Objectives

- Review of pain physiology
- Evaluate need for continuing opioid substitution therapy
- Review Neuraxial and Periperal Regional Anesthesia
- Learn ways to decrease or abstain from the use of opioids in the perioperative arena

Opioid Use In The United States

- US consumes 80% of all opioids while only having 5% of the world's population
- Highest-risk group is between ages 35-54 years old
- Opioid related deaths exceed mortality from firearms and motor vehicles
- Approximately 4% of prescription opioid users start using heroin
- 80% of heroin users started using prescription opioids initially
Post-op Opioid Use
- Study of 39,140 opioid-naïve patients having major surgery
  - 49.2% D/C with opioid prescription
  - 3.1% on opioids 90 days after surgery

Post-op Opioid Use
- Study of 391,139 opioid-naïve patients having short-stay surgery
  - 7.7% prescribed opioids 1 year after surgery
  - 44% more likely to be on opioids at 1 year if prescribed within 7 days of surgery

Post-op Opioid Use
- CDC study of 1.3 million patients demonstrated probability of long term opioid use increased after 5 days of opioid use
  - 6% on opioids at 1 year with 5 days use
  - 13.5% on opioids at 1 year with ≥ 8 days use
  - 29.9% on opioids at 1 year with ≥ 31 days use
Is Opioid Addiction A Surgical Complication?

- Study of 36,177 patients
  - 80.3% had minor surgical procedure
  - 19.7% had major surgical procedure
- Minor surgical procedure had 5.9% persistent opioid use
- Major surgical procedure had 6.5% persistent opioid use

Anatomy of Pain
Anatomy Of Pain
○ 2 types of afferent nociceptive fibers
  ○ Aδ fibers
  ○ C fibers

Aδ Fibers
○ Lightly myelinated and small diameter (2-5 µm)
○ Respond to mechanical and thermal stimuli
○ Transmit rapid, sharp pain
○ Allow localization of pain
○ Responsible for initial response to acute pain

C Fibers
○ Unmyelinated and smallest fiber (<2µm)
○ Respond to chemical, mechanical, and thermal stimuli
○ Transmit slow, diffuse, dull pain
Substances Released By Nociceptive Fibers
- Aδ fibers release glutamate
- C fibers release both Substance P and glutamate

Glutamate
- Key excitatory neurotransmitter in the somatosensory system
- Activates postsynaptic AMPA and NMDA receptors

NMDA And Mg²⁺
- NMDA receptors are inactive due to Mg²⁺ ion
- Constant depolarization of NMDA receptor causes Mg²⁺ ion to release
- Release of Mg²⁺ ion causes influx of Ca²⁺
- Ca²⁺ increases NO production causing increased release of glutamate
Substance P
- Key excitatory neuropeptide in the somatosensory system
- Released by C fibers primarily
- Activate NK1 receptors in Lamina I and II

Types of Pain
- Somatic pain
  - Well-localized pain
  - Described as sharp, crushing, tearing pain
  - Follows a dermatomal pattern
- Visceral pain
  - Poorly localized
  - Described as dull, cramping, or colicky pain
  - Associated with peritoneal irritation, dilation of smooth muscle or a tubular passage

Stages of Pain
- Transduction- stimulus converted to electrical signal
- Transmission- converted electrical activity conducted through the nervous system
- Modulation- Alteration of signal along the pain transmission pathway
- Perception- final stage of where there is a subjective sensation of pain
Peripheral Sensitization
- Tissue injury causes release of numerous chemicals (i.e., bradykinin, prostaglandins, serotonin, cytokines, and hydrogen ions)
- These chemicals may:
  - Directly induce pain transmission
  - Increase excitability of nociceptors and decrease pain threshold

Central Sensitization
- Known as Wind up
- Constant release of glutamate and Substance P
- Results from peripheral nerves being sensitized

Opioid Induced Hyperalgesia
MOA Of Opioids
- Activate intracellular G-proteins
- Hyperpolarization of afferent neuron
- Inhibition of excitatory neurotransmitter release (Glutamate and Substance P)
- Stimulate postsynaptic opioid receptors
- Antagonize the depolarizing effects of Substance P and glutamate

Opioid Mechanism of Action

Opioid Induced Hyperalgesia (OIH)
- State of nociceptive sensitization caused by exposure to opioids
- Patient becomes more sensitive to certain painful stimuli
- May occur after single dose of an opioid
  - Remifentanil>Fentanyl>Morphine
Causes Of OIH
- Central glutaminergic system
- Spinal dynorphins
- Descending inhibitory pathways

Glutamate Role In OIH
- Glutamate plays a central role in development of OIH
- Opioids activate Gs protein which increases the amount of glutamate released
- Activation of NMDA receptors increases NO production and decreases postsynaptic µ- opioid receptor function
- Inhibition of NMDA receptor prevents tolerance and OIH

Spinal dynorphins
- Dynorphin levels increase with prolonged mu-receptor agonist administration
- Increased dynorphin levels cause release of excitatory neuropeptides such as calcitonin gene related peptide, which increases pain transmission
- Studies show that reversal of dynorphin can restore analgesic effects of morphine
Descending Inhibitory Pathway OIH

- Opioid modulation of pain at the supraspinal level has a unique action on a subset of neurons in the RVM.
- There is an actual increase in spinal nociceptive processing when they are activated by opioids.
- Lesioning of the dorsolateral funiculus prevents the release of excitatory neuropeptides.
- Injection of local anesthetics into the RVM prevented or reversed OIH and tolerance to opioids.

Opioid Substitution Therapy

- Buprenorphine
  - Partial δ-agonist and high affinity
  - 1mg reduce δ opioid receptor binding by 79 to 99%
  - δ and μ receptors antagonists
  - Long half-life (24 to 60 hours)
- Methadone
  - δ-agonist and NMDA antagonist
  - Withdrawal suppression of 24 hours
**Perioperative Management of Patient Taking Methadone**

- Continue treatment day of surgery
- May change from oral to IV dose
  - IV given 50% of oral dose divided into q 6 hours dosages
  - i.e. PO 80mg, give 10mg q 6 hours IV

**Perioperative Management of Patient Taking Buprenorphine**

- No consensus or high-level evidence exists on optimal acute pain management
- Type of surgery and expected pain influences continuation vs discontinuation
  - University of Michigan protocol
  - Discontinue 72 hours prior to surgery
  - Provide alternative modalities to decrease post-operative pain

**Dilemmas of Discontinuing Buprenorphine**

- Logistics of management of opioid replacement therapy by prescribing physician
  - 2 to 4 week for full tapering period
  - Reinitiation period post-surgery
  - Risk for opioid-induced respiratory depression
  - Risk for relapse
Opioid Free Anesthesia

What Is Opioid Free Anesthesia (OFA)
- The absence of using mu-receptor agonist opioids intraoperatively
- It is not the total absence of opioids in the entire perioperative period, but use of opioids as the last line of treatment instead of the first in the postoperative period
- It is a scientifically-based, systematic treatment of the surgical patient

Why use opioids?
- Opioids were primarily used initially because their safe intraoperative profile
  - minimal cardiac depression
  - Blunting of pain transmission
  - Provide the basis of postoperative pain control
Why Not To Use Opioids
- Negative side effect profile
  - Respiratory depression, N/V, pruritus, urinary retention
  - Opioids suppress the immune response
  - Suppression of Natural Killer cells
  - Cause cognitive/sleep dysfunction
  - Increased risk for addiction postoperatively
  - Increased risk of chronic pain with opioid administration

Benefits Of OFA
- Stable hemodynamics intraoperatively
- Decreased risk of respiratory depression
- Prevention of chronic pain
- Increased effectiveness of opioids administered postoperatively
- Decreased incidence of N/V, pruritus, constipation, urinary retention, immune suppression, and cognitive/sleep dysfunction

Methods Of OFA
- Management of peripheral sensitization
- Management of central sensitization
- Prevention of OIH
- Weight based dosing on drugs
  - IBW
- Adjusted body weight for patients whose actual body weight is 30% greater than IBW
Peripheral Sensitization
- Inflammatory process caused by tissue injury
- Release of inflammatory mediators i.e. bradykinin, prostaglandins, interleukins, and substance P
- Decreased pain threshold of C and Aδ fibers
- Increased frequency and amplitude of pain signal to spinal cord

Management Of Peripheral Sensitization
- Local Anesthetics
  - Neuraxial blocks
  - Peripheral nerve blocks
  - Lidocaine infusion
- Steroids
  - Decadron
- NSAIDS
  - Toradol
  - Celebrex
  - Cannaboids

Neuraxial Regional Anesthesia
- Spinal anesthesia
  - Placement of local anesthetic in cerebral spinal fluid
  - Adequate surgical anesthesia for abdominal and lower extremity surgeries
  - Limited to one administration of local anesthetic
Neuraxial Regional Anesthesia

- Epidural anesthesia
  - Placement of catheter outside of the dura
  - Local anesthetic blocks at spinal nerves exiting foramen
- Segmental anesthesia
- Adequate for thoracic, abdominal, and lower extremity anesthesia
- Possible to use for post-op analgesia

Peripheral Regional Anesthesia
Upper Extremity Nerve Blocks

Interscalene Nerve Block

- Injection of local anesthetic medication at the root level of brachial plexus
- Adequate surgical anesthesia and analgesia for shoulder, clavicle, and upper arm
- Caution in patients with compromised respiratory system

Interscalene Nerve Block

![Ultrasound anatomy image]

Courtesy of Block Buddy App
Supraclavicular Nerve Block
- Injection of local anesthetic medication at the trunk level of brachial plexus
- Adequate analgesia for shoulder, arm, wrist, and hand surgery

Infraclavicular Nerve Block
- Injection of local anesthetic medications at the cord level of brachial plexus
- Adequate analgesia for arm, wrist, and hand surgery
Infraclavicular Nerve Block

Axillary Nerve Block
- Injection of local anesthesia medications around terminal branches of brachial plexus
- Adequate analgesia for distal arm, wrist, and hand surgery
Terminal Nerve Blocks
- Injection of small amounts of local anesthetic around individual nerves as they pass distal to brachial plexus
- Most common is median nerve block
  - Carpal Tunnel Release

Cervical Plexus Blocks
- Injection of local anesthetic in neck at level of C4 deep to the Sternocleidomastoid muscle
- Subcutaneous injection of local anesthetic along the posterior border of Sternocleidomastoid muscle
- Provides analgesia for carotid endarterectomy, clavicle surgery, and supplementation for shoulder surgery

Cervical Plexus Block
Lower Extremity Nerve Blocks

Fascia Iliaca Block
- Injection of local anesthesia medications in fascial plane above iliacus muscle
- Reliably blocks lateral femoral cutaneous, femoral nerve, and obturator
- Adequate analgesia for hip and femoral shaft surgery

Courtesy of Block Buddy App
Femoral Nerve Block

- Injection of local anesthetic medication around femoral nerve
- Provides adequate analgesia for knee and medial ankle surgery

Adductor Canal Block

- Injection of local anesthetic medication in mid thigh between sartorius and vastus medialis muscles to block the saphenous nerve
- Adequate analgesia for knee and medial ankle surgery
- Preserves quadriceps strength
**Adductor Canal Block**

**Popliteal Sciatic Block**
- Injection of local anesthetic around the sciatic nerve or individual common peroneal and tibial nerves
- Provides analgesia for lower extremity below knees, except for medial aspect

*Courtesy of Block Buddy App*
IPACK Block

- Injection of local anesthetic medication between popliteal artery and capsule of knee
- Provides adequate analgesia for posterior knee
- Useful for knee arthroscopy, knee arthroplasty, and ACL reconstruction

Truncal Blocks
Subcostal TAP Block
- Somatic pain coverage of T7 to T10 dermatomes
- Adequate postop analgesia for surgeries with incision above the umbilicus
- Cholecystectomy
- Colectomy
- Upper ventral hernia repair

Midaxillary TAP Blocks
- Somatic analgesia for dermatomes T10-L1
- Adequate postop analgesia for surgeries with incision at or below umbilicus
  - Appendectomy
  - Umbilical hernia repair
  - Inguinal hernia repair
  - Colectomy
  - C-section
Ilioinguinal-Iliohypogastric TAP Block

- Somatic analgesia covering L1 dermatome
- Provides analgesia for inguinal hernia repair and c-section
Rectus Sheath Blocks
- Somatic pain coverage of T7 to L1
- Length of analgesia is inferior to TAP block
- Adequate coverage for midline incisions

Rectus Sheath Block

Quadratus Lumborum Block
- Provides somatic and visceral coverage of T7 to L1 dermatomes
- Most ideal for large abdominal surgeries
Quadratus Lumborum Block

- Injection of local anesthetic between pectoralis major and pectoralis minor at level of 3rd rib
- Blocks the lateral and medial pectoral nerves
- Adequate analgesia for portacaths, cardiac implants, anterior thoracotomies

PECS 1 Block

- Injection of local anesthetic between pectoralis major and serratus anterior muscles at level of 4th rib
- Adequate for tumor resections, mastectomies, sentinel node biopsies, and axillary incisions

PECS 2 Block
PECS Blocks

Erector Spinae Plane Block
- Provides somatic and visceral coverage at thoracic or abdominal area
- Erector Spinae block is done at either T5 or T8 transverse process
- T5 adequate for thoracic surgeries
- T8 adequate for abdominal surgeries
Continuous Nerve Blocks

- Placement of small indwelling catheter after injection of local anesthetic
- Provides continuous administration of local anesthetic
- May be used up to 4 days postoperatively
- Significantly decreases need for postop analgesics

Exparel

- Bupivacaine packaged in liposomal vesicles
- Lasts up to 96 hours
- FDA approved for field blocks
  - PECS 1&2
  - TAP Blocks
  - Erector Spinae Blocks
  - Quadratus Lumborum

Systemic Management of Peripheral Sensitization
Lidocaine Infusion
- Anti-inflammatory effect by prostaglandin inhibition
- Useful in abdominal and urological procedures
- Avoid use concomitantly with PNB
- Dosage
  - Initial bolus: 1.5mg/kg
  - Maintenance: 2mg/kg/hr
  - Postoperative: 1.33mg/kg/hr

Decadron
- Glucocorticoid steroid
- Inhibits the production of prostaglandins, bradykinin, histamine and leukotrienes
- Caution in diabetic patients
  - Advise that insulin requirement may be increased for next 24 hours
  - Literature disputes any wound healing effects
- Dosage
  - 0.2mg/kg (10-20mg on average)

Toradol
- Inhibits production of prostaglandins, bradykinin, and histamine
- Strong analgesic effect
- Equi-potent to morphine 10mg
- Caution in elderly, renal failure, or platelet dysfunction
- Dosage
  - 15mg at induction, 15mg at end
    - Half dosages for elderly
Celebrex
- COX-2 inhibitor
  - Inhibits prostaglandin synthesis
  - Decreased risk of bleeding, GI side effects, and AKI
  - Usage postoperatively decreases narcotic use and duration
- Dosage:
  - Preoperatively 400mg PO
  - Postoperatively 200mg PO BID for 7 days

Cannabinoids
- Endocannabinoid system is a major endogenous pain control system
- Anti-inflammatory and analgesic properties
- Promising studies involve inhibiting the enzymes that are released during stress that inhibit the endocannabinoid system from functioning
- Ligands that activate CB1 receptors are promising for nociceptive alteration
- Ligands that activate CB2 receptors are promising for anti-inflammatory properties

CR845
- Peripherally acting Kappa Opioid Receptor Agonist
- Analgesic, anti-inflammatory, and anti-pruritic
- Poor blood-brain barrier penetrating capability
Management Of Central Sensitization

- Substance P inhibition
- Clonidine
- Dexmedetomidine
- Glutamate antagonist
- Ketamine
- N₂O
- Magnesium
- Gabapentinoids

Substance P Inhibitors

Clonidine

- a2-adrenoreceptor agonist
- Decreases sympathetic outflow from lower brainstem region
- Decreases release of NE at both peripheral and central terminals
- Analgesic properties are due to both peripheral and central a2-adrenoreceptor agonism
Clonidine
- Peripheral analgesia
  - Blocking of pain transmission conducted through C fibers
  - Result of interaction with inhibitory G coupled proteins
- CNS analgesia
  - Activation of α2-adrenoceptors in the dorsal horn
  - Decreased release of Substance P and NE
  - Activation of α2-adrenoceptors in locus coeruleus responsible for supraspinal analgesia and sedation

Clonidine
- Avoid in patients with:
  - Bradyarhythmias
  - Patients who are afterload dependent
    - ie severe AS
  - Coronary artery disease due to possible HOTN
  - Strong considerations
    - Renal patients require less dose
    - Low starting BP

Clonidine
- PO dose:
  - 3-5mcg/kg (IBW) given 1-2 hours preop
    - Bioavailability is 75-95%
- IV dose:
  - Give 1.5mcg/kg (IBW) on induction, following incision if a sympathetic response is detected give additional 1.5mcg/kg
    - Total dose 3mcg/kg, may give up to 5mcg/kg (increased SE and sedation)
    - Dose may be given over 30 minutes in preop
  - Long half life up to 18 hours with both PO and IV dose
Dexmedetomidine

- Strong a2-adrenoreceptor agonist (1600:1)
- Same MOA as clonidine
- Less SE profile than clonidine
- Stronger analgesic effect than clonidine

Use with caution in patients with:
- Heart block
- Severe ventricular dysfunction
- Hypovolemic patients
- Diabetes
- Uncontrolled hypertension
- Elderly

Dosage:
- Initial bolus: 0.5-1mcg/kg over 10 minutes in preop
- Maintenance: 0.3-0.5mcg/kg/hr
- Postoperative infusion: 0.2-0.5mcg/kg/hr
- Short half-life of 2-2.6 hrs
Glutamate Antagonists

Ketamine
- NMDA antagonist
  - Prevents glutamate from activating NMDA receptor
  - Reverse opioid tolerance and opioid induced hyperalgesia
  - Recent research shows efficacy in treating CPRS, PTSD, anxiety, and depression
  - Low dose over long infusion times for repeated exposures

Ketamine
- Dosage:
  - Initial bolus: 0.5mg/kg
  - Maintenance: 5-10mcg/kg/min
  - Alternative use is to administer 10-20mg prior to administration of opioid
  - Subanesthetic dose decreases risks of postoperative hallucinations
**N₂O**
- NMDA antagonist
- Minimal acute pain analgesia
- Short duration of action may be reason why
- Strong evidence may prevent development of chronic pain in at risk patients

**Magnesium**
- Supplementation with exogenous magnesium changes concentration gradient and prevents disassociation of Mg²⁺ ion from NMDA receptor channel, preventing depolarization of postsynaptic neuron
- Dosage
  - Initial bolus 20-50mg/kg over 10-15 minutes
  - Maintenance 10-25 mg/kg/hr

**Gabapentinoids**
- Presynaptic binding to the α-2-δ subunit of voltage-gated Ca²⁺ channels inhibiting Ca²⁺ influx
- Prevents release of glutamate, norepinephrine, substance P, and calcitonin gene-related peptide
- Gabapentin and Pregabalin
Gabapentin
- Originally used as an anticonvulsant medication to treat epilepsy
- Decreases opioid use and decreases PONV
- Dosage
  - Initial: 300mg-1200mg PO
  - At least 1 hour prior to surgery
  - Maintenance: 300mg-600mg PO BID

Pregabalin
- Faster absorption and onset than gabapentin
- Analgesia effects similar to gabapentin
- Dosage
  - Initial: 150-300mg PO
  - At least 1 hour prior to surgery
  - Maintenance: 75-150mg PO BID

Analgesics
Analgesics
- Acetaminophen
- Esmolol
- Nubain

Acetaminophen
- CB1 agonist in RVM
- AM-404 metabolite
- PO vs IV (Ofirmev)
- Best to give either prior to incision
- Dosage
  - Initial: 1gm PO or IV
  - Maintenance 1gm PO or IV q 6-8 hours

Esmolol
- Selective β1-adrenoreceptor antagonist
- Metabolized by RBC esterase
- Analgesic MOA theories
  - Central analgesia by inhibition of β-adrenoreceptors altering G protein activation
  - Inhibition of neurotransmitter release in substantia gelatinosa neurons
Esmolol
- Dosage
  - Initial: 0.5-1mg/kg bolus
  - Maintenance: 5-15 mcg/kg/min

Nubain
- Mechanism of action
  - Full kappa agonist and partial mu antagonist
- Potency
  - Equivale to morphine
  - 1/4 potency of Narcan
- Dosage
  - Induction: 0.2mg/kg
  - PACU: 5-10mg up to total dose of 20mg
- Side effects
  - Sedation, HOTN, bradycardia

Cocktail Maintenance Infusion
- Lidocaine 2mg/kg/hr, Ketamine 5mcg/kg/min, Magnesium 10mg/kg/hr, Precedex 0.4mcg/kg/hr
- 100mL bag remove 20mL
- Inject Lido 2% 20mL, Ketamine 60mg, Magnesium 2gm, and Precedex 80mcg into bag
- Infuse at 0.5mL/kg/hr
- Run infusion up until starting incision closure
Emergent Ectopic Rupture

36 yo Female
Ectopic pregnancy rupture
Hgb 7,
transfused 2 units of PRBC
OFA technique

Transverse Colectomy

32 yo Female
Bilateral QL3 block
OFA technique
Required
Morphine 4mg
right of surgery
Bowel function returned next morning
Discharged POD2