Chronic Pain Management in the Perioperative Period

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Conflicts

- None

Learning Objectives

- Develop management strategies for surgical patients taking buprenorphine
- Understand the peri-operative implications of common implantable devices for pain
- Develop a peri-operative pain management plan for the chronic pain patient

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Chronic Pain

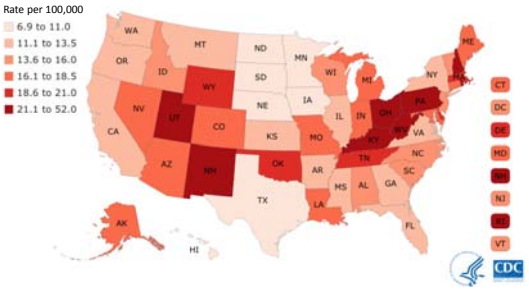
- Pain lasting >3 months or beyond the "normal time" of tissue healing
- In 2012, it was estimated that almost 40 million Americans have persistent pain that occurs daily or on most days
  - 1 out of 5 patients with chronic non-cancer pain is being treated with opioids

Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. J Pain. 2015;16(8):769-80.
Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain – United States, 2016. JAMA. 2016;315(15): 1624–1645.

Management of Patient on Chronic Opioid Therapy

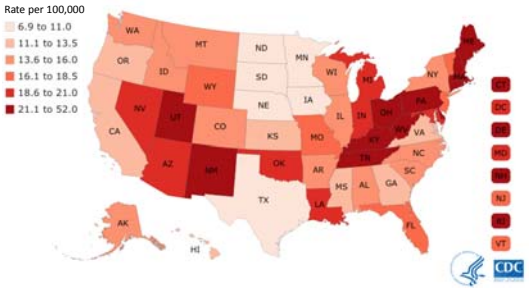
- Why is it challenging?
  - Tolerance and inadequate analgesia from standard opioid regimens
    - Fear of respiratory depression at high doses
  - Lower pain threshold among patients on chronic opioid therapy
    - Opioid-induced hyperalgesia?
  - Fear of relapse if history of OUD
    - No evidence that exposure to opioids for acute pain increases relapse risk
      - Has been suggested that the stress of uncontrolled pain may trigger relapse
  - Concern about diversion
- Important part of pre-operative evaluation includes Expectations
  - What is patient's pre-operative pain baseline?
  - What is patient's target number?
    - 0/10 is not a reasonable goal!
    - Focus on function (ambulation, PT, sleep) rather than #

Rates of drug overdose deaths by state, 2014



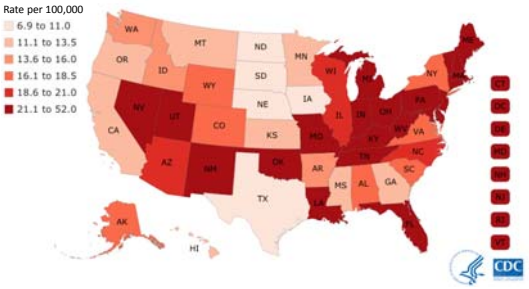
https://www.cdc.gov/drugoverdose/data/statedeaths.html

Rates of drug overdose deaths by state, 2015



https://www.cdc.gov/drugoverdose/data/statedeaths.html

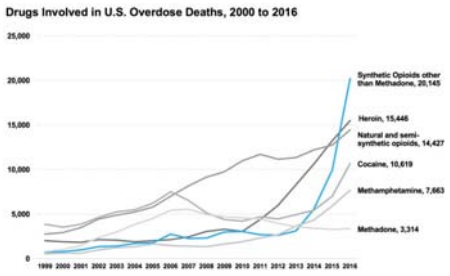
Rates of drug overdose deaths by state, 2016



https://www.cdc.gov/drugoverdose/data/statedeaths.html

Opioid Overdose Deaths

- The opioid prescribing rate has dropped since its peak in 2012, but the rate of death due to opioid overdose is on the rise



Management of Patient with OUD

- No RCTs of acute pain management in patients on maintenance therapy for OUD
- Has not actually been studied in opioid-tolerant patients, but it is widely recommended to use a multi-modal approach in such patients where opioids may be ineffective
  - regional anesthesia
  - NSAIDs or COX-2 Inhibitors
  - acetaminophen
  - NMDA antagonists
  - α_2 agonists
  - anti-convulsants

Sen S, Arulkumar S, Cornett EM, Gayle JA, Flower RR, Fox CJ, et al. New Pain Management Options for the Surgical Patient on Methadone and Buprenorphine. Curr Pain Headache Rep. 2016;20(3):16.

Methadone

- Long-acting
  - Half-life is >1 day (15-40 hours)
    - Highly lipophilic
      - High bioavailability (36-100%)
    - Protein bound: α1-acid glycoprotein
    - Metabolized by CYP450 → inactive metabolites (fecal and renal clearance)
    - High inter-individual variability!
  - 2 isomers
    - R-isomer is NMDA receptor antagonist
      - 40% of pain relief from methadone is via non-opioid activity (ie, can't block with naloxone)
    - S-isomer is an agonist at mu and delta opioid receptors
      - Binding at mu receptor prevents withdrawal, reduces craving
      - Causes tolerance that reduces euphoria with additional opioid use

Sen (2016)
(Goodman and Gilman
J Pain Symp Mgmt 28(5):497-504, 2004
***

Methadone

- Variable opioid conversion
- Higher doses of chronic opioid equivalent to **less** methadone/ MED than lower doses

- morphine→methadone ≠ methadone→morphine
- Conversions for chronic opioid use:

MED/day	<100	101-300	301-600	601-800	801-1000	>1001
MED:methadone	3:1	5:1	10:1	12:1	15:1	20:1

Methadone	Factor
Up to 20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
>60 mg/day	12

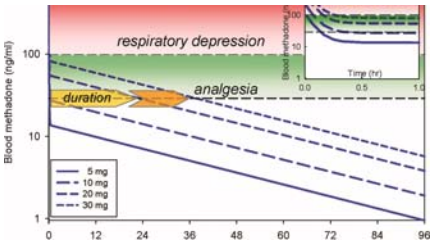
http://www.agencymeddirectors.wa.gov/MethadoneFactors.asp
Journal of Community Hospital Internal Medicine Perspectives. 2012;2(4):10.3402/jchimp.v2i4.19541

Methadone: Perioperative Management

- Continue daily dose before, during and after surgery
  - Verify correct dose with prescribing physician
  - If cannot take daily PO methadone post-op, can give IV:
    - Given high but wide-ranging bioavailability (30-100%), variable pharmacokinetics, use 2:1 ratio for oral:IV
      - May need to escalate to 3:2, 1:1 or even 1:2
      - Best to divide parenteral dose into BID to QID
    - Rapid onset IV (4 min) despite long half-life
  - Commonly held that duration of analgesic effect is 8hr vs 24hr dosing for OUD maintenance/withdrawal avoidance
    - Thus may divide single daily dose into TID to help with pain
    - Pharmacokinetics suggest that a single large dose (>20mg IV) provides a prolonged analgesic effect (but in opioid-naïve patients)
      - Relationship between elimination half-life and effect depends on dose

Anesth Analg. 2011 Jan; 112(1): 13–16
Ther Clin Risk Manag. 2017;13:1163-73

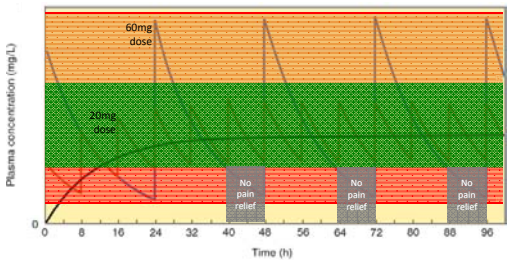
Methadone Pharmacokinetics: Dose and duration of analgesic effect



Kharasch, E. D. (2011). Intraoperative methadone: Rediscovery, reappraisal, and reinvigoration? *Anesthesia and Analgesia*, *112*(1), 13–16.

Pharmacokinetics:

Big dose/long interval vs Small dose/short interval



Holford NG. Pharmacokinetics & Pharmacodynamics: Rational Dosing & the Time Course of Drug Action. In: Katzung BG. eds. *Basic & Clinical Pharmacology, 14e*New York, NY: McGraw-Hill

Buprenorphine

- Growing in use with the rise in OUD
  - Buprenorphine prescriptions increased from 48,000 in 2003 → 1.9 million in 2007 → >9 million in 2012 and 2013
  - Why?

Buprenorphine

- 33 times as potent at morphine (IV to IV)
  - Antagonist at kappa-opioid receptors
    - May be involved in efficacy in opioid-induced hyperalgesia, but this phenomenon only studied in healthy volunteers
  - Partial agonist at mu-opioid receptors
    - High affinity for the receptor: binds tightly, but doesn't activate fully
      - Slow dissociation ($t_{1/2}$= 166 min vs 7min for fentanyl; 50% by 1 hr vs 100% by 1 hr) → plasma levels may not parallel clinical effects
    - Less respiratory depression
    - Ceiling effect (no increase in agonist effects at dose >32mg/day)
      - 16mg SL occupies 79-90% of μ-opioid receptors but doses >24-32mg do not result in greater opioid effect despite >95% receptor occupancy
      - Reduced risk of respiratory depression vs full μ-opioid receptor agonists
    - Can precipitate withdrawal in opioid dependent patient

https://www.deadiversion.usdoj.gov/drug_chem_info/buprenorphine.pdf. Am J Psychiatry. 2007; 164:979.
Drug Alcohol Depend. 2009; 99: 345-349. Br J Anaesth. 1985;57(2):192-6. Acta Anaesthesiol Scand. 1980;24(6):462-8.

Buprenorphine

- Long half-life, highly variable (24-60 hours)
  - 20-30 hours (buccal, transdermal or SL) vs 3-5 hours IV
- Used as maintenance therapy for OUD, most commonly SL:
  - Subutex or Suboxone (buprenorphine:naloxone in 4:1 ratio) film
  - Relatively easy to get a Waiver to rx for OUD
  - Can be prescribed for chronic pain with "opioid dependence"

https://www.deadiversion.usdoj.gov/drug_chem_info/buprenorphine.pdf. Am J Psychiatry. 2007; 164:979. Drug Alcohol Depend. 2009; 99: 345-349. Br J Anaesth. 1985;57(2):192-6. Acta Anaesthesiol Scand. 1980;24(6):462-8.

Buprenorphine

- 30-35% bioavailable SL but high first-pass hepatic metabolism when taken orally
  - Hepatic metabolism by CYP450 to *active* metabolite, norbuprenorphine (20% of parent compound activity)
    - Renal clearance of metabolites, but most drug is excreted unchanged in feces

Sen 2016. Walter and Inturrisi, 1995. Anderson, 2017. Johnson, 2005. Palliat Ved 20:517-523 (2006) Goodman and Gilman

Buprenorphine for Pain

- Butrans
  - transdermal patch
  - 5-20mcg/hr dose
  - Patch worn for 7 days
    - Single application C_{max} for 20mcg/hr patch 0.48ng/ml
    - Steady state achieved after 3 days
    - For 10mcg/hr patch, steady state C_{max} 0.2ng/ml
  - Must taper to ≤30mg MED
    - "may not provide adequate analgesia" for patients requiring >80 MED/day
- Belbuca
  - buccal film
  - 75-900mcg
    - Bioavailability 46-51%
    - Mean C_{max} 1200mcg 1.43+-0.45ng/mL
  - Once to twice daily
    - $T_{1/2}$ 4-15 hours
  - Must taper to ≤30mg MED
    - "may not provide adequate analgesia" for patients requiring >160 mg MED/day

https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207932s000lbl.pdf

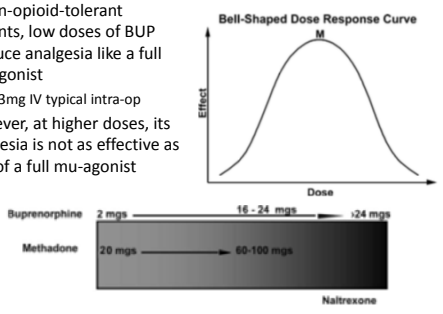
Buprenorphine Induction

- Patient must be in withdrawal from chronic opioid use:
  - "first dose of buprenorphine SL should only be administered when objective and clear signs of moderate opioid withdrawal appear, and not less than 4 hours after the patient last used an opioid." (Subutex website)
    - 24 hours if using long-acting opioid like methadone
  - 8-16mg/day is approximately equivalent to methadone 60mg/day

Drug Alcohol Depend. 2003;70(2 Suppl):S59-77.
https://www.suboxone.com/content/pdfs/SUBUTEX_Prescribing_Information.pdf

Buprenorphine

- In non-opioid-tolerant patients, low doses of BUP produce analgesia like a full mu-agonist
  - 0.3mg IV typical intra-op
- However, at higher doses, its analgesia is not as effective as that of a full mu-agonist



Drug Alcohol Depend. 2003;70(2 Suppl):S59-77. Johnson, 2005

Buprenorphine: perioperative challenges

- High affinity, only partial agonism → acute pain difficult to treat with other opioids
- Case reports
  - 47 y/o woman with chronic pain on bup/nal 16mg BID, gabapentin, SNRI and nabilone (synthetic THC) having thoracic surgery. Bup/Nal continued
    - Good pain control until POD5 with epidural, intraoperative ketamine and hydromorphone PCA, worsening. By POD11, in addition to bup/nal using ~1300 MED per day in hydromorphone (PO + IV)
      - Bup/nal dose halved to QD and pain control improved immediately; IVPCA d/c'd 10 days later and Bup/nal halved again with transition to PO hydromorphone
    - Yet buprenorphine has been shown to reduce hyperalgesia and central sensitization in addition to direct analgesic effects!

Can J Anaesth. 2014;61(9):826-31.

Buprenorphine Can Make Post-Operative Pain Difficult to Control

- Numerous other case reports of patients maintained on buprenorphine whose pain could not be controlled
  - Continued peri-operatively with severe pain; control improved greatly when buprenorphine discontinued or dose reduced
  - Uncontrollable pain if buprenorphine taken day of surgery even if not continued post-operatively
    - Direct effect of buprenorphine?
    - Opioid tolerance?
    - Opioid-induced hyperalgesia?
    - Evidence of sensitization?
      - (Remind me why they ended up on SL buprenorphine for pain…?)

Can J Anaesth. 2014;61(9):826-31 J Opioid Manag. 2009;5(3):175-9. Pain Med. 2013;14(8):1187-91

Adjunctive Medications to Reduce Pain in Patients Maintained on BUP

- Dexmedetomidine
  - Has been used to treat pain unresponsive to high doses of hydromorphone PCA (Brummett, 2009)
    - 0.5μg/kg bolus, then 0.5μg/kg/hr
- Use ketamine infusion
  - Shown to reduce post-operative opioid requirement **specifically** in opioid-tolerant surgical patients!
    - 0.5mg/kg bolus at induction plus infusion of 10μg/kg/min before incision until closure complete
- Maximize other multimodal treatments: scheduled APAP, NSAIDs, gabapentinoids, local anesthetic techniques

J Opioid Manag. 2009;5(3):175-9. Anesthesiology. 2010;113(3):639-46.

Buprenorphine: Perioperative Management

- Coordinate with prescribing provider for procedures that are non-emergent
- Decide whether to continue or hold
  - Consider continuing for
    - Surgeries with only mild to moderate pain expected
    - Procedure and pain amenable to continuous local anesthetic techniques
    - Patients at high risk for relapse
      - OUD with chronic pain associated with more craving possibly putting at high risk for relapse, but may also have most difficult to control pain
  - May require monitored setting if continued
    - Theoretical risk for respiratory depression if BUP held and given full μ-receptor agonist

Anderson, 2017. Drug Alcohol Depend. 2016;166:26-31.

Buprenorphine: Perioperative Management

- Strategy 1: Discontinue buprenorphine prior to surgery
  - Gradual taper over 2-3 weeks w/ decrease by 2mg/day and off **72 hours** before surgery (Sen, 2016)
    - Can taper rapidly over 3 days but higher relapse rates (Sen, 2016)
    - If can't tolerate withdrawal, replace with methadone or other opioid
  - Goal window without buprenorphine depends on dose (Anderson, 2017)
    - » 0-4mg per day – stop 24 hours before surgery
    - » >4-8mg per day – stop 48 hours before surgery
    - » >8-12mg per day – stop 48 hours before surgery
    - » >12mg per day – need preop plan with buprenorphine prescriber
  - OR transition to oral methadone in ratio of 1:5; typically 30-40mg/day
    - titrate methadone by 5-10mg/day
  - Use additional full mu agonists for acute pain
  - Post-op:
    - Discharge on pure opioid agonist with plan to taper and resume buprenorphine w/ outpatient maintenance clinic
    - OR inpatient induction with buprenorphine once acute pain controlled
  - Reschedule elective case if patient doesn't hold?

Anderson, 2017. Sen 2016. Ann Intern Med. 2006;144(2):127-34.

Buprenorphine: Perioperative Management

- Strategy 2: Continue buprenorphine throughout the perioperative period
  - Discontinuation of buprenorphine in stressful pre-operative period may risk relapse
  - Numerous case reports of successful pain management despite concomitant SL buprenorphine treatment.
    - Treat acute pain with higher-than-usual doses of opioid agonists
      - Use opioids with higher intrinsic affinity for the receptor: Hydromorphone, fentanyl, morphine

Sen 2016. Br J Clin Pharmacol 1981: 12(2):117-22. Clin J Pain 2008; 24: 93-97

Buprenorphine

Table 2. μ-Opioid Receptor Binding Affinities (Ki) for Commonly Used Opioids and Antagonists

Opioid	Ki (nM)
Sufentanil	0.1380[3]
Buprenorphine	**0.2157**[3]
Hydromorphone	0.3654[3]
Morphine	1.168[3]
Fentanyl	1.346[3]
Naloxone	1.518[3]
Methadone	3.378[3]
Remifentanil	21.1[4]
Oxycodone	25.87[3]
Hydrocodone	41.58[3]
Codeine	734.2[3]
Tramadol	12,486[3]

Leighton BL, Crock LW. Case Series of Successful Postoperative Pain Management in Buprenorphine Maintenance Therapy Patients. Anesth Analg. 2017;125(5):1779-83.

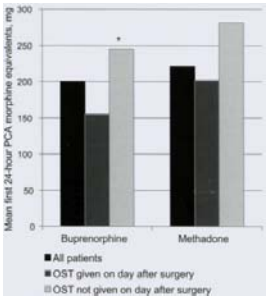
Buprenorphine: Perioperative Management

- Strategy 2: Continue buprenorphine throughout the perioperative period
  - Discontinuation of buprenorphine in stressful pre-operative period may risk relapse
  - Numerous case reports of successful pain management despite concomitant SL buprenorphine treatment. Tactics include:
    - Treat acute pain with higher-than-usual doses of opioid agonists
      - Use opioids with higher intrinsic affinity for the receptor: Hydromorphone, fentanyl, morphine
        - » Use PCA
    - Divide once daily dose of buprenorphine (opioid maintenance) into TID or QID dosing to better match the pharmacodynamics of analgesia
      - Half life for effective analgesia shorter than half life of the drug
      - Only for mild to moderate pain due to ceiling effect at doses >32mg/day SL
    - Consider additional sublingual or IV buprenorphine
      - 0.3mg IV ≈ 10mg morphine IV; usually 0.3-0.6mg IV intraoperatively
    - Employ multimodal pain management

Sen 2016. Br J Clin Pharmacol 1981: 12(2):117-22. Clin J Pain 2008; 24: 93-97

Post-operative pain management on continuous buprenorphine

- Retrospective review: patients on methadone (n=29) or buprenorphine (n=22) who required IV PCA for post-op pain (w/o LA techniques)
  - Similar intra-operative MED
  - Average pre-op buprenorphine dose 13.7±6.6mg/day (range 4-32mg)
    - 63% received dose day of surgery, 50% also give day after
      - Those who did not receive BUP dose the day after surgery had significantly higher (p=0.02) PCA MED for first 24 hours than those given their usual dose
      - No difference in pain scores for BUP vs methadone, trend towards more pain if dose held



Anaesth Intensive Care. 2013;41(2):222-30.

Post-operative pain management on continuous buprenorphine

- Case series (2010): successful post-operative pain management with continuation of buprenorphine
  - None of the 5 patients (7 surgeries) used bup/nal for chronic pain
  - Maximum pre-operative daily bup dose was 24mg
    - some patients who remained on bup had dose increased for post-op pain, max from 24 to 32mg
    - Not continued post-op in all cases but held (or dose reduced) until several days after surgery
  - All received multimodal analgesia: epidural or surgical site catheter with pump, ±ketamine, morphine or hydromorphone PCA

Am J Ther. 2010;17(5):523-8

Post-operative pain management in patients on buprenorphine

- Use regional anesthesia when possible
  - Case series of 4 patients on buprenorphine undergoing C/S or post-partum BTL
    - Buprenorphine continued at home dose and schedule
    - All patients administered ketorolac 30mg Q6 hours x 24 hours, then PO NSAID (ibuprofen 800mg PO TID)
      - 2/4 also received epidural infusion of bupivacaine 0.0625% maintained for 48 hours
        - » Pain maintained at 0/10 and 2/10
      - 2/4 administered intrathecal bupivacaine + opioid
        - » Pain at 5/10 (c/s) and 1-2/10 (BTL)

Anesth Analg. 2017;125(5):1779-83.

Perinatal buprenorphine management

- Both methadone and buprenorphine are category C
  - Methadone used since 1970s
  - metabolism is increased during pregnancy so need dosing adjustment
  - Safety of buprenorphine not yet proven so has been recommended to transition to methadone
    - Methadone in pregnancy associated with better treatment retention
    - But better maternal and fetal outcomes with buprenorphine
      - Same rate of NAS but sxs less severe with buprenorphine
- Neonatal abstinence syndrome (NAS)
  - OK to breastfeed, but due to poor bioavailability infant buprenorphine exposure not sufficient to prevent NAS
- Hyperalgesia → may require more and stronger analgesics than opioid-naïve
  - Women on methadone required ~70% more opioid in the first 24hr after c/s

(Sen 2016). (Meyer 2007)

Perinatal buprenorphine management

- In general, adequate postpartum pain management possible despite continued BUP
  - 20 women randomly assigned to methadone or buprenorphine (blinded)
    - All achieved adequate pain control with additional opioid agonist then transition to ibuprofen, although the patients on methadone required more NSAID

Am J Drug Alcohol Abuse. 2009;35(3):151-6.

Perinatal buprenorphine management

- Neuraxial anesthesia safe and preferred
  - IT opioids are fine but may not be enough to prevent withdrawal if maintenance opioid discontinued
  - **Avoid** mixed (κ)agonist-(μ)antagonists like nalbuphine, butorphanol and pentazocine, which can precipitate withdrawal
  - regional techniques (TAP blocks) as adjunct to IT as needed for pain in first 24 hours

(Sen, 2016). Goodman and Gilman's Pharmacological Basis of Therapeutics 13th Ed. Br J Anaesth. 2012;109(5):679–87.

Buprenorphine: Legal Issues

- A physician may **not** provide a ***prescription*** of buprenorphine for **opioid dependence** without obtaining a DATA 2000 Waiver
  - A Waiver is NOT required to prescribe or administer buprenorphine for **pain**
  - Currently high interest in increasing the number of physicians with a Waiver, many states have programs to support training (8 hours)
    - https://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training
- However, special circumstances do exist…

https://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/legislation-regulations-guidelines/special

Buprenorphine: Legal Issues

- Providers **without a Waiver MAY provide buprenorphine** to treat withdrawal in patients with opioid dependency or OUD in the course of a hospitalization for another medical issue. According to SAMHSA:
  - "A patient with an opioid dependency who is admitted to a hospital for a primary medical problem other than opioid dependency, such as myocardial infarction, may be ***administered*** opioid agonist medications such as methadone and buprenorphine **to prevent opioid withdrawal** that would complicate the primary medical problem."

https://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/legislation-regulations-guidelines/special

Buprenorphine: Legal Issues

- In addition, an exception known as the "three-day rule" allows a provider without a Waiver to ***administer*** but NOT *prescribe* buprenorphine for the treatment of withdrawal symptoms while arranging for referral for treatment as long as:
  - Only one day's medication is given at a time and
  - Treatment is not carried out for >72 hours
  - This 72-hour period cannot be renewed/extended

https://www.samhsa.gov/programs-campaigns/medication-assisted-treatment/legislation-regulations-guidelines/special

Buprenorphine: Continue or Hold?

- 37 y/o woman on buprenorphine (8mg SL TID) for chronic pelvic pain who underwent 2 surgeries
  - Also on chronic lorazepam 1mg QID
  - 1st: buprenorphine continued:
    - pt reported uncontrolled pain
  - 2nd: buprenorphine discontinued 5 days prior and replaced with hydromorphone 4mg Q4-6 hrs (max 20mg/d)
    - Pain control on hydromorphone adequate before surgery
      - Fentanyl challenge: patient tolerant to effects, remaining alert and conversant after 1000μg IV
      - Given ketorolac intraop, also additional 100μg fentanyl; required 1000μg more fentanyl prior to arrival in PACU
        - » Complaining of pain but appeared comfortable
        - » Hydromorphone PCA and ketorolac continued post-op
        - » Discharged home on hydromorphone with plan to follow-up with buprenorphine provider
- Tolerance? Hyperalgesia? Both?

J Anesth Clin Res. 2013;3(250).

Opioid-Induced Hyperalgesia

- First described in animals
  - Chronic opioid exposure results in lower pain threshold in most pain models tested
- Data in humans more limited
  - Unknown what minimum daily MED will cause tolerance or OIH
    - Described within one month of chronic oral morphine use (range 30-120mg/day)
  - Clearly described for remifentanil
  - Reports of pain improving following opioid detoxification

Drug Alcohol Depend. 2001;63(2):139-46. Pain. 2001;90(1-2):91-6.

Opioid-Induced Hyperalgesia

- Clinical data
  - Patients on methadone maintenance display hyperalgesia
    - Patients on methadone (or buprenorphine) for OUD had lower tolerance for experimental cold (but not mechanical or electrical) pain than those with OUD not on opioid
  - Patients receiving high-dose fentanyl infusion in OR have higher pain scores for first 8 hours after surgery and require more fentanyl in first 16 hours post-op
    - Conversely, numerous reports of opioid-sparing anesthesia with β-blocker infusion resulting in lower pain scores and opioid consumption for 12-24 hours after surgery

Drug Alcohol Depend. 2001;63(2):139-46. Pain. 2001;90(1-2):91-6. Can J Anaesth. 1999;46(9):872-7. J Anaesthesiol Clin Pharmacol. 2015;31(3):375-9. - Korean J Pain. 2015;28(3):198-202. - J Clin Anesth. 2013;25(1):36-41. - J Invest Surg. 2017:1-7.

Opioid-Induced Hyperalgesia: Possible Treatments

- NMDA antagonists: ketamine, memantine
  - glutamate receptor and ion channel
  - Activated in setting of prolonged morphine
    - activated allows flux of cations (Na^+, K^+, Ca^{2+})
    - NMDA receptor mediated neuronal apoptosis in the dorsal horn
- Adrenergic blockade?
  - Alpha: successful use of dexmedetomidine (clonidine?) to treat refractory pain in opioid tolerant patients
  - beta blockers?
    - Propranolol reduces secondary hyperalgesia seen with remifentanil
    - Can be used for opioid-sparing anesthetic

Pain. 2012;153(5):974-81.

Pre-operative Opioid Weaning

- Numerous studies documenting poor outcomes in patients on chronic opioid therapy
  - Infection
    - Odds increased by 50% in highest opioid use vs lowest
  - GI complications
    - Ileus
  - Respiratory complications
    - Respiratory depression with atelectasis and pneumonia
  - Increased length of stay, discharge to rehab facility and cost
  - DVT
  - compromised wound healing
  - reduced arthroplasty or intervertebral fusion success
    - Less pain relief from the intervention in the case of TKA!

Preoperative Reduction of Opioid Use Before Total Joint Arthroplasty

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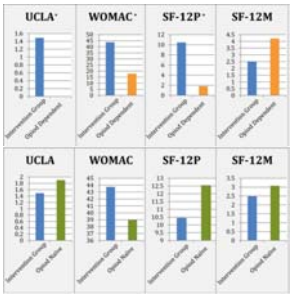
- 3 cohorts of patients prior to joint arthroplasty:
  - Patients who weaned chronic opioid by >50% before surgery
  - Patients who maintained baseline chronic opioid dose
  - Opioid-naïve patients
- Functional outcomes
  - Patients who weaned fared better on all measures than those who did not and had post-surgical functional outcomes comparable to opioid-naïve patients



J Arthroplasty. 2016;31(9 Suppl):282-7.

Other adjuncts: Anticonvulsants

- Gabapentinoids: pregabalin and gabapentin
  - Bind $\alpha_2\delta$ subunit of N-type voltage-gated Ca^{2+} channel → reduce neuronal excitability
    - May also impact immune pathways in pain
    - These effects may explain animal evidence and reports of **reduction in opioid-induced hyperalgesia**
  - Typical doses:
    - gabapentin 300-1200mg pre-op (300-600mg TID)
    - pregabalin 75-300mg (75-150mg BID)

Other adjuncts: Gabapentinoids

- Single dose pre-operatively or several doses peri-operatively can reduce post-operative pain scores
  - Pregabalin shown to reduce incidence of chronic pain after TKA when continued for 14 days post-op
  - Gabapentin also shown to reduce pain at 6 months after orthopedic, ENT, breast and abdominal/pelvic surgery
    - In a recent RCT, gabapentin did not accelerate cessation of post-operative pain, but increased probability of opioid cessation after surgery (by 24%) and reduced duration of post-operative opioid therapy (mean 25 days vs 32 days for placebo)
  - Less constipation but may be associated with more post-op sedation, delirium, rash, visual disturbances

Multimodal Pain Management: Membrane stabilizers

- APS/ASRA/ASA Panel Recommendations:
  - Consider use of gabapentin or pregabalin as part of a multimodal analgesia regimen (strong recommendation, moderate-quality evidence)
    - Both are associated with reduced opioid requirement after major or minor surgery
    - Some reports of lower post-operative pain scores
    - Administer as a dose of 600 or 1200mg of gabapentin or 150 or 300mg of pregabalin given 1-2 hours pre-operatively
      - Some trials also postoperative dosing to be effective (gabapentin 600 mg as a single or in multiple doses and pregabalin 150 or 300 mg after 12 hours)
    - Higher doses may be more effective but also may be more sedating
    - Particularly for opioid-tolerant patients

Reduce doses in renal dysfunction

Chou et. Al. J Pain (2016); 17: 131-157

Use of Acetaminophen and/or NSAIDs as part of a multi-modal regimen

- APS/ASRA/ASA Panel Recommendations:
  - Clinicians provide acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs) as part of multimodal analgesia for management of postoperative pain in patients without contraindications (strong recommendation, high-quality evidence)
    - Round-the-clock, scheduled
  - Most studies show use of acetaminophen or NSAIDs in conjunction with opioids is associated with less postoperative pain or opioid consumption than opioids alone
    - Evidence that a single pre-emptive dose of APAP prior to surgery reduces pain scores 6 hours after surgery (Khalili et al 2013)
  - Acetaminophen and NSAIDs have different mechanisms of action and the combination of acetaminophen with NSAIDs may be more effective than either drug alone
    - NNT<2

Chou et. Al. J Pain (2016); 17: 131-157. Anesth Analg 2010;110(4):1170-9. Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD010794

Multimodal Pre-treatment: COX-2 Inhibitor

- APS/ASRA/ASA Panel Recommendations:
  - Consider giving a preoperative dose of oral celecoxib in adult patients without contraindications (strong recommendation, moderate-quality evidence)
    - Preoperative celecoxib in patients who undergo major surgery (200 - 400 mg, 30-60 min. preoperatively)
    - Associated with reduced opioid requirements after surgery
    - Some studies reported lower postoperative pain scores
      - May not reduce opioid use per day in opioid tolerant patients like it does in opioid-naïve patients, but does signficantly reduce pain scores

Celecoxib: gastrointestinal bleeding and ulceration, cardiovascular history, sulfa allergy

Clin J Pain. 2015 Oct;31(10):903-8. Chou et. Al. J Pain (2016); 17: 131-157

NSAIDs

- Act both **peripherally** and **centrally**
  - In peripheral, afferent pathway: block COX, preventing conversion of arachidonic acid to prostaglandins
    - Prevents **sensitization** of pain receptors after injury
  - In central pathways:
    - Block COX-2 facilitated production of PGE2 in the spinal dorsal horn
    - **Activate** medullary and cortical areas involved in descending inhibition

Gupta Curr Pain Headache Rep 2016

NSAIDs

- Perioperatively, NSAIDs/COX-2 inhibitors:
  - Reduce opioid requirements and thus opioid-induced side effects like nausea, vomiting, somnolence
  - Improve patient satisfaction
  - Reduce PACU times
  - Reduce post-operative morbidity
- Similar efficacy for nonselective NSAIDs and COX-2 inhibitors
  - Formulation may matter: liquid ibuprofen faster and better analgesia than tablet
- Lower NNT than APAP (3.0 v 3.9)
- Effective in a wide range of surgeries, from ambulatory procedures to abdominal surgery to orthopedic surgery and spine surgery (laminectomy/discectomy)

Gupta Curr Pain Headache Rep 2016. PAIN 107:86-90 (2004)

NSAID Precautions

- Renal
  - 2007 Cochrane review found only transient, clinically insignificant reduction in renal function in adults without pre-operative renal impairment (Lee, 2007)
- Hematologic
  - Bleeding risk: a 2007 meta-analysis found no significant difference in postoperative bleeding between ketorolac and control group (Gobble, 2014)
    - However, there may be a greater risk of bleeding (GI and operative) among patients ≥75 years old, with a dose-response relationship (Strom, 1996)
      - Lower OR of GI but not surgical bleeding when ketorolac given <5 days
- ASA-induced asthma
- Cardiovascular
  - COX-2 inhibition leads to reduction in PG synthesis and relative over-production of thromboxane A2 → increased vasoconstriction without reduced platelet aggregation (COX-1)

***

NSAID precautions

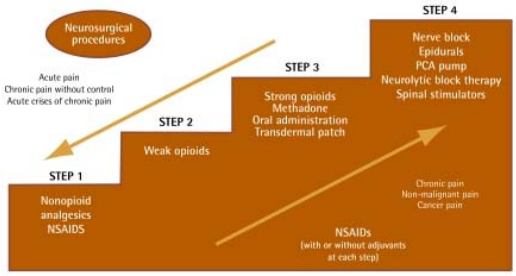
- Surgical
  - Anastomotic leakage after colonic resection → use with caution in colorectal surgery
  - Bone fusion: concern from animal studies
    - 2011 meta-analysis of clinical trials examining effects of perioperative NSAIDs in spinal fusion
      - **normal dose** (ketorolac <120mg/day, diclofenac <300mg in all, celecoxib 200-600mg/day), **short-duration** (<14 days) NSAIDs had **NO adverse effects on fusion** rates
        - » At high doses, ketorolac may impair spinal fusion

Local Anesthetic Techniques for Opioid-Tolerant Patients

- Epidural anesthesia can be effective
  - more lipophilic opioids superior to morphine for opioid-tolerant patients
  - Likely need systemic opioids to prevent withdrawal
- Role of peripheral nerve blockade not well studied in opioid tolerant patients
  - Animal evidence of a dose-dependent loss of local anesthetic potency in sciatic nerve with opioid tolerance
    - These effects persist for >30 days after morphine discontinuation, but morphine tolerance resolved within 7 days of stopping
    - Coresponding clinical data is sparse although some such reports exist

Learning Objectives

- Develop management strategies for surgical patients taking buprenorphine
- Understand the peri-operative implications of common implantable devices for pain
- Develop a peri-operative pain management plan for the chronic pain patient



Vargas-Schaffer G. *Can Fam Physician* . 2010; 56(6): 514-7

Intrathecal Drug Delivery Systems

Indications for Intrathecal Drug Delivery

- Pain unresponsive to high doses of opioids (VAS ≥ 5 despite ≥200mg MED)
- Intolerable side effects from opioids
  - Chronic non-cancer pain
    - Postherpetic neuralgia
    - Peripheral neuropathy
    - Failed back surgery syndrome
    - CRPS
    - Visceral pain (eg, pancreatitis)
  - Cancer pain
    - Life expectancy >3 months
- CLEAR pain diagnosis
- Failure of conservative treatment

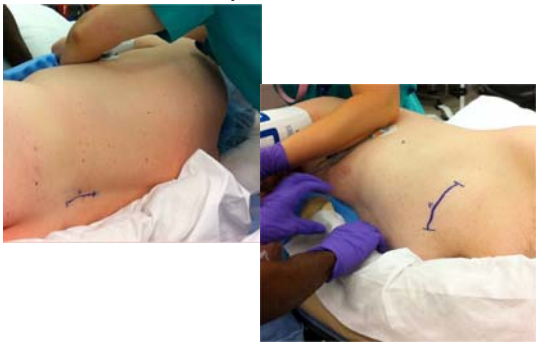
Intrathecal Drug Delivery for Pain Common Medications

Table 14. Cancer or Other Terminal Condition-Related Pain With Diffuse Nociceptive or Neuropathic Pain.

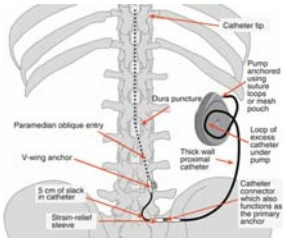
Line 1A	Ziconotide			Morphine		
Line 1B	Hydromorphone			Morphine or hydromorphone + bupivacaine		
Line 2	Hydromorphone or morphine + clonidine			Morphine or hydromorphone + ziconotide		
Line 3	Hydromorphone or morphine or fentanyl + bupivacaine + clonidine	Ziconotide + bupivacaine		Ziconotide + clonidine	Hydromorphone or morphine or fentanyl + bupivacaine + ziconotide	Sufentanil
Line 4	Sufentanil + ziconotide	Baclofen	Sufentanil + bupivacaine	Sufentanil + clonidine	Bupivacaine + clonidine + ziconotide	Bupivacaine + clonidine
Line 5	Sufentanil + bupivacaine + clonidine		Sufentanil + bupivacaine + ziconotide		Sufentanil + clonidine + ziconotide	
Line 6	Opioid* + bupivacaine + clonidine + adjuvants†					

*Opioid (all known intrathecal opioids).
†Adjuvants include midazolam, ketamine, ocinotide.

IT Pump Placement



Bottros MM & Christo PJ. *J Pain Res 2014; 7*: 615–626.

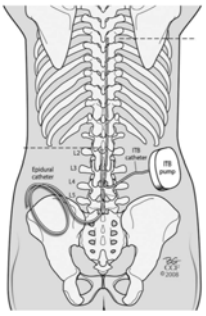


- Side port bypasses reservoir, connects directly to catheter
  - Filled with very concentrated opioid
  - In theory could bolus through port but must aspirate first
  - Risk of infection, etc.
  - Preferable to perform single shot spinal below IT entry

Rork JF et al. J Pain Symptom Manage. 2013 Dec;46(6):859-73
Bottros MM & Christo PJ. *J Pain Res 2014; 7*: 615–626.

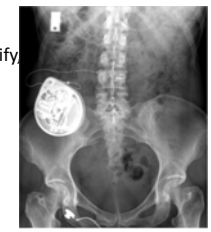
Implications for Anesthesia

- Neuraxial anesthetic techniques
  - Risk of damage to catheter
    - 20g silastic catheter
  - Infection
  - Communication between epidural and intrathecal around catheter?
  - Numerous case reports of successful epidural analgesia for labor in patients with IDDS
    - Entry described both above and below IT catheter entry
    - Use of ultrasound: identify and avoid catheter as well as dural puncture?
    - Prophylactic antibiotics?



Other IT Pump Issues

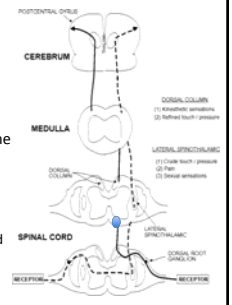
- MRI
  - Causes pump to stop
    - normally will resume function within 20min to 2 hours but needs to be interrogated to verify, particularly if baclofen
- Chronic management
  - Recent dose changes?
  - Last refill?
  - Next refill? Battery?



Spinal Cord Stimulation

How does it work?

- The neurostimulator delivers mild electrical impulses to the leads located within the epidural space
  - Stimulation targets dorsal column neurons to spinal cord, **not** the nerve **roots**
    - Lead location does NOT follow typical dermatomal locations
- This disrupts pain signals traveling between the spinal cord and brain, providing pain relief
- Typical, "paresthesia-based" stimulation produces paresthesias in the area normally affected by pain
  - Newer, "high frequency" programs deliver stimulation at a frequency below the threshold of detection for the patient

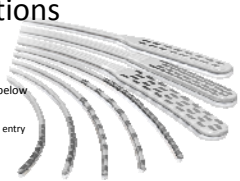


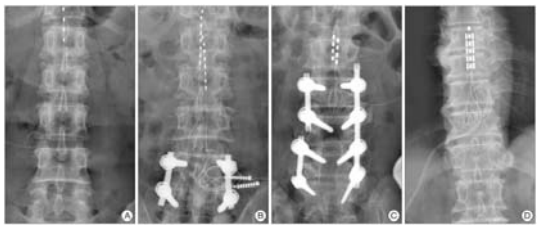
Indications: Chronic Pain

- Failed Back Surgery Syndrome (FBSS)
- Post-Laminectomy Pain
- Radicular Pain
- Complex Regional Pain Syndrome
- Epidural Fibrosis
- Arachnoiditis

SCS: Epidural Anatomical Considerations

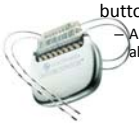
- Paddle
  - placed through incision at level of electrodes
  - Requires laminectomy
- Percutaneous
  - typically enter the epidural space at least 2 levels below lowest electrode in lead
    - Most commonly between T12/L1 or L2/L3
    - Anchored to supraspinous ligament one level below entry
- Final position of contacts determined by pain region:
  - Pelvis: S2-S4
  - Legs: T9-L1
  - Low back: T8-T10 (T8-T9 most common)
  - Abdomen: T5-T7
  - Chest, angina: C6-T2
  - Arms: C4-T1
    - Leads terminating in thoracic or cervical spine may enter from lumbar and course w/in epidural space or be tunneled subcutaneously from flank/buttock IPG site to enter epidural space in thoracic/cervical spine
  - Also may be placed subcutaneously along peripheral nerves
    - Eg, occiput, face, sciatic nerve





SCS: Anatomical Considerations

- IPG
  - Leads tunnel subcutaneously from midline supraspinal incision to IPG
    - IPG location typically flank or buttock
      - Abdomen, chest also possible

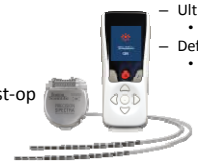


Electromagnetic Interference

- Sources of EMF
  - Cautery, lithotripsy, defibrillation, endoscopy with biopsy, ECT, nerve stimulation
- Possible consequences of EMI
  - Turning device on/off
  - Changing settings/programming (frequency, amplitude)
  - Transmission of current along electrodes
  - Damage to battery power/destruction of IPG

Perioperative Sources of EMI

- Electrocautery
  - Bipolar OK
  - Monopolar is incompatible
    - If must use monopolar (endoscopy, eg), then:
      - Turn SCS OFF
      - Turn voltage to "0"
      - Place grounding pad far from IPG and leads
      - Interrogate after surgery
- INCOMPATIBLE with:
  - Diathermy
  - Lithotripsy
  - (TMS)
- Interrogate post-op



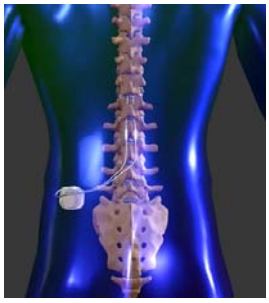
- Imaging
  - CT scans OK but can cause temporary increase in stimulation → Turn voltage to "0" and device OFF
  - MRI
    - Most devices INCOMPATIBLE
    - Several newer devices MRI CONDITIONAL (head/extremities vs full body) but most only at 1.5 Tesla
  - Ultrasound
    - Don't place directly over IPG
  - Defibrillation:
    - Place paddles as far from device as possible and perpendicular to leads

Neuraxial Anesthesia and SCS

- Single shot spinal or catheter OK BELOW level where SCS leads enter
  - Ultrasound
- Lumbar epidural OK BELOW cervical SCS IF cervical epidural entry
- Epidural catheter could disrupt stimulator leads

Neuraxial Anesthesia and SCS

- Epidural catheter could disrupt stimulator leads
  - Lead migration is a common complication
    - Reports???
      - Fibrous tissue develops around epidural leads and may protect from this
      - SCS lead diameter 1.3-1.4mm, paddle » 20g catheter < 0.8mm
  - Epidural anesthesia has been used successfully w/o SCS complication for labor analgesia
    - SCS leads placed from T12/L1; do not attempt of leads enter epidural space from low lumbar
- Risk of infection of SCS hardware
- Risk/Benefit of neuraxial
- Discuss with chronic pain physician



Conclusions

- Chronic pain can make management of acute pain challenging
  - Implantable devices may limit neuraxial anesthetic
    - Caution with EMF
  - Opioid use is not diminishing despite drop in prescriptions
    - For OUD, continue methadone through perioperative period
    - Consider continuing buprenorphine depending upon indication, dose, pain history and surgical procedure
      - Use high-affinity short-acting opioids as needed
      - If discontinuing, hold for 72 hours before surgery
    - Strongly consider weaning chronic opioids for pain before elective surgery
      - Many patients find even chronic pain unchanged or improved on a lower dose!
  - Maximize multimodal therapies
    - Use regional/neuraxial when possible
    - Administer non-opioid analgesics
      - On a SCHEDULED basis