

Current Trends in Opioid Free Anesthesia



MEGAN A. HORNYAK, SRNA
UPMC HAMOT SCHOOL OF
ANESTHESIA/GANNON UNIVERSITY

Objectives



- Understand the impact of the opioid epidemic on healthcare and anesthesia practice
- Define opioid free anesthesia and indications for use
- Discuss the impact of opioid free anesthetics and enhanced recovery after surgery protocols on patient outcomes
- Review techniques and medications used in opioid free anesthetics

Opioid Epidemic at the National Level



THE OPIOID EPIDEMIC BY THE NUMBERS

IN 2016...



116

People died every day from opioid-related drug overdoses



11.5 m

People misused prescription opioids¹



42,249

People died from overdosing on opioids²



2.1 million

People had an opioid use disorder¹



948,000

People used heroin¹



170,000

People used heroin for the first time¹



2.1 million

People misused prescription opioids for the first time¹



17,087

Deaths attributed to overdosing on commonly prescribed opioids²



19,413

Deaths attributed to overdosing on synthetic opioids other than methadone²



15,469

Deaths attributed to overdosing on heroin²



504 billion

In economic costs³

Sources: ¹ 2016 National Survey on Drug Use and Health, ² Mortality in the United States, 2016 NCHS Data Brief No. 293, December 2017, ³ CEA Report: The underestimated cost of the opioid crisis, 2017

History of Opioid Use in America

1840-1890

- Opioid consumption increased by 538%
- Etiology of pain conditions poorly understood
- Few alternative treatments to offer
- Sale of morphine poorly controlled
- 4.59 opioid-addicted persons per 1000

1920

- Introduction of stricter prescribing laws and physician education resulted in decreased opioid prescribing
- Opioid prescribing became a hallmark of older and less competent practitioners
- 1.97 opioid-addicted persons per 1000

History of Opioid Use in America

1986

- Paper published claiming opioids were safe for long-term use with very little addictive potential
- Poor quality evidence
- Widely cited to advocate for increased use of opioids
- Gradual increase in opioid prescribing

1995

- American Pain Society introduced campaign to institute pain as the 5th vital sign
- Adopted by VA Health System, Joint Commission and American Academy of Pain Medicine
- Introduction of OxyContin onto market

History of Opioid Use in America

1996-2002

- Rapid increase in opioid use
- Purdue Pharma (manufacturer of OxyContin) sponsored 20,000+ educational programs to prescribers encouraging long-term use of opioids
- Campaign included financial support to the American Pain Society, American Academy of Pain Medicine, Federation of State Medical Boards, Joint Commission and pain patient groups
- In turn, these groups advocated for increased use of opioids

2009-2010

- Physicians prescribed opioids in more than 50% of 1.14 million nonsurgical hospital admissions in high doses
 - Attributed to federal incentives via reimbursement to improve pain management scores
- 900% increase in patients seeking treatment for opioid addiction since 1997

History of Opioid Use in America



2016

- CMS removed pain management questions from HCAHPS survey for purposes of reimbursement (takes effect in 2018)
- Field testing alternative questions related to pain management

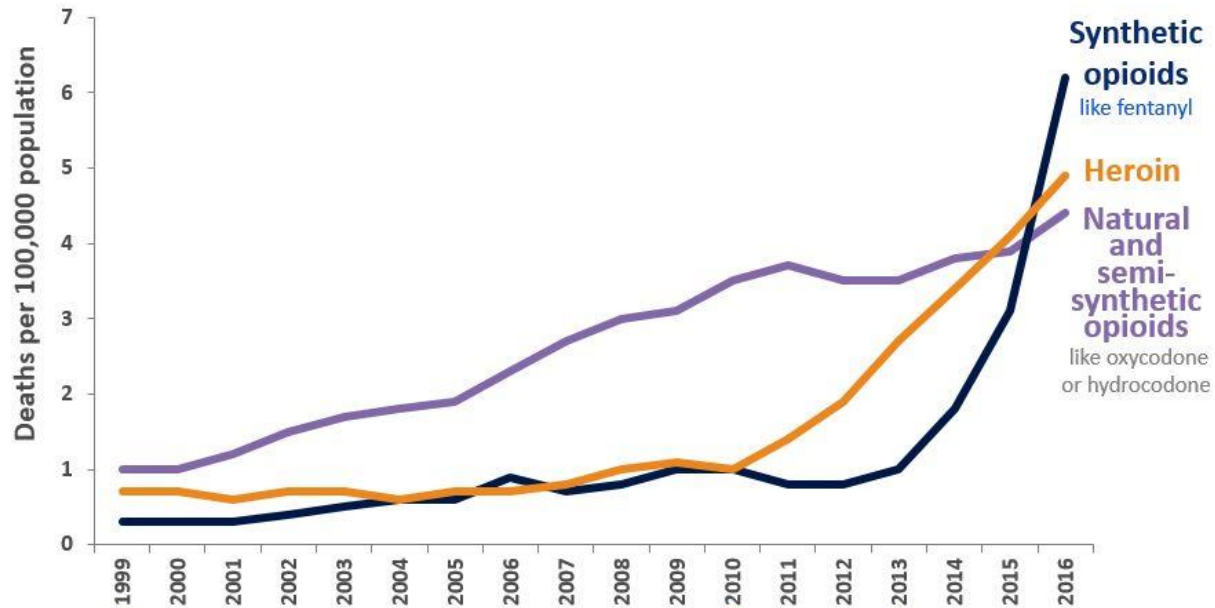
2017

- Opioid crisis declared a public health emergency

History of Opioid Use in America



3 Waves of the Rise in Opioid Overdose Deaths



Wave 1: Rise in Prescription Opioid Overdose Deaths

Wave 2: Rise in Heroin Overdose Deaths

Wave 3: Rise in Synthetic Opioid Overdose Deaths

SOURCE: National Vital Statistics System Mortality File.

Impact of the Opioid Epidemic



- U.S. life expectancy has decreased for the first time in more than 20 years
 - Attributed to increase in unintentional drug-related deaths due to opioid and heroin abuse
- Increased number of children entering foster care in 75% of states
 - Parental substance abuse cited as primary reason
- Increased number of babies born with neonatal abstinence syndrome due to parental exposure to opioids
 - Rate has quadrupled over the past 15 years
- Strain on emergency rooms due to increased visits for nonmedical opioid use and drug seeking behavior

Impact of the Opioid Epidemic

- Overall cost to the U.S. = \$55.7 billion/year
 - Loss of workplace productivity = \$25.6 billion
 - Healthcare expenses = \$25 billion
 - Criminal justice expenses = \$5.1 billion
- Cost since 2001 = \$1 trillion
- Costs expected to exceed \$500 billion over the next 3 years



The Role of the CRNA in the Opioid Epidemic



- Conduct a careful preoperative assessment to identify patients at risk of opioid misuse, opioid-induced hyperalgesia or respiratory depression
- CRNAs are involved in all stages of the perioperative period as well as chronic pain management
 - Multiple opportunities for patient education
 - Responsible prescribing practices
- Participate in ongoing education on multimodal pain management strategies

Postoperative Opioid Use



- Studies suggest that between 3% and 7% of previously opioid naive patients continue to treat with opioids one year after surgery
- Healthcare providers tend to overestimate post-discharge opioid requirements and give larger amounts to reduce the need for follow up
 - As many as 72% of prescribed opioid pills go unused
 - Can lead to diversion and misuse
- 75% of heroin users report their substance abuse started with opioid pain relievers
 - Switched to heroin because it is less expensive and easier to obtain

Postoperative Opioid Use



- Incidence of new persistent opioid use after surgery is a common complication of elective surgeries
 - 5.9-6.5% of patients continued persistent use of opioids after recovery from their surgery
 - No significant difference between patients who had minor or major surgery
 - Risk factors independently associated with persistent opioid use: smoking, substance abuse disorders, mood disorders, anxiety, preoperative pain disorders
- Despite ongoing routine use of opioids, up to 22% of patients experience inadequately treated postoperative pain
 - Leading to delayed recovery, decreased patient satisfaction and impaired rehabilitation

Drug Shortages

- Dilaudid
 - Fentanyl
 - Ketamine
 - Lidocaine
 - Morphine
 - Nitrous oxide
 - Rocuronium
-
- Shortages are expected to continue through 2019



What is opioid free anesthesia?

- Anesthesia administration that avoids the use of opioids
- Focuses on multimodal approach to pain management
- Opioids are considered a last resort for treatment of pain as opposed to a first line drug of choice



Who is a candidate for opioid free anesthesia?



Patients at risk for opioid-induced respiratory depression

- **Strong predictors**

- Substance use disorder
- Bipolar/schizophrenia
- Cerebrovascular disease
- Renal disease
- Heart failure
- Nonmalignant pancreatic disease
- Concurrent use of benzodiazepines or antidepressants

- **Moderate predictors**

- Recurrent headache
- Chronic pulmonary diseases
- Sleep apnea
- Use of extended-release or long-acting opioid medications
- Daily morphine equivalence dose greater than 100mg

Who is a candidate for opioid free anesthesia?



Patients at risk for opioid misuse/abuse

- Nonfunctional status due to pain
- Exaggeration of pain level
- Unclear etiology of pain
- Young age
- Smoking
- Poor social support
- Personal history of substance abuse
- Psychological stress/trauma
- Psychological disease
- Psychotropic substance use
- Focus on opioids
- Preadolescent sexual abuse
- History of legal problems
- History of substance abuse treatment
- Craving for prescription drugs
- Mood swings
- Childhood adversity

Benefits of Opioid Free Anesthesia



- Minimizes respiratory depression
- Increased hemodynamic stability intraoperatively
- Decreases risk of cancer recurrence
- Reduces postoperative opioid consumption
- Reduces risk of opioid-induced hyperalgesia
- Reduces risk of opioid-related side effects
 - Dysphoria
 - N/V
 - Constipation
 - Respiratory depression
 - Tolerance
 - Urinary retention
 - Pruritus

Reduction of Postoperative Opioid Consumption



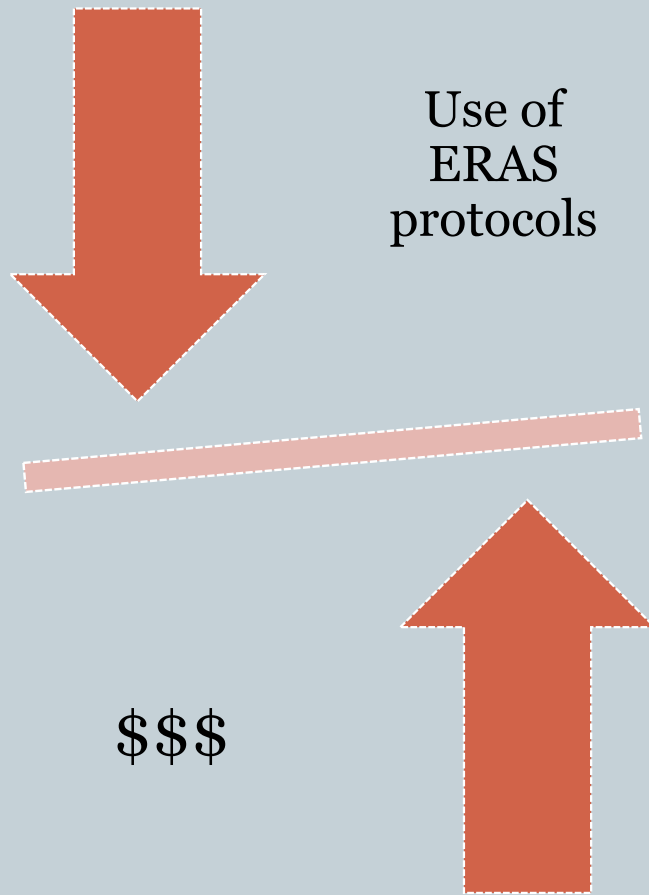
- Study comparing post-operative opioid consumption in patients receiving opioid-sparing, opioid-free and standard opioid anesthetics
 - Patients receiving standard opioid anesthetics and opioid-sparing anesthetics required double the opioids in PACU compared to the opioid free group
 - Opioid-free group required less ondansetron
 - 73% of opioid free patients required no postoperative opioids
 - ✦ Compared to 37% of the opioid-sparing patients and 52% of the standard opioid patients
 - Standard opioid patients had longer PACU times

Barriers to Implementation



- **Cost of opioid-free therapies**
- **Provider discomfort**
 - Insufficient guidelines for practice
 - Unfamiliarity with medications used for opioid free anesthesia
 - Off-label use
 - Perceived increased workload and effort
- **Insufficient evidence**
- **Patient refusal**
 - Administration of opioids for pain control is considered a standard part of surgical care by patients
 - Significant education required

Debunking Barriers to Implementation



- ERAS protocols are associated with decreased costs
 - 20-30% reduction in length of stay
 - 50% reduction in postoperative complications

Medications for Opioid Free Anesthesia

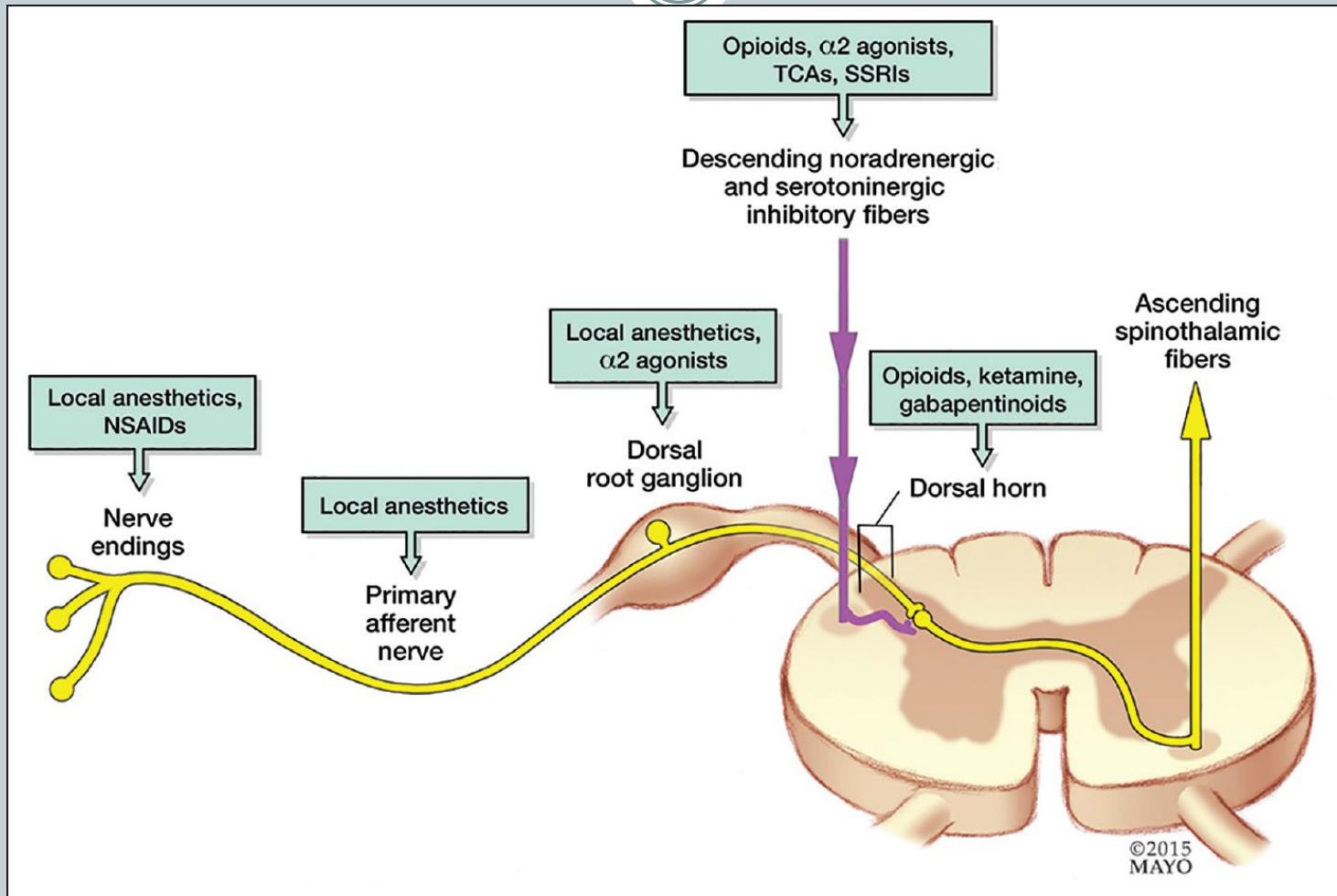


Nociception



- **Nociception: neural response to pain and other noxious stimuli**
 - **Transduction:** noxious stimulus is translated into electrical activity at sensory nerve endings
 - ✦ Medications that alter transduction: COX-2 inhibitors, local anesthetics, NSAIDs
 - **Transmission:** propagation of action potential along spinothalamic pathway
 - ✦ Medications that alter transmission: local anesthetics
 - **Modulation:** dampening or amplifying of pain signal along the pathway
 - ✦ Medications that alter modulation: clonidine, dexmedetomidine, opioids
 - **Perception:** subjective sensation of pain
 - ✦ Medications that alter perception: acetaminophen, alpha-2 agonists, ketamine, pregabalin

Pharmacologic Sites of Action



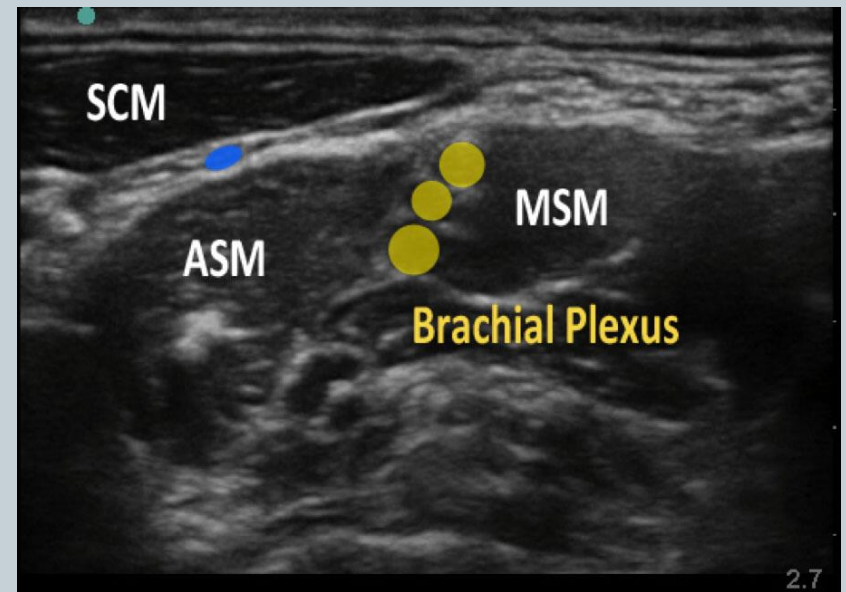
Opioid-Induced Hyperalgesia



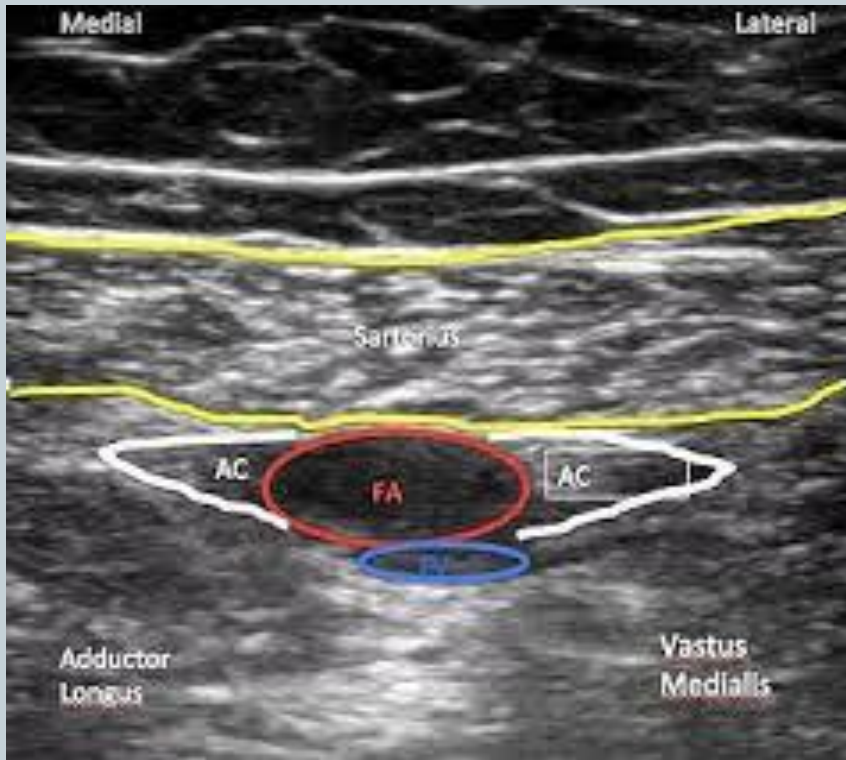
- Paradoxical increase in patient's pain sensitivity and decrease in pain tolerance following administration of opioids
- Can occur after a single dose of an opioid
 - Most commonly associated with remifentanyl
 - Fentanyl > morphine
- Cause of hyperalgesia not well understood
 - May have a genetic component
 - More common in women
- Risk factor for development of chronic pain syndrome

Peripheral Nerve Blocks

- Upper extremity blocks
 - Interscalene
 - Supraclavicular
 - Infraclavicular
 - Axillary
 - Distal nerve blocks
 - Bier block



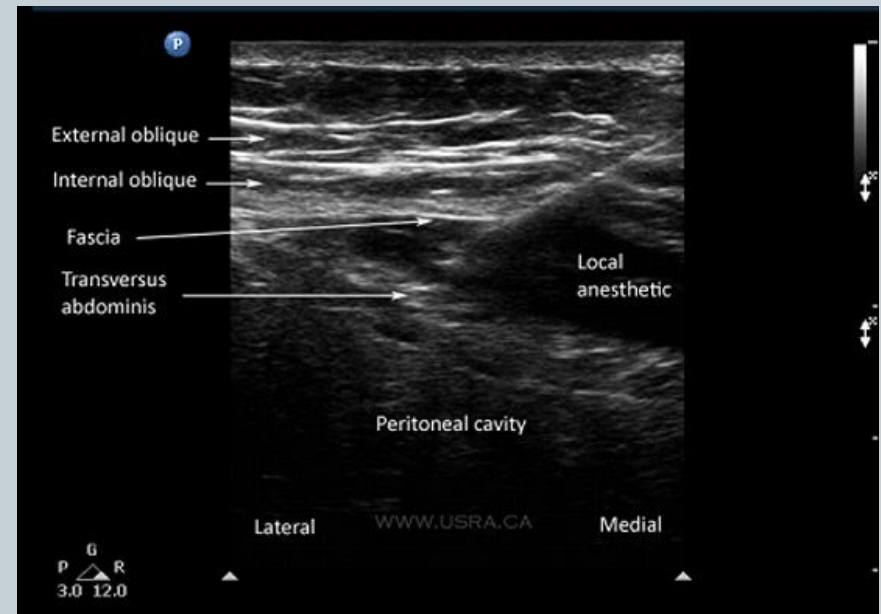
Peripheral Nerve Blocks



- Lower extremity blocks
 - Lumbar plexus block
 - Femoral block
 - Adductor canal block
 - Fascia iliaca block
 - Saphenous nerve block
 - Sciatic nerve block
 - Popliteal block
 - Ankle block

Peripheral Nerve Blocks

- Truncal blocks
 - TAP block
 - Rectus sheath block
 - Quadratus lumborum block
 - PECS block
 - Iliohypogastric block
 - Ilioinguinal block



Peripheral Nerve Blocks



- **Decreased postoperative pain scores and opioid consumption**
 - Improved pain scores compared to PCA pump
- **Adjuvants can be used to improve analgesia**
 - E.g., precedex, dexamethasone, epinephrine, magnesium, tramadol
- **Timing of block does not appear to have clinical significance**
 - Significant anti-hyperalgesic effect occurs if local anesthetic is present during the postoperative period
 - Presence of local anesthetic during surgery not essential for post-operative action
- **Discuss surgical wound infiltration with surgeon**



Gabapentin

Pregabalin

Ketamine

Magnesium

Nitrous oxide



Glutamates



Gabapentin

Brand name:
Neurontin

Recommended Dose:

300-600 mg PO 1
hour prior to surgery

- Class: gabapentinoid
- MOA: inhibits glutamate at NMDA receptor
- Side effects: sedation, headache, visual disturbances
- Administration: pre-operative
- Considerations
 - Concurrent administration with narcotics can lead to respiratory depression
 - Postoperative confusion in elderly
 - Associated with decreased intraoperative opioid administration, decreased postoperative analgesic requirements, decreased PONV and decreased use of volatile anesthetics



Pregabalin

Brand name: Lyrica

Recommended dose:

50-150 mg PO 1
hour prior to surgery

- Class: gabapentinoid
- MOA: inhibits glutamate at NMDA receptor
- Side effects: dizziness, somnolence, blurry vision
- Administration: pre-operative
- Considerations
 - Administer 1-2 hours preoperatively
 - Superior oral absorption and fewer side effects compared to gabapentin



Ketamine

Brand name: Ketalar

Recommended Dosing:

Bolus: 0.5 mg/kg

Infusion: 5-10
mcg/kg/min

1-time dose: 10-
20mg

- **Class:** phencyclidine derivative
- **MOA:** noncompetitive NMDA receptor antagonist
 - Also effects opioid, muscarinic and GABA receptors
- **Side effects:** emergence delirium, increased secretions, nystagmus
- **Administration:** induction dose, maintenance and/or post-op infusion
- **Considerations:**
 - Reduces incidence of opioid tolerance and hyperalgesia
 - Decreases need for postop opioids in first 24 hours
 - Consider subanesthetic doses of ketamine to avoid delirium and hallucinations



Magnesium

Recommended dosing:

Loading dose: 30-50 mg/kg

Infusion: 8-10 mg/kg/hr

Toxic levels:

5-7 g/dL = therapeutic

8-10 g/dL = decreased reflexes

10-15 g/dL = respiratory depression

> 20 g/dL = cardiac arrest

Treat toxicity with calcium

- **Class:** antiarrhythmic, bronchodilator, anticonvulsant
- **MOA:** antagonizes glutamate at NMDA receptor
- **Side effects:** hypocalcemia, hypotension, bradycardia, decreased deep tendon reflexes
- **Administration:** maintenance
- **Considerations:**
 - Potentiates the effects of muscle relaxants
 - Undergoes renal clearance; use with caution in renal patients
 - First sign of toxicity = loss of deep tendon reflexes
 - Not necessary to check preoperative level



Nitrous oxide

MAC = 104%

- Class: volatile anesthetic
- MOA: noncompetitive inhibition of NMDA subtype glutamate receptors; analgesic MOA unclear
- Side effects: N/V, vertigo, restlessness, increased ICP, diffusion hypoxia, loss of consciousness
- Administration: maintenance
- Considerations:
 - 50% N₂O is equivalent to 15mg of morphine
 - Contraindications: pneumothorax, vitamin B12 deficiency, hypoxia, recent inner ear or eye surgery



Celecoxib

Ketorolac

Decadron



Anti-inflammatory Agents



Celecoxib

Brand name: Celebrex

Recommended Dosing:

200-400 mg PO (1
hour prior to
surgery)

- **Class:** NSAID
- **MOA:** selectively inhibits COX-2 to prevent/decrease inflammation
- **Side effects:** N/V, abdominal pain
- **Administration:** preoperative
- **Considerations:**
 - Avoid in liver resections, active GI bleed, sulfa/aspirin allergies, pregnancy
 - Parecoxib (a parenteral COX-2 inhibitor) results in greater reduction in pain and opioid consumption than oral celecoxib
 - ✦ Also eliminates potential GI side effects



Ketorolac

Brand name: Toradol

Recommended dosing:

15-30 mg IV

Max: 120 mg/day

- Class: NSAID
- MOA: inhibits production of prostaglandins, bradykinins and histamine
- Side effects: GI bleeding
- Administration: maintenance, postoperative
- Considerations:
 - Use with caution in patients with renal failure, hepatic impairment, platelet dysfunction, asthma, active bleeding or pregnant women



Dexamethasone

Brand name: Decadron

Recommended dosing:

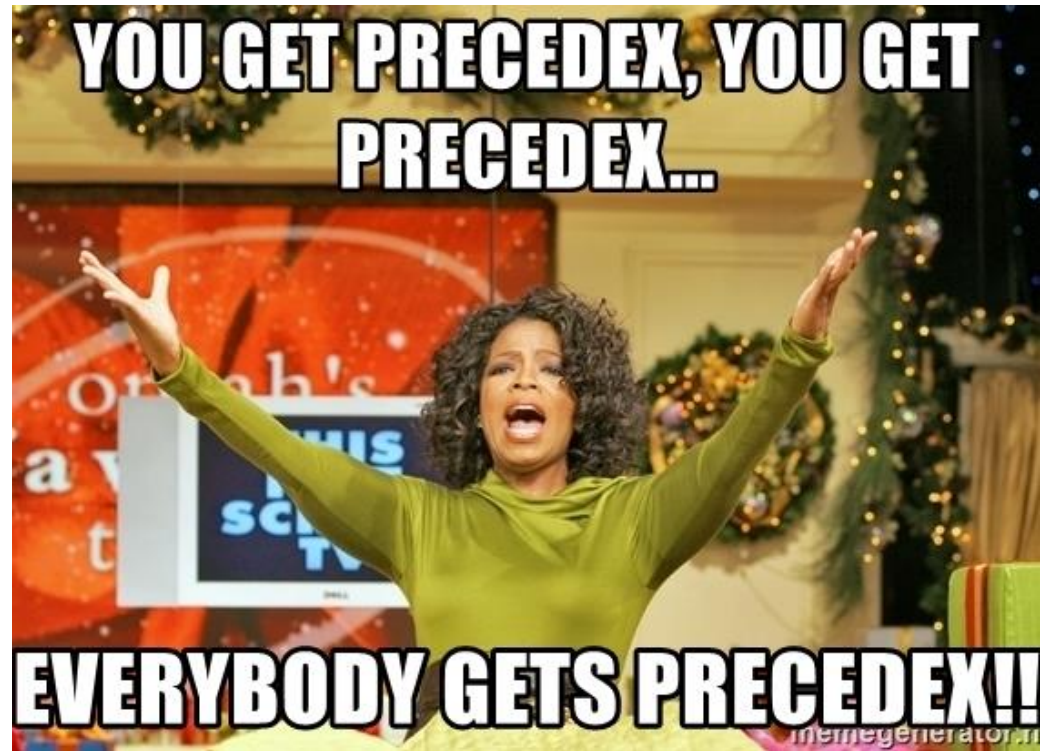
4-10 mg IV on
induction

- Class: glucocorticoid steroid
- MOA: inhibits prostaglandin synthesis leading to decreased surgery-induced inflammation
- Side effects: urticaria, rash
- Administration: induction
- Considerations:
 - Use with caution in diabetic patients (increases blood glucose for 24 hours)
 - Concern for delayed wound healing after dexamethasone administration (not supported in the literature)



Clonidine

Dexmedetomidine



Substance P



Clonidine

Brand name: Catapres

Recommended dosing:

3-5 mcg/kg IBW PO
1-2 hours
preoperatively

1.5 mcg/kg IBW on
induction

Can give additional
1.5 mcg/kg IBW if
sympathetic
response noted

Total dose: 3
mcg/kg IBW

- Class: alpha-2 agonist
- MOA: decreases norepinephrine levels resulting in analgesia and sedation
- Side effects: dry mouth, bradycardia
- Administration: maintenance
- Considerations:
 - Use caution in patients with bradyarrhythmias, severe aortic stenosis, coronary artery disease
 - Can produce prolonged sedation in elderly patients
 - Decreases analgesic dosage requirements
 - Provides sedation and anxiolysis



Dexmedetomidine

Brand name: Precedex

Recommended dosing:

Bolus: 0.5-1 mcg/kg
over 10 minutes

Maintenance: 0.3-
0.5 mcg/kg/hr

Postoperative: 0.2-
0.5 mcg/kg/hr

- **Class:** alpha-2 agonist
- **MOA:** decreases norepinephrine levels resulting in sedative and analgesic effects
- **Side effects:** dry mouth, bradycardia, hypotension
- **Administration:** maintenance, post-op infusion
- **Considerations:**
 - Stronger analgesic effects compared to clonidine
 - Fewer side effects than clonidine
 - Use with caution in patients with heart block, hypovolemia or hypotension
 - Provides analgesia without respiratory depression
 - Dose reduction in patients with hepatic dysfunction

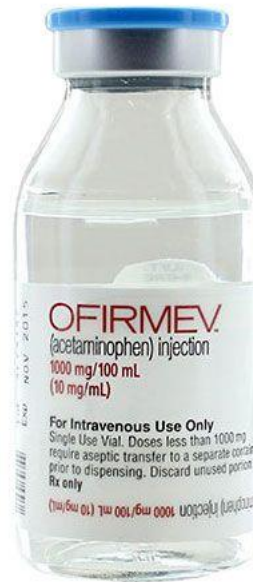


Acetaminophen

Duloxetine

Esmolol

Lidocaine



Miscellaneous Medications



Acetaminophen

Brand name: Tylenol

Recommended Dosing:

PO: 1gram

IV: 1 gram (> 50 kg)
or 15 mg/kg (< 50
kg)

- Class: other analgesics
- MOA: unknown
- Side effects: nausea, rash, headache, hepatotoxicity
- Administration: preoperative, intraoperative, postoperative
- Considerations:
 - Associated with decreased pain, narcotic consumption and length of stay
 - Oral versus IV route: no evidence to support one over the other
 - ✦ IV bioavailability = 70%



Duloxetine

Brand name:
Cymbalta

Recommended
dosing: 60 mg

- **Class:** serotonin and norepinephrine reuptake inhibitor
- **MOA:** serotonin and norepinephrine modulate descending inhibitory pathway
- **Side effects:** agitation, headache, N/V
- **Administration:** preoperative
- **Considerations:**
 - Useful in patient's with pre-existing neuropathic pain
 - Study showed that treatment with duloxetine for 2 weeks of perioperative period resulted in decreased intraoperative, 48-hour postoperative and first postoperative week consumption of analgesics



Esmolol

Brand name: Brevibloc

Recommended Dosing:

Initial: 0.5-1 mg/kg

Maintenance: 5-15
mcg/kg/min

- **Class:** selective beta-1 adrenergic antagonist
- **MOA:** unknown
- **Side effects:** hypotension, bradycardia, bronchospasm
- **Administration:** induction, maintenance
- **Considerations:**
 - Use associated with reduced anesthetic requirements, decreased use of perioperative opioids, decreased N/V and earlier discharge
 - Contraindicated in patients with greater than 1st degree heart block, cardiogenic shock or heart failure
 - Use caution in patients with bronchospastic disease
 - Safe for use in patients with impaired renal or hepatic function at doses of 50-300 mcg/kg/min



Lidocaine

Brand name: Xylocaine

Recommended Dosing:

Bolus: 1.5 mg/kg

Infusion: 2mg/kg/hr

- **Class:** amide local anesthesia, class 1B anti-arrhythmic
- **MOA:** blocks Na⁺ channels, uncouples G-protein, blocks NMDA receptor, reduces circulating inflammatory cytokines and prevents hyperalgesia
- **Side effects:** anxiety, drowsiness, tinnitus, metallic taste
- **Administration:** induction, maintenance, post-op infusion
- **Considerations**
 - Useful in treating neuropathic pain, diabetic neuropathy and opioid-induced hyperalgesia
 - Avoid use with concurrent peripheral nerve block (increased risk of toxicity)

Case Study



- Patient: 28 year old male with NKDA
- PMH: heroin abuse, clean for 3 years
- Procedure: hydrocele repair
- Pertinent information: patient continued his suboxone sublingual per his regularly scheduled dosing regimen due to anxiety and concerns of withdrawal
 - Patient instructed to discontinue suboxone prior to surgery
- Preoperative medications
 - Gabapentin
 - Celebrex
- Intraoperative medications
 - General with LMA – 2% sevoflurane
 - Versed – 2 mg
 - Toradol – 60 mg
 - Ketamine – 50mg
 - Propofol – 350mg
 - Lidocaine – 300 mg
 - ✦ 100 mg on induction
 - ✦ 200 mg lidocaine placed in 1 liter IV bag for steady infusion
 - Surgeon localized before incision and at the end of case with a 50/50 mixture of 1% lidocaine with epi and 0.5% Marcaine (total of 20ml)

Case Study



- **Postoperative Course**

- Patient woke up in an uneventful manner
- 0/10 pain
- Rounded on patient 2 hours later, still 0/10 pain, received no medications from PACU nurses
- Discharged the same day to home with instructions to take ibuprofen, acetaminophen, and continue suboxone as prescribed

References



- Albrecht, E., Kirkham, K., Liu, S., & Brull, R. (2013). Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. *Anaesthesia*, *68*(1), 79-90. doi:10.1111/j.1365-2044.2012.07335.x.
- Barreveld, A., Witte, J., Chahal, H., Durieux, M. E., & Strichartz, G. (2013). Preventative analgesia by local anesthetics: The reduction of postoperative pain by peripheral nerve blocks and intravenous drugs. *Anesthesia & Analgesia*, *116*(5), 1141-1161.
- Brummett, C. M., Waljee, J. F., Goesling, J., Moser, S., Lin, P., Englesbe, M. J., . . . Nallamothu, B. K. (2017). New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surgery*, *152*(6). doi:10.1001/jamasurg.2017.0504.
- CMS finalizes hospital outpatient prospective payment changes for 2017. (2016, November 1). Retrieved from <https://www.cms.gov/newsroom/mediareleasedatabase/fact-sheets/2016-fact-sheets-items/2016-11-01-3.html>
- FDA Drug Shortages . (n.d.). Retrieved March 8, 2018, from <https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>
- Greco, M., Capretti, G., Beretta, L., Gemma, M., Pecorelli, N., & Braga, M. (2014). Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. *World Journal of Surgery*, *38*(6).
- Griffis, C. A., Giron, S. E., & Darna, J. R. (2017). The opioid crisis and the certified registered nurse anesthetist: How can we help?. *AANA Journal*, 19-23.
- Harless, M., Depp, C., Collins, S., & Hewer, I. (2015). Role of esmolol in perioperative analgesia and anesthesia: A literature review. *AANA Journal*, *83*(3), 167-177.
- How to Manage Pain During Buprenorphine Treatment. (n.d.). Retrieved April 04, 2018, from <https://www.buppractice.com/howto/pain>

References



- James, M., & James, M. M. (2009). Magnesium: an emerging drug in anaesthesia. *BJA: The British Journal Of Anaesthesia*, 103(4), 465-467. doi:10.1093/bja/aep242
- Muller, Jan. (2015). Who, when why Opioid free anaesthesia. Overview of actual use of OFA worldwide.. 10.13140/RG.2.1.3068.6482.
- Kandil, E., Melikman, E., & Adinoff, B. (2017). Lidocaine infusion: a promising therapeutic approach for chronic pain. *Journal of Anesthesia and Clinical Research*, 8(1). doi:10.4172/2155-6148.1000697.
- Kolodny, A., Courtwright, D. T., Hwang, C. S., Kreiner, P., Eadie, J. L., Clark, T. W., & Alexander, G. C. (2015). The prescription opioid and heroin crisis: A public health approach to an epidemic of addiction. *Annual Review of Public Health*, 36, 559-574.
- Nicol, A., Hurley, R. W., & Benzon, H. T. (2017). Alternatives to opioids in the pharmacologic management of chronic pain syndromes: A narrative review of randomized, controlled and blinded clinical trials. *Anesthesia & Analgesia*, 125(5), 1682-1703.
- Oseka, L., & Pecka, S. (2018). Anesthetic management in early recovery after surgery protocols for total knee and total hip arthroplasty. *AANA Journal*, 86(1), 32-39.
- Saoud, A., & Elkabarity, R. (2013). Effective of perioperative duloxetine on postoperative pain relief following anterior cervical microdiscectomy and fusion. *World Spinal Column Journal*, 4(2), 57-66.
- Samuels, D., Abou-Samra, A., Dalvi, P., Mangar, D., & Camporesi, E. M. (2017). Opioid-free anaesthesia results in reduced post-operative opioid consumption. *Journal of Clinical Anesthesia and Pain Medicine*, 1(2).
- Society for Opioid Free Anesthesia (2018). Retrieved April, 5, 2018 from <http://www.goopioidfree.com>.
- Stone, A.B., Wick, E.C., Wu, C.L., & Grant, M.C. (2017). The US opioid crisis: A role for enhanced recovery after surgery. *Anesthesia and Analgesia*, 125(5).
- Stuit, D., & O'Sullivan, C. (2017). Ketamine as part of a multimodal approach to postoperative pain management. *AANA Journal*, 85(5), 369-374.
- U.S. Department of Health and Human Services. (2018, March 6). About the U.S. opioid epidemic. Retrieved from <https://www.hhs.gov/opioids/about-the-epidemic/index.html>
- Webster, L. (2017). Risk factors for opioid-use disorder and overdose. *Anesthesia & Analgesia*, 125(5), 1741-1748.
- Zhang, J, Ho, KY, and Wang, Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. *Br J Anaesth*. 2011; 106: 454-462.