation, initiation of an epidural two days prior to surgery greatly reduced phantom limb pain

• Improvement in COPD patients
  – Epidurals decrease postoperative complications (pneumonia and mortality) in chronic obstructive pulmonary disease patients undergoing major abdominal surgery

• Reduce perioperative morbidity and mortality after major abdominal and thoracic surgery
  • Improved cardiac and intestinal morbidity
  • Improved pain
  • Benefit in fast track and laparoscopic surgeries is questionable
  – May reduce tumor progression
Benefits of Epidural Analgesia Cont.

• Cancer Recurrence:
  – Intraoperative neuraxial anesthesia (epidural) resulted in increased relapse-free survival in patients undergoing cytoreductive surgery for ovarian cancer (12).
  – Retrospective review of patients undergoing radical retropubic prostatectomies receiving intraoperative sufentanil (97%) vs. epidural analgesia (52%)
    - Sufentanil group had a higher incidence of cancer relapse (13).
  – 35 patients undergoing exploratory laparatomy and colon resection for suspected cancer received either epidural or PCA for postoperative pain.
    - Epidural group had reduced inflammatory profiles, immunosuppression, and complications (14).
Benefits of Epidural Analgesia Cont.

- Patients undergoing surgery for serous adenocarcinoma receiving either epidural or IV opioids for post operative pain
  - 78% and 61% 3 and 5 year survival for epidural group
  - 58% and 49% 3 and 5 year survival for IV opioid

• A large cohort study found that epidural use is associated with improved survival in patients with nonmetastatic colorectal cancer undergoing resection but does not support an association between epidural use and decreased cancer recurrence
  - 61% v. 55% survival
Benefits of Epidural Analgesia Cont.

• Surgical site infection:
  – 300,000 women in Taiwan underwent caesarian section from 2002-2006
  – 95% received neuraxial anesthesia (epidural or spinal)
  – 5% received general anesthesia
  – The incidence of surgical site infection was twice as common in the general anesthesia group (1.9% v. 0.9%)

• Laparoscopic Surgery
  – 91 patients undergoing laparoscopic colorectal surgery receiving either epidural, spinal or PCA for postoperative pain control
  – Epidural group had longer discharge times (1d) and return to bowel function with no improvement in pain (v. spinal) or pulmonary morbidity
Combining Opioid and Local Anesthetic Drugs is the Key

- Synergistic
- Allows less of each to be used in combination leading to less side effects and faster recovery
- PCEA more effective than continuous infusion (Bupivacaine 0.1% with Dilaudid 15mcg/cc)
  - 8 mL basal
  - 4 mL bolus dose
  - 15 minute lockout interval
Opioids: Mechanism of action

• Diffuses across the dura mater into the cerebrospinal fluid
• Binds with opioid receptors in the dorsal horn of the spinal cord and modify the transmission of pain impulses to the brain
Opioids

Equianalgesia Among Routes

• Delivery of the drug close to the opioid receptors allows pain relief with smaller doses and decreased side effects
Opioids
Mechanism of Action

• The pharmacokinetics of epidural opioids are almost entirely dependent on their lipid/water solubility characteristics

Relative Lipid Solubility

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<tr>
<td>Fentanyl</td>
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</table>
Opioids

• Morphine
  – First used in 1979 following discovery of opioid receptors in dorsal horn of spinal cord
  – Highly water soluble, not lipid soluble
  – Wide spread in CSF covering many dermatomes
  – Slower onset of action: 15 to 60 minutes
  – Peak: 60-90 minutes and 12 hours
  – Long duration of action: 8 to 24 hours
  – Well documented delayed respiratory depression
  – Typical epidural dosing
    • Bolus 2-4mg
    • Infusion 20-50mcg/cc
  – **Patients should undergo closer post operative monitoring if bolus delivered!!**
Opioids

- Fentanyl
  - Highly lipid soluble
  - Diffuses rapidly into CSF and binds quickly with opioid receptors
  - Narrow “segmental” spread in CSF
  - Rapid onset of action: 5-10 minutes
  - Peak: 10-20 minutes
  - Short duration of action: 1 to 3 hours
  - Typical epidural dosing
    - Bolus 25-50mcg
    - Infusion 1-5mcg/cc

- Likely, no spinal analgesic effect when used in infusion
Opioids

- Hydromorphone
  - Low lipid solubility, more water soluble
  - Moderate spread in CSF
  - Onset of action: 5 to 15 minutes
  - Peak: 30 minutes
  - Duration of action: 6 to 16 hours
  - Moderate risk of delayed respiratory depression
  - Typical epidural dosing
    - Bolus: 200-500mcg
    - Infusion 5-15mcg/cc
Case Scenario #2 cont.

- You plan on a prolonged thoracic epidural for this patient plus a multimodal regimen

- But the surgeon states that epidurals never work and are dangerous!!
Thoracic Epidurals, cont.

- You explain to the surgeon that the efficacy of thoracic epidurals is difficult to assess but is probably in the range of 70% in the hands of an experienced practitioner.

- Other side effects include:
  - Infection: 1:100,000
  - Bleeding/hematoma 1:10,000-1:150,000
  - Neurologic Damage 1:10,000
  - LE weakness
  - Urinary Retention: 2-4%
  - Itching, nausea/vomiting
Case Scenario #2

- After surgery, this patient is placed on a PCEA, IV methadone is started and transitioned to PO methadone. An NSAID, acetaminophen, and antinociceptive agent are implemented. Pt. is discharged home on P.O.D. #5 with adequate pain control.
Case Scenario #3

- A 48 yo male with congenital scoliosis and a history of chronic back pain/failed back surgeries presents for a hardware removal and T1-L5 spinal fusion

- PMHx: Chronic Pain with failed spinal cord stimulator, hypertension, and depression

- Medications: Oxycontin 300mg BID, Oxycodone 20-40mg 6-8x day, actiq (fentanyl lollipops) 600mcg every 2-3 hours

- NKDA

- Perioperative Plan???
Case Scenario #3 Cont.

- You propose to this patient a general anesthetic, an IV PCA, an intraoperative/postoperative ketamine infusion, conversion (titrating down) to methadone, an anxiolytic, an NSAID (surgeon preference), acetaminophen, and an antinociceptive agent.
Case Scenario #3 Cont.

- Pt. inquires about the use of ketamine, antiinflammatories, and antinociceptive agents. He asks why he just can’t have more pain meds???
Opioid Induced Hyperalgesia (OIH)

- Opioid-induced hyperalgesia (OIH) refers to a phenomenon whereby excessive opioid administration results in a lowering of pain threshold, increasing opioid tolerance, worsening pain despite accelerating opioid doses, and abnormal pain symptoms such as allodynia.

- The underlying pathophysiology of this phenomenon, although still unclear, appears to be related to an opioid-induced imbalance between the antinociceptive and pronociceptive systems.

- Treatment strategies include opioid dose reduction, opioid rotation, use of agents with NMDA receptor antagonism, and a properly timed NSAID.
Ketamine

- NMDA antagonist
- Used as an anesthetic
- Produces catatonic state, psychotomimetic effects during recovery (“dissociative” state)
- Analgesic in low doses
- Can be very effective in crisis situation: tolerant patient with severe pain, unresponsive to high dose opioids
- Analgesic doses typically start at 0.25-0.5mg/kg bolus and infusion at 5-30mg/hours
- Side effects (although rare at these doses) include hallucinations, sedation, and sympathetic stimulation
- Very little (less than opioids) respiratory depression
- Can be implemented on the floors
- Provide anxiolysis
Ketamine Cont.

- Very inexpensive
- Extremely opioid sparing
- Prevention of conversion to chronic pain
- May improve postoperative rehabilitation when compared to IV opioids
  - Ability to decrease postoperative (up to six weeks) opioid consumption and pain in the chronic pain patient
  - Potentially effective in treating opioid induced hyperalgesia
Methadone

- Oral/IV NMDA antagonist
- Originally used for drug addiction
- Very non-addictive
- Very cheap
- Good data supporting its use to decrease pain in complex spine surgery
- Dosing orally is 2.5mg-5mg 3-4x/day to start
- Very long half life (10-100 hours)
- Maximum dose 120mg/day
- Can be sedating when starting
- Potential Qt prolongation
NSAIDS

• NSAIDs have consistently been demonstrated to reduce opioid requirements by 20% to 40%.
• 25% of randomized postoperative studies of NSAID treatment demonstrate improvement in outcome secondary to reduction of opioid related side effects.
• A 2012 metaanalysis (13 randomized trials) showed that 60mg single dose ketorolac:
  – Reduces postoperative pain
  – Reduces postoperative nausea and vomiting
Ketorolac (Toradol)

• Only commonly used injectable NSAID
• Indicated for short term (up to 5 days) management of moderately severe acute pain that would normally be treated with an opioid
• Increasing dose beyond label recommendations does not increase efficacy and does increase risk of serious adverse events
• Dose loading does not increase efficacy
• 30 mg IV/IM q 6h standard dose, 15 mg IV/IM standard dose for > 65 y.o., less than 50 kg, frail, renally impaired
• 30mg of Ketorolac is equivalent to 10mg of IV morphine
NSAIDS Mechanism of Action

• Suppression of prostaglandin synthesis through inhibition of the COX enzyme

• Prostaglandins are potent mediators of inflammation and pain, as well providing protective homeostatic activity

• Cox-1 “Constitutive”: always present, normal protective homeostatic/housekeeping functions: kidney, stomach, platelet function (Thromboxane A2)
  – Caution with renal dysfunction, stomach upset, and bleeding

• Cox-2 “Inducible”: made by body in response to tissue injury, expressed mainly at sites of inflammation
Advantages of COX-2 Inhibitor Drugs

• Do not have significant effect on platelet function and can be administered peri/postop
• Possible decrease in GI side effects
• Little to no difference in renal effects
• Numerous studies demonstrating:
  – decreased opioid consumption and associated side effects
  – Improved pain relief
  – Faster recovery
• Celecoxib (Celebrex)
Acetaminophen

- Orally:
- Cochrane database states that it is effective as a sole agent in about half of the population
- When used as multimodal regimen, effective
- 650mg-1000mg 3-4x daily
Acetaminophen Cont.

- Intravenous:
  - There are six published randomized controlled trials (RCTs) that have evaluated single or repeated dose administration of IV acetaminophen in patients undergoing spinal disc surgery
    - All support a significant decrease in pain scores v. placebo
  - There are six published randomized controlled trials (RCTs) that have evaluated IV acetaminophen as part of a multimodal pain management regimen in orthopedic surgery
    - All supported a significant decrease in pain scores v. placebo
    - Decrease in morphine consumption
  - Dosing is 15mg/kg or 1 gram three to four times daily
Dexamethasone

- 8mg of intravenous dexamethasone improved emotional state, physical state, nausea and pain scores one day after surgery in patients undergoing laparoscopic cholecystectomy.

- A large metaanalysis also showed that patients undergoing a variety of surgeries (24 trials in total) who received greater than 0.1mg/kg of dexamethasone had:
  - Reduced postoperative pain
  - Reduced opioid consumption
  - Appears to be more effective if given preoperatively
  - Of the studies that addressed safety, no episodes of wound infection/decreased healing
Antinociceptive Agents

- Most typically used/studied perioperatively:
  - Gabapentin (Neurontin)
  - Pregabalin (Lyrica)
- Mechanism of action:
  - Calcium channel blocker (alpha 2 delta subunit)
  - Originally used for seizure prophylaxis
  - Appears to inhibit pain as well as seizure transmission
- Main side effect is sedation
- In outpatient setting, sedation may be an issue
- Dose is 75-300mg orally for pregabalin
Antinociceptives Cont.

- 900mg or 1200mg of gabapentin administered to patients undergoing lumbar laminectomy either pre or post operatively
  - significantly decreased pain and morphine requirements for the first 12 hours.

- Pregabalin 75mg administered twice daily for one day in patients undergoing mastectomies
  - Significantly reduced postoperative pain

- Patients undergoing open nephrectomies received either 300mg of pregabalin (lyrica) or placebo prior to surgery
  - The pregabalin group had significantly less hyperalgesia
  - The pregabalin group consumed 40% less postoperative opioids (48 hours)
Anxiolytics/Antispasmodics

• A substantial component of chronic/perioperative pain is due to anxiety.
• Some basic science research states that the GABA (α) receptor even has some analgesic properties.
• Therefore perioperative anxiolysis is a must
  – Valium (Diazepam)
  – Ativan (Lorazepam)
  – Klonopin (Clonazepam)
  – Baclofen
Patient number three cont.

- Patient has been previously treated with ketamine and does not like its side effect profile

- You recommend precedex (dexmedetomidine)
- Currently FDA approved for pre/post operative sedation
- Mechanism of action:
  - Selective Alpha 2 agonist resulting in decreased release of substance P
- Not well studied but has shown opioid sparing effects in bariatric surgery patients
- Dose range is 0.2-0.7mcg/kg/hour
- Side effects include sedation, bradycardia, hypotension
- ICU level of monitoring necessary
Case Scenario #3 cont.

- A dexmedetomidine infusion is run during the case as a supplement to the general anesthesia. It is continued postoperatively for 24 hours. The patient is also given a PCA, IV methadone, IV acetaminophen, valium, and perioperative NSAID/antinociceptives. Oral methadone is titrated to 30mg PO QID with 20-40mg of oxycodone for breakthrough pain. Pt. is discharged home on postoperative day number 8.
# Equianalgesic Chart

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<th>Opioid</th>
<th>IV</th>
<th>PO</th>
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<tbody>
<tr>
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<td>Hydromorphone</td>
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</tr>
<tr>
<td>Fentanyl</td>
<td>0.1 mg</td>
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<tr>
<td>TD Patch 100 mcg/hr</td>
<td>100 mg</td>
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</tr>
<tr>
<td>Methadone</td>
<td>10 mg</td>
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<tr>
<td>Oxycodone</td>
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<td>Oxycontin</td>
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<tr>
<td>Hydrocodone</td>
<td>--</td>
<td>30 mg</td>
</tr>
<tr>
<td>Meperidene</td>
<td>75 mg</td>
<td>300 mg</td>
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</table>
Equianalgesic Chart

- Dose listed is for severe pain in opioid naïve pt.
  - reduce by 50% for moderate pain and 75% for mild
  - reduce again by 25-50% for elderly or debilitated

- Use as a guide only - high inter and intra individual variability

- Titrate to patient response and clinical situation
  - assess and reassess often

- The dose that works is the dose that works!
Summary

• 1. For any surgery, a **multimodal pain** plan improves patient satisfaction, decreases patient side effects, shortens hospital length of stay, and may decrease conversion to chronic pain.

• 2. Detection of opioid tolerant patients is important as it will change your postoperative pain management. As these patients do not have a traditional response to opioids, an alternative plan should be formed prior to their surgery.

• 3. In situations where regional/neuraxial anesthesia is not an option, other intravenous/oral options exist which can provide optimal pain relief.
Thank You

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