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Anesthetic Management of Illicit Drug Use

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Management of Patients Using Opioids

Chronic Pain
Opioid Use Disorders

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Chronic Opioid Patients

- Chronic pain patients
- Active opioid addictive patients
- Opioid Addictive patients in treatment

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Chronic Opioid Use

- Opioid abuse is a growing problem in US
- Only 12 to 15% of dependent patients are in methadone programs
- Drug Addiction Act of 2000
 - legally prescribe opioid to treat addiction
 - buprenorphine (Subutex)
- 2002 FDA approved buprenorphine/naloxone
 - Suboxone
 - sub lingual dose

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2016 Opioid Use in United States

- 11.5 million people misused opioid prescription
- Overdose Deaths
 - 42,249 opioid deaths
 - 15,469 heroin deaths
 - 116 deaths per day

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Suggestive Risk Factors for Opioid Abuse

Non-functional Status Because of Pain	Unclear Cause of Pain
Exaggeration of Pain	Psychological Stress, Trauma, or Abuse
Poor Social Support	Focus on Opioids
Mood Swings	Cravings for Prescription Drugs
History of Legal Problems	History of Substance Abuse

Curr Opin Anesthesiol.2019;32:427

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Buprenorphine

- Semi synthetic agent
 - partial mu (μ) agonist
 - kappa receptor antagonist
 -

Pain Med.2018;1-4

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Opioid Receptors

μ 1	analgesia, miosis, urinary retention, nausea & vomiting, pruritis
μ 2	sedation, respiratory depression, decreased GI motility
δ	analgesia, alterations of affective behavior
κ	analgesia, sedation, decrease in GI motility, psychotomimesis, dysphoria, & miosis
σ	dysphoria, psychotomimesis

- opioids act primarily on mu (μ) receptor for surgical pain analgesia

Buprenorphine

- Mu receptor agonist
 - analgesia for chronic pain patients
 - opioid agonist therapy (OAT) for opioid addiction
 - OUD = opioid use disorder
 - decreases cravings for illegal drug
- Kappa receptor antagonist
 - kappa receptor is blocked
 - no dysphoria or unpleasant mood → block depressive effects of OUD

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Buprenorphine

- Mu binding affinity
 - 1000 X greater than morphine
 - greater affinity than other full mu opioid agonists
 - greater affinity than naloxone
 - extremely slow dissociation from receptor
- Prevents other opioids from binding to mu & kappa receptors
 - prevents patient relapse
- Displace full opioid agonists from mu receptor

Buprenorphine

- High potency opioid
 - 25 to 50 times as potent as morphine
- Low efficacy
 - efficacy = dose effect
 - drug is a partial agonist → does not fully activate the receptor
 - ceiling effects for
 - euphoria and respiratory depression
 - no analgesic ceiling effect at typical clinical doses

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Buprenorphine

- Highly lipophilic
- Rapid onset sublingual
 - onset 30 to 60 minutes
 - peaks in 100 minutes
- Duration of action → **dose dependent**
 - 2 mg 2 to 6 hours
 - 4 mg 3 to 27 hours
 - 32 mg 20 to 70 hours

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Buprenorphine

- Bioavailability
 - PO 3 to 14%
 - SL 30 to 50%
- Safer agent than **methadone**
 - **less respiratory depression**
- Less euphoria than full agonists
 - **prevents withdrawal** in addiction
 - patient has no cravings for illicit drug & can function in society

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Buprenorphine

- Management of chronic pain
 - 4 to 8 mg per day → usual dose
 - analgesia typically lasts → 6 to 12 hours
 - increase analgesia duration by splitting up the dose → Q, 6 to 8 hour dosing → don't exceed 32 mg/day
- **OAT to treat opioid addiction**
 - most patients stabilize on 8 to 16 mg/day
 - can use up to 32 mg per day → rare

J Palliative Med.2012;15-613

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Buprenorphine

- Patient actively taking opioids
 - **buprenorphine will displace the full agonist**
 - can precipitate withdrawal symptoms but they are usually mild
- Time to initiate buprenorphine
 - when the patient exhibits the onset of withdrawal
 - now the **mu receptor can be partially activated & prevents full withdrawal**

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Opioid Withdrawal Symptoms

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Withdrawal Signs & Symptoms

- starts 4 to 6 hours after last drug dose
- peaks in 48 to 72 hours
- **increased sympathetic activity**
 - restlessness
 - insomnia
 - mydriasis
 - tachycardia
 - tachypnea
 - hypertension

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Buprenorphine

- Buprenorphine (Subutex)
 - used to **acutely detoxify patient**
 - 2 mg or 8 mg dose
- Buprenorphine/ naloxone (Suboxone)
 - **maintenance therapy for addiction**
 - **management of chronic pain**
 - 4:1 dosing sublingual → buprenorphine: naloxone
 - 2/0.5 mg 4/1.0 mg 8/2.0 mg 12/3.0 mg

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Suboxone

- Naloxone added to prevent abuse
 - as sublingual tab → naloxone is not bioavailable at low dose
 - if tablet goes into solution for injection → naloxone will be bioavailable and can precipitate withdrawal by reversing illegal agent
 - naloxone conc increases 15 X → buprenorphine by only 2 X
- Street value
 - if street drugs unavailable → **prevents withdrawal until illegal drug can be obtained**

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Chronic Opioid Use & Surgery Anesthesia

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Patients with OUD

- Patient potential fears & concerns
 - will they be treated fairly or face discrimination by medical providers
 - will they receive adequate pain control
 - will they experience perioperative opioid withdrawal
 - will they potentially relapse back to opioid abuse
- Reality of chronic opioid use & abuse
 - lowered pain tolerance
 - increased sensitivity to pain → hyperalgesia
 - medical comorbidities which increase morbidity

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Provider Concerns

- Can you trust the patient
 - disclose all opioid use
 - disclose additional drugs they are abusing
 - will they follow the treatment plan → not supplement with illicit pain medications or heroin
 - will they respect doctor – patient contract
 - office visits by appointment
 - no phone requests for analgesics

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Consultation

- Discussion about perioperative pain
 - need to accept pain from surgery → lasts for few days then subsides
 - severity & duration of pain associated with procedure
 - medications typically used for management
 - what are patient's expectations about pain & are they realistic
 - does the patient expect perioperative opioids
 - is the patient willing to accept some postoperative pain
- Relapse history
 - multiple attempts at rehab → perioperative opioids may increase risk of relapse

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Doctor

- Consult with patient's opioid use physician
 - patient's compliance & relapse issues
 - perioperative management of methadone, buprenorphine, or naltrexone → hold, maintain, or restarting
 - use of short, acting opioids perioperatively
- Pain contract → agreement on how pain will be managed
 - signed agreement between → Pain MD – Patient – Surgeon

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Misconceptions About Pain Management & Anesthesia

- Applies to patients taking **methadone** or **buprenorphine** for
 - **chronic pain** patients
 - opioid **dependent** patients
- **Perioperative Concerns**
 - issues with management of their acute pain
 - issues with management of their anesthetic
- **Opioid Agonist Therapy (OAT)**
 - patients receiving methadone or buprenorphine

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Misconception #1

- Maintenance Opioid Agonists Provide Analgesia
 - patients on these agents → **do not have sustained analgesia**
 - duration of action for analgesia is ~ **6 to 12 hours**
 - duration of **withdrawal suppression** is **24 to 48 hours**
 - drug is usually given once a day for addiction management
 - patients only get **short term pain relief**

J Pall Med. 2012;15:613

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Misconception #1

- Maintenance Opioid Agonist Provides Analgesia
 - **anesthesia & surgery will require additional medications for perioperative pain**
 - **if you use opioids** → require higher doses & increased frequency
 - **multi modal therapy will provide more effective analgesia**

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Misconception #2

➤ Opioids for Analgesia May Result in Relapse

- **no evidence** that exposure to opioids in presence of acute pain increases rates of relapse → dosing to **relieve pain** → but **no euphoria**
- euphoria → can induce cravings & lead to relapse
- stress associated with **unrelieved pain is a more likely trigger for relapse** than treatment with opioids

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Misconception #2

- Need to have this discussion with patients preoperatively
 - some patients fear relapse potential → respect concern & avoid opioids perioperatively
- Pain is still possible → even if use opioids → especially if you are on high dose buprenorphine or naltrexone

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Misconception #3

➤ Opioids + OAT cause Respiratory Depression

- never been proven that opioids + OAT cause severe respiratory depression → theoretical risk
- **tolerance** to respiratory depression & CNS depression from opioids **develops rapidly & reliably**
- **acute pain** acts as natural **antagonist** to opioid **respiratory depression**

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Buprenorphine & Surgery

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Buprenorphine & Surgery

- Most recommendations are based on case reports & institutional experience
- Do you stop or maintain the buprenorphine?

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Preoperative Concerns

- Abrupt discontinuation of buprenorphine preoperatively
 - patients have an opioid deficit
 - will start to experience withdrawal symptoms within 12 hours
 - need to start short duration opioids to prevent withdrawal
 - avoid codeine → some reports also recommend avoid hydrocodone
 - hydromorphone is best followed by oxycodone
 - potential for these short acting opioids to → ↑ cravings & relapse

Pain Med.2019;20:425

J Pall Med.2012;15:613

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Postoperative Concerns

- Restarting buprenorphine post operatively
 - need to be opioid free for 12 to 24 hours before restart
 - want to see onset of withdrawal before restart
 - patient experiences pain & anxiety
 - potential for relapse

Pain Med.2019;20:425

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Options for Surgery & Buprenorphine

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Surgical Options with Buprenorphine (BUP)

- **Option 1** : Continue preoperative BUP dose + additional BUP to manage perioperative pain
- Indications → Cases expecting zero to minimal pain
- Analgesia properties of buprenorphine
 - single dose duration → 6 to 12 hours
 - analgesic dose don't exceed → 32 mg/day
 - prolong analgesia by evenly dividing the dose → Q 6 to 8 hours
 - no perioperative opioids

Can J Anesth.2014;61:826

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Surgical Options with Buprenorphine

- **Option 2** : Continue buprenorphine dose & add opioids
- Use perioperative full mu agonist opioids for pain
- Intraoperative → fentanyl, hydromorphone, sufentanil, & remifentanyl
- Postoperative opioids → hydromorphone & oxycodone
 - avoid codeine & hydrocodone
- Historically → **pain difficult to manage**

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Surgery and Buprenorphine

- Continuing buprenorphine perioperatively
 - multiple case reports → full agonist opioids for perioperative pain management → require doses in excess of normal
 - ↑↑↑↑ dosing requirement
- Case report: 16 mg suboxone per day
 - PCA pump post op → hydromorphone 15-20 mg/24 hr to 50 to 70 mg/24 hr with pain scores of 10/10 (uncontrolled)
 - stopped Suboxone → hydromorphone dropped to 15-25 mg/24 hr

Can J Anesth.2014;61:826

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Does Naloxone have effect?

- Suboxone → 32 mg dose → contains 8 mg naloxone
- SL naloxone \geq 4 mg has precipitated withdrawal symptoms in opioid dependent patients
- Higher doses of Suboxone → may produce antagonist effects at receptor
 - prevent opioids from binding to receptors for pain relief
 - possible mechanism?

Can J Anesth.2014;61:826
Drug Alcohol Depend1990;25:27

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Surgical Options with Buprenorphine

- **Option 3** : Discontinue buprenorphine before surgery + Use perioperative opioids
- Several case reports recommend this approach
- Stop buprenorphine up to **72 hours pre op**
- Rationale for stopping buprenorphine
 - “free up” the mu opioid receptors
 - opioids can be used perioperatively & be effective

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Buprenorphine & Surgery

- **Option #3: Discontinue buprenorphine pre op**
- When stop buprenorphine → need to monitor for signs of withdrawal
 - 12 hours after last dose → MD starts methadone, oxycodone, hydromorphone, or others to prevent withdrawal
 - hydromorphone 4 mg Q 4 to 6 h
 - oxycodone 10 mg Q 6 h
 - hydrocodone 10 mg Q 8 h → has been used → not as effective as above

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Option #3

- **Option 3: Discontinue Buprenorphine**
 - Use full agonist opioids perioperatively
 - Opioid doses may be excess of what typically use
- What opioids should be used?
 - best to use opioid with high binding affinity (K_i)
 - lower the K_i → stronger the binding

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Opioid Binding

- Hydromorphone has excellent affinity → similar to BUP
 - with increased doses = respiratory depression is problem
- Affinity of fentanyl for mu receptor < hydromorphone
 - rapid onset & short half life compared to hydromorphone
- Affinity of remifentanyl for mu receptor < fentanyl
 - more rapid onset than fentanyl & shorter duration

Pain Medicine.2013;14:1187

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Drug	Mu Receptor Affinity	
<i>Sufentanil</i>	0.14	Intraoperative Opioids
Buprenorphine	0.22	
<i>Hydromorphone</i>	0.36	
Morphine	1.17	
<i>Fentanyl</i>	1.35	
<i>Remifentanyl</i>	2.6	Postoperative Opioids
Methodone	3.4	
<i>Oxycodone</i>	25.9	
Hydrocodone	41.6	
Codeine	734.2	
Tramadol	12000+	Hydromorphone Oxycodone

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Option #3

- Stopping buprenorphine preoperatively
 - should be done over several days
 - risk of relapse → need opioids to prevent withdrawal
 - patient may get cravings on opioids and relapse
- Opioids can be used perioperatively now
- Still should employ multimodal therapy
 - Acetaminophen, NSAIDs, Ketamine, Dexmedetomidine, & long acting local anesthesia

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IV Remifentanyl - Propofol

- Open airway deep sedation – GA anesthesia
 - 2 pumps
 - Propofol → start at 100 to 125 mcg/kg/min
 - Remifentanyl → start at 0.05 mcg/kg/min
 - adjust up or down depending on airway obstruction, decreased respiratory (< 8 to 9 per minute), hypoventilation, **hyponeic hypoventilation**, or patient discomfort
 - range is 0.05 to 0.1 mcg/kg/min in most cases
 - opioid dependent patient will take more

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IV Remifentanyl - Propofol

- Open airway deep sedation – GA anesthesia
 - single pump technique
 - 20 ml propofol = 200 mg propofol
 - remifentanyl vial → 1 mg vial = 1000 mcg
 - dilute 1 mg vial → 2 ml of saline = 500 mcg/ml
 - TB syringe → draw up 0.2 ml of diluted remifentanyl
 - 0.2ml X 500 mcg/ml = 100 mcg Remifentanyl
 - **100 mcg diluted by 20 ml propofol = 5 mcg Remi per ml**

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Remifentanyl – Propofol Single Pump

- Bolus at start of case
 - 150 mcg/kg → 2 up to 4 bolus to start
 - range → 100 to 200 mcg/ml
- Infusion after bolus
 - start at 70 mcg/kg/min
- Infusions without bolus therapy at start
 - 100 mcg/kg/min

Bosack Single Pump Remifentanyl

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Option #4: Buprenorphine & Surgery

- Option #4 → Decrease the preoperative dose of BUP & use perioperative opioids
- Historical Perspective → case reports recommended completely stop BUP preoperatively → “free up” mu receptors
 - perioperative full agonist opioids can now bind to receptors
- Question: Will decreasing but not eliminating BUP be effective?

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Option #4: Buprenorphine & Surgery

- Potential benefit to just decreasing the dose
 - decreased risk of withdrawal symptoms preop & postop
 - decrease risk of cravings for euphoria → decrease risk of relapse
- PET scan data
 - BUP at 32 mg dose → block → 94 – 98% mu receptors
 - no receptor sites for opioids to bond
 - opioids become ineffective

Pain Medicine. 2018:1-14 Quaye & Zhang

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Option #4: Decreasing Dose BUP

Daily Dose BUP	% Mu Receptor Availability	<u>BUP at 24 to 32 mg</u>
1 mg	71 to 85%	Few receptors available for mu opioids to bind
2 mg	53 to 72%	
4 mg	36 to 55%	Need lower dose of BUP for effective use opioids
8 mg	11 to 22%	
12 mg	13 to 24%	
16 mg	9 to 20%	
24 mg	4 to 15%	
32 mg	2 to 12%	

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Option #4: Reducing BUP

- Moderate dose BUP → 8 to 12 mg daily dose
 - ~ 20% receptors available for binding with opioids
 - should be enough for effective binding of high affinity opioids
- Goal → What dose of BUP do we want preop?
- How long does it take for reduction to work?

8 to 12 mg BUP → ~ 20% mu receptors are available for binding with opioids

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Option #4: Reduce BUP

- Study: 16 mg BUP per day
 - holding dose & PET scan to determine receptor availability

Hours Hold Dose	Receptor Availability
4 hr	30%
28 hr	54%
52 hr	67%
76 hr	82%

Hold BUP for 24 hours → about 50% of mu receptors are available for binding opioids

What about withdrawal symptoms?

Pain Med. 2018

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Option #4

- Withdrawal Symptoms in 16 mg BUP case
 - expect withdrawal symptoms when hold opioid
 - symptoms at 4 hours → similar to symptoms at 28 hours
 - symptoms at 52 hours → far greater than at 4 or 28 hours
- Conclusion
 - prevent withdrawal symptoms → need 50 to 60% of receptors occupied by BUP

Pain Med. 2018

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Option #4

- Conclusion
 - unlike previous studies → don't need to completely stop high dose buprenorphine preoperatively
- Decreasing the dose preoperatively
 - can free up mu receptors for analgesia
 - still prevent withdrawal symptoms preoperatively & postoperatively

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Option #4

- Boston & Stanford protocols may be the best way to treat the patients → will discuss shortly
- Postoperatively
 - use opioids for pain; taper the dose down
 - use MD guidelines for taper and increasing back to preop buprenorphine dose

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Protocols

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University of Michigan Protocol

First Protocol That Was Widely Used

Being Replaced by Boston & Stanford
Protocols

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Michigan Protocol Elective Surgery

- Step 1: No pain to minimal pain perioperatively
- Step 2: Buprenorphine is not stopped preoperatively
- Protocol
 - make pain management MD aware of surgery
 - continue buprenorphine perioperatively
 - no perioperative opioids used
 - intraop: dexamethasone, ketamine, dexmedetomidine, ketorolac, LA
 - preop and postop: NSAIDS, Tylenol, consider Lyrica or Neurotin

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Michigan Protocol Elective Surgery

- Step 1: No pain to minimal pain perioperatively
- Step 2: Patient's buprenorphine is stopped preoperatively
- Protocol
 - consult buprenorphine provider for stopping, restarting, & opioid doses
 - **0 to 4 mg:** hold buprenorphine for 24 hr before surgery
 - **5 to 8 mg:** hold agent for 48 hr before surgery
 - **9 to 12 mg:** hold agent for 72 hr before surgery
 - **> 12 mg:** BUP provider input for perioperative management

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Buprenorphine Stopped

- **Use perioperative opioids**
- Multimodal perioperative therapy → dexamethasone, ketamine, dexmedetomidine, ketorolac, long acting local anesthesia, NSAIDS, & acetaminophen
- When pain adequately managed → need opioid free period of 12 to 24 hours before restart buprenorphine
 - follow pain management MD protocols

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Michigan Protocol Elective Surgery

- Step 1: Moderate to Severe Pain
- Step 2: Patient's buprenorphine is stopped preoperatively
- Protocol
 - BUP provider consult → protocol for stopping BUP & opioid coverage
 - **perioperative opioids → used perioperatively expect ↑↑ dosing**
 - multimodal therapy → acetaminophen, NSAIDs, dexamethasone, opioids, ketamine, dexmedetomidine, lyrica, & neurotin
 - long acting local anesthesia
 - BUP provider for restarting BUP

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Michigan Protocol Elective Surgery

- Step 1: Moderate to severe pain surgery
- Step 2: Still taking buprenorphine
- Protocol
 - **cancel surgery**
 - return to pain management MD to stop drug & start short acting opioids
 - 0 to 4 mg: hold buprenorphine for 24 hr
 - 5 to 8 mg: hold drug for 48 hr
 - 9 to 12 mg: hold drug for 72 hr

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Stopping Buprenorphine

- Patient will need short acting opioids to prevent relapse
- Transition to short acting opioid → Oxycodone 40 mg/day → 10 mg Q6h or use hydromorphone
- Return for surgery → opioids will be more effective
- Opioids intraop + post op
- Michigan Protocol → completely stopping BUP preop risks withdrawal + relapse → adjusting dose seems more reasonable

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Buprenorphine & Surgery

- Patients should be in mild withdrawal before buprenorphine is restarted by MD
 - buprenorphine partially activates the receptor to avoid precipitation of full acute withdrawal
- Need to coordinate with pain management MD to treat pain & get patient off opioids and back on buprenorphine

Curr Pain Headache Rep. 2016;20:16

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Boston Protocol

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Boston Group Protocol

- Mild Pain vs Moderate to Severe Pain Protocol
- Mild Pain Protocol
 - maintain BUP dose throughout the perioperative period
- Moderate – Severe Pain
 - BUP dose > 16 mg/day → taper to 16 mg day before surgery → 8 mg day of surgery & throughout perioperative period
 - 8 mg dose → perioperative opioids effective

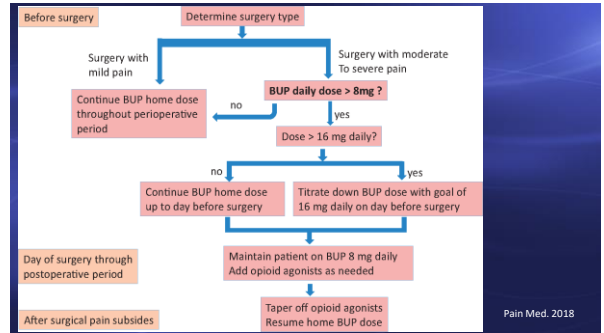
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Boston Group Rationale

- Why 16 mg BUP preop?
 - 16 mg BUP → 4 to 20% of mu receptors are available
 - block euphoric effects of opioids → if < 20% receptors available
 - less risk of withdrawal & patient stress if reduce to this level
- 24 hours later → receptor availability now at 40%
- Maintain at 8 mg perioperatively to increase free receptors

16 mg BUP frees up mu receptors for opioid use + prevents withdrawal symptoms
8 mg BUP allows for more effective opioid binding intraop + postop

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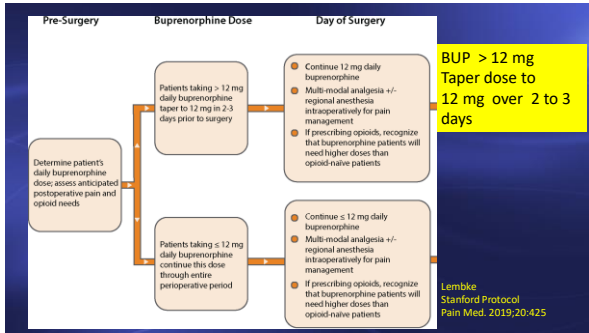
Boston Group

- Can use opioids for post op pain and will be effective
- Taper the opioid dose down
- Resume preop dose of buprenorphine
- Use Pain management MD guideline for tapering

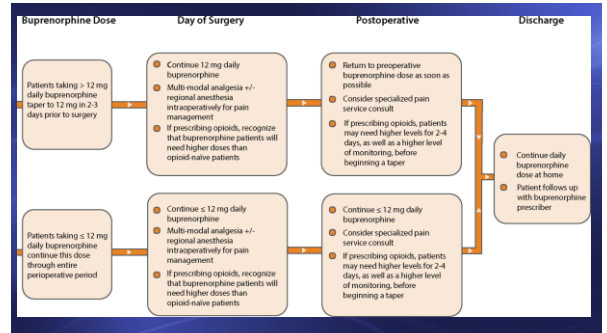
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Stanford Protocol

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Stanford Protocol

- 12 mg dose
 - based on receptor availability → Boston group used 16 mg then 8 mg the day of surgery
- Continue the 12 mg dose → 1 to 3 days post op
 - if need opioids for pain → more effective
 - begin tapering down the dose of opioids
 - then return to preoperative dose of BUP
 - use pain management MD guidelines for tapering

Pain Med. 2019;20:425

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Summary Buprenorphine

- Minimal pain producing procedures
 - maintain preoperative dose of BUP
 - multimodal anesthesia & postoperative non opioid analgesia
- Moderate to severe pain producing procedures
 - reduce preoperative day of surgery BUP dose → < 16 mg SL

Can J Anesth. 2019;66:201-217

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Naltrexone

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Naltrexone

- Semisynthetic opioid antagonist
 - mu (μ) antagonist → partial kappa (κ) agonist
 - no effect on delta (δ) receptors
 - **greatest effect is on mu receptor** → competes & displaces opioids from receptors
 - **prevents euphoria from opioid use**
 - **reduces cravings** in patients after detox program

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Naltrexone

- Used to treat opioid addiction & alcoholism
- Oral formulation & IM depot injection (Vivitrol)
 - oral is once a day dosing
 - IM is once a month

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Naltrexone

- Chronic use of opioid antagonists causes
 - **↑ density** of opioid receptors in brain
 - opioids & naltrexone will compete for these receptors
- Receptors are **upregulated** → **↑ sensitivity to opioid exposure**
 - small doses of opioids will have increased effect
 - **↑ risk of opioid complications** → respiratory depression, hypotension, & bradycardia

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Naltrexone

- Naltrexone can also down regulate receptors
 - ↓ sensitivity to opioids
 - need increase dose of opioids → to achieve analgesia
 - need to increase dose by 30 to 100%
 - low dose opioids may not alleviate perioperative pain
- Naltrexone blockage can be overcome
 - give ↑↑↑ doses of opioids → 10 to 20 X usual dose

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Naltrexone

- Half life
 - oral naltrexone = 4 hours
 - active metabolite = 13 hours
- PO dose effective for 24 hours → once a day PO dosing
- IM dose effective for 3 to 4 weeks → once a month dose

Curr Opin Anesthesiol.2014;27:359-364
Anesth Analg.2018;127:539-47
A&A Case Reports.2014;3:142-4

Curr Opin Anesthesiol.2019;32:427-437
Anesthesiology Clin.2018;36:345-359

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Oral Naltrexone & Surgery

- Oral naltrexone continued perioperatively
- Non opioid anesthetic
 - No perioperative opioids → naltrexone prevents binding to receptor
 - Office anesthesia → multimodal approach
 - TIVA anesthesia → midazolam, propofol, dexamethasone, ketamine, ketorolac, & dexmedetomidine (IV Tylenol or Ibuprofen)
 - Inhalation general anesthesia
 - Post op medications
 - acetaminophen, NSAIDs, Lyrica, or Neurotin

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Oral Naltrexone & Surgery

- Opioid based anesthetic
- Naltrexone should be held 24 to 72 hours (3 days safe)
 - perioperative opioid dose → ↑↑ doses may be necessary
 - respiratory depression may be deeper & prolonged
 - use short acting opioids → remifentanyl, fentanyl, & sufentanyl
 - post op pain → oxycodone or non opioids
- Patients should be opioid free for 3 to 5 days before naltrexone is restarted

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Naltrexone XR & Anesthesia

- IM naltrexone (Vivitrol)
- Little data on anesthetic management
- Opioid based anesthetic
 - first 2 weeks after injection → very refractory to opioids
 - minimal to no analgesia because opioid is blocked
 - last 2 weeks especially the 4th week → naltrexone can be overcome by ↑↑ doses of opioids
 - will increase risk of respiratory depression

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Naltrexone XR & Elective Surgery

- Best to wait for 1 month for procedure
 - case reports → no analgesia from opioids in first 2 weeks
 - opioids more effective after 1 month → even if just for post op pain
- Opioids have unpredictable response
 - upregulated receptors → ↑ sensitivity
 - downregulated receptors → ↓ sensitivity
 - opioids may ↑ respiratory depression → monitor for hypoventilation

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Naltrexone XR & Elective Surgery

- Anesthesia in office
 - TIVA → midazolam, propofol, ketamine, dexamethasone, & dexmedetomidine
 - IV acetaminophen, or ibuprofen
 - try to avoid opioids perioperatively → if necessary use short acting remifentanyl
 - can also use inhalation anesthesia

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Naltrexone XR & Surgery

- Post operative pain & opioids
 - little data
 - effect will depend on timing of last naltrexone injection
 - effective dose may be multiples of what you typically give a patient
- Need to be opioid free for 7 to 10 days to restart med
- Best approach is multi modal therapy
 - no analgesic medications prn → dose at specific intervals

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Methadone

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Methadone

- Synthesized in WWII Germany due to morphine shortage
 - introduced as analgesic in 1947
- Indication for use → manage chronic pain & OUD
- 2 isomers
 - S isomer → mu (μ) & delta (δ) agonist
 - R isomer → NMDA receptor antagonist → chronic pain use
 - Nepi and Serotonin reuptake inhibitor
 - Management of opioid induced hyperalgesia

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Methadone

- Oral onset of action → 60 minutes
- Peaks → 2 to 4 hours after ingestion
- Effective dose → 60 to 120 mg/day
- 2 Phase Elimination
 - alpha α phase → 8 to 12 hours for analgesia
 - beta β phase → 30 to 60 hours for withdrawal suppression

Anesthesiology Clin.2018;36:345 Curr Opin Anesthesiol.2019;32:427 Anesth Analg.2018;127:539
 Curr Pain Headache Rep.2016;20:16 Curr Opin Anesthesiol.2014;27:359

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Methadone

- Full mu agonist
 - buprenorphine is partial mu agonist
 - opioids used for anesthesia → full mu agonists
 - potentiate effects of other full agonist opioids
 - can increase respiratory depression
- **Less euphoria** than other opioids
 - less abuse potential than other opioids & reduces opioid cravings
 - at high dose → prevents euphoria from other opioids

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Methadone

- Induces QT prolongation & dysrhythmias
 - increased risk of Torsades
 - patient history & ECG
- Decrease dose in liver disease
- Metabolized by liver
- Chronic pain patients
 - 40% relief from NMDA
 - 60% from opioid receptors

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Methadone & Surgery

- Maintain methadone dose perioperatively
- Use full agonist opioids intraoperatively
 - short acting → remifentanyl, fentanyl, & sufentanyl
- Daily dose of methadone for OUD → inadequate to provide acute perioperative pain relief
- Multimodal anesthesia
- As with buprenorphine → discuss with methadone MD

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Methadone

- Patient who continue to actively abuse opioids
 - can use Methadone for perioperative pain
- 30 to 40 mg/day PO in addition to multimodal
- 2.5 to 5 mg IV Q 6 to 8 hours
- Consult pain service for management of all actively OUD patients

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Summary

- Chronic opioid patients require
 - 2 to 3 X amount of opioid as opioid naïve patient
 - also need ↑ number of days of post op opioids
- Avoid agonist – antagonist drugs
 - can induce withdrawal
- Presence of acute pain → ↓ euphoric effect of opioid

Pain Med.2018:1-14. Quaye & Zhang

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Summary

- Analgesics are not given prn → use set time
- Presence of acute pain will ↓ euphoric effect of opioid

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Multi Modal Therapy

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Multi Modal Analgesia

- Opioids
- Ketamine
- NSAIDs
- Acetaminophen
- Long acting local anesthesia
- Lyrica (Pregabalin) & Neurotin (Gabapentin)
- Dexamethasone

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Suggested Protocols Pre-op

Drug	Route	Dose 2 hr pre-op
Acetaminophen	PO	1000 mg
Celebrex	PO	200 to 400 mg
Pregabalin	PO	75 to 150 mg
Gabapentin	PO	900 to 1200 mg

Anesthesiology Clinics.2016;34:287-301

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Major Surgery Pre-op Medications

1 to 2 hours pre-op	Dose
Acetaminophen	1000 mg PO
Dexamethasone	4 to 8 mg IV
Celebrex	200 mg PO
Gabapentin	1200 mg PO
Before incision	-----
Ketamine	0.1 to 0.3 mg/kg IV

Advances in Anesthesia 2009;27:25-54

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Drug	Route	Dose
Acetaminophen	PO/IV	1000 mg Q6h (pt > 50 kg)
Ibuprofen	PO	600 mg Q6h
Ketorolac	PO/IV	15 to 30 mg Q6h
Celebrex	PO	200 to 400 mg Q12h
Gabapentin	PO	600 to 800 mg Q8h
Pregabalin	PO	75 to 150 mg Q12h
Ketamine	IV	0.5 mg/kg bolus

Anesthesiology Clinics.2016;34:287-301

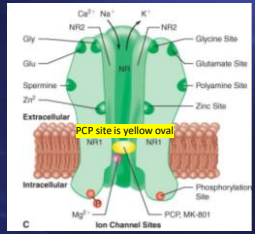
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Ketamine

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Ketamine

- ketamine binds to PCP site on NMDA receptor
 - blocks the open channel
 - prevents flow of ions in & out of cell
 - inhibits depolarization of post synaptic neuron
 - blocks excitation



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Ketamine

- Rapid onset

– IV	~ 20 to 30 secs	peak plasma conc	~ 1 min
– IM	~ 2 to 3 mins		~ 5 min
– PO	~ 12 to 20 mins		~ 30 min
- Redistribution from IV route ⇔ 7 to 15 mins
- Elimination half life
 - adults 2 to 3 hours
 - children 1 to 2 hours

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Ketamine for General Anesthesia

- Adult dosing of ketamine
 - onset < 60 secs
 - duration of single dose ~ 10 to 15 min
- IV 0.5 to 2.0 mg/kg
 - 5 to 20 mg IV as needed
 - infusion 50 mcg/kg/min
- Maintenance IV
 - 0.1 to 0.3 mg/kg IV prn Q 10 to 15 mins

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Subanesthetic Doses of Ketamine in Opioid Patient

- IV bolus dosing intra op → 0.15 to 0.50 mg/kg IV
- Infusions intra op → 0.12 to 0.5 mg/kg/h Pain Med.2015;16:383
- Low dose ketamine in opioid dependent patients
 - 0 to 1 mg/kg IV bolus → infusions up to 48 hr. post op at < 1.2 mg/kg/h → reduce opioid requirements by 40% Pain Med.2015
- Intraoperative bolus → 0.5 mg/kg IV → then infuse at 0.1 to 0.3 mg/kg/h Curr Opin Anesthesiol.2019;32:427

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Subanesthetic Doses of Ketamine

- Infusion
 - start infusion in adults → 0.12 mg/kg/h based on IBW
 - 0.06 to 0.3 mg/kg/h based on IBW
- Post op → need monitored bed → consult pain service
 - intraop bolus ≤ 0.35 mg/kg → post op infusions ≤ 1mg/kg/h

Curr Opin Anesthesiol.2019;32:427

Reg Anesth Pain Med.2018;43(5):456

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Emergence Delirium

- Many agents are associated with emergence delirium
- Dexmedetomidine can reduce the incidence
 - prophylactic dose in at risk patients
 - 0.25 mcg/kg in two divided doses intraoperatively
 - if develop ED post op: give another 0.25 mcg/kg dose
 - no prophylaxis & develop ED
 - 0.5 mcg/kg dose slowly

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NSAIDS

- Nonselective COX inhibitors
 - inhibit cyclooxygenase (COX) to decrease production of PGE2
 - PGE2 causes inflammation and pain
 - drugs → ibuprofen, naproxen, & ketorolac
- COX-2 specific inhibitors
 - COX-2 is specific enzyme for inflammation
 - COX-1 is involved with gastric & platelet effects
 - drug → celecoxib (Celebrex)

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NSAIDS

- Ibuprofen
 - 400 mg Q4h
 - 600 mg Q6h
 - 800 mg Q8h
- Celebrex
 - 200 mg BID
 - 400 mg BID
- Ketorolac IV dose 15 to 30 mg
 - 30 mg IV Q6h maximum dose 120 mg
- NSAIDs reduce opioid requirements by 20 to 30%

Curr Pain Headache Rep.2016;20:16

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IV Ibuprofen

- IV dosing: 400 to 800 mg Q6h
 - maximum: 3200 mg/day
 - infuse 30 or more minutes
- 400 mg dose: dilute in 100 ml of fluid
- 800 mg dose: dilute in 200 ml of fluid
 - fluid = NS, D5W, or LR



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Acetaminophen

- Oral, rectal, or IV
- Inhibits cyclooxygenase (COX) enzyme in CNS
- IV acetaminophen
 - reduced opioid use by 24% during first 4 hours postop
 - 50% reduction in postop pain
- 3 gram total dose per day
- Data → IV was no better than PO

Anesthesiology Clinics.2018;36:345

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IV Acetaminophen

Dosing of OFIRMEV for adults, adolescents, and children ≥2 years old*

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum single dose	Maximum total daily dose of acetaminophen (by all routes)
Adults and adolescents (13 years and older) weighing ≥50 kg	650 mg	1000 mg	1000 mg	4000 mg in 24 hours
Adults and adolescents (13 years and older) weighing <50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg/kg in 24 hours (up to 3750 mg)
Children 2 to 12 years old				

1000 mg/100 ml 10 mg/ml
Infuse over 15 minutes



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Dexmedetomidine

- highly selective for α_2 adrenergic receptors
- more selective than clonidine
- α_2 to α_1 selectivity
 - clonidine 220 to 1
 - dexmedetomidine 1620 to 1
- no GABA activity

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Options for Infusion

- 1 mcg/kg IV infusion over 10 minutes
 - maintenance 0.2 to 0.7 mcg/kg/hr → or 0.5 to 1.0 mcg/kg/hr
 - adjustment in rate dependent upon
 - level of anesthesia, hypotension, or bradycardia
- Onset 5 minutes or less
- Peak effect in 15 minutes
- stop infusion 20 to 30 minutes prior to end of surgery to shorten recovery time

J Opioid Management. 2009;5(3):175

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Options for Bolus

- Bolus 0.25 to 0.5 mcg/kg
 - slow injection in divided doses ~ 5 minutes
 - should reduce transient ↑ in BP
 - sedation without respiratory depression
- Bolus 1 mcg/kg over 10 minutes
 - then infuse 0.2 to 0.7 mcg/kg/hr
- Some skip the loading dose and go directly to infusions

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Gabapentinoids

- Gabapentin & pregabalin
- Used as anticonvulsants
- Pain → inhibit neurons involved in central pain
- Side effects are sedation & dizziness
- Drugs are adjuncts to those previously mentioned

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Gabapentinoids

- Pregabalin (Lyrica) dosing options
 - 75 to 150 mg PO Q12h
 - 50 to 100 mg PO Q8h
- Gabapentin (Neurontin) for major surgery
 - 900 to 1200 mg PO pre-op
 - 300 mg PO Q8h

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Lidocaine

- Perioperative use will decrease pain & opioid requirements
 - first 24 hours postoperatively
- Intraoperative bolus dose → 1 to 1.5 mg/kg IV over 10 min
- Follow with infusion → 0.5 to 3.0 mg/kg/h → IBW
- Narrow therapeutic index → 2.5 to 3.5 mcg/ml
 - CNS toxicity starts at 5 mcg/ml

Anesth Clinics.2018;36 Curr Opin Anesthesiol.2019;32:427

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Magnesium

- NMDA antagonist
- Loading dose IV → 30 to 50 mg/kg IV bolus
 - then infuse 8 mg/kg/hr during surgery
- Potentiates other analgesics
- As a solo agent → no analgesia

Anesth Clinics. 2018;36

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Anest Analg.2018;127:539
 Curr Pain Headache Rep.2016;20:16
 Curr Opin Anesthesiol.2014;27:359
 AA Case Reports.2014;3:142
 BMC Anesthesiology.2019;19:68
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 Anesthesiology.2017;126(6):1180
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 J Pall Med.2012;15:613
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 Can J Anesth.2019;66:201
 Anesth Clinics. 2018;36:245
 Pain Med.2015;16:383
 Reg Anesth Pain Med.2018;43(5):456
 Front Pharm.2014;5:article 108 May 2014 Remifentanyl
 Curr Opin Anesthesiol.2019;32:427

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Marihuana

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Psychoactive Components

- Primary psychoactive component is → THC
 - δ -9 – tetrahydrocannabinol
- 60 other cannabinoids in plant
 - cannabinol → psychoactive properties
 - cannabidiol (CBD) → no psychoactive properties → pain relief
- 340 other chemical compounds in plant

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CNS Effects

Euphoria	Heightened sensory perception
Relaxation	Laughing
Drowsiness	Dizziness
Anxiety	Dysphoria
Loss of Control	Impaired short term memory

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CNS Effects

- Euphoria → “High”
 - varies with dose, mode of administration, & personality of user
- Dysphoria
 - not uncommon especially in naïve users
 - severe anxiety & panic, loss of control, fear of dying
 - some subjects euphoria & dysphoria alternate

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CVS Effects

- Low dose THC causes ↑ **sympathetic activity**
 - see slight hypertension + tachycardia
- Tachycardia seen within few minutes
 - increase is related to dose of drug
 - rate increase → 20 to 50% → up to 100% increase
 - last up to 3 hours
 - ↑ in CO (up to 30%) & ↑ myocardial oxygen consumption

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CVS Effects

- AMI is rare → younger population
 - patients with CAD → potential risk due to imbalance of myocardial oxygen supply & demand
- ECG
 - occasional non specific ST – T wave changes
 - may see ventricular ectopy
 - unstable dysrhythmias are rare

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CVS Effects

- Low dose THC = sympathomimetic effects
- High doses of THC
 - inhibit sympathetics & stimulate parasympathetics
 - may see bradycardia & hypotension

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Respiratory Effects

- Adverse effects similar to chronic cigarette smoking
 - cough, sputum production, occasional wheeze
 - exposed to carcinogens
 - airway reactivity
- 3 to 4 “joints” per day → same incidence of acute & chronic bronchitis as smoking 20+ cigarettes

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Marihuana & Anesthesia

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Anesthesia

- Cannabis may enhance sedative – hypnotic effects of anesthetic agents
 - benzodiazepines, propofol, methohexital, & opioids
- Smoking causes lung impairment
 - deep breaths + holding → carboxyhemoglobin levels → 5X that of cigarette smoking
 - need at least 3 or more days to normalize
 - smoke can cause oropharyngeal & uvular swelling
 - ↑ risk of airway obstruction

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Anesthesia

- Airway Reactivity
 - recent smoking exposure caused increase in laryngospasm for at least 4 hours
- Sputum, cough, or wheeze
 - consider the use of pre op albuterol
 - initiate steroids
 - wheezing may require pre op optimizations days in advance

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Anesthesia

- CVS irritability
 - acute use causes an increase in HR, ectopy, and myocardial oxygen supply & demand issues
 - avoid anesthetic agents → atropine, ketamine, and epinephrine in local anesthesia
- Chronic marijuana & tolerance issues
 - developed a tolerance to induction dose of propofol
 - possibly do same to other anesthetic agents

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Anesthesia

- Inhalation agents can cause some myocardial depression
 - marijuana will add to this depression
- Additive effects with opioids
 - increase in respiratory depression
- **Incidence of major anesthetic interactions with marijuana are rare**
 - not much published data

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Anesthesia

- Drug remains in tissues for weeks
- When can you do the case?
- How long do you want the patient to hold marijuana?
- Want at least 3 or more days to reduce carbon monoxide in lungs

Crit Rev Oral Bio Med. 1992;3:163-84

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Case Presentation

- 25 y.o. male
- PMH: no significant history
- Chief Complaint
 - pain in tooth #30
- Secondary complaint
 - cyclic episodes of severe N/V
 - multiple vomiting episodes per day
 - lasts for several days then stops then recurs in few months
 - severe abdominal pain
 - only relief is taking hot showers

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Cannabinoid Hyperemesis Syndrome (CHS)

- 1st reported in 2004
- CHD Features
 - weekly cannabis use > 1 year history
 - most cases → 1 to 5 year history
 - cyclic episodes of severe N/V
 - may last for several days then recur months later
 - abdominal pain accompanies the N/V
 - resolution of N/V if stop using cannabis
 - symptomatic relief with hot showers & baths
 - cannabis use frequently started in teenage years

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CHS Possible Etiology

- some evidence for the following
- CB 1 receptors dysregulation
 - low dose THC = antiemesis
 - high dose THC = proemesis
- genetic mutations in cytochrome P450 enzymes
- CB 1 receptors in GI tract
 - alter gastric motility → food & fluids remain in stomach

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Treatment of CHS

- only definitive treatment is to stop using marijuana
- IV fluids for supportive care
- anti- emetics for supportive care
- hot showers & baths for symptomatic relief

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Thank you

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Buprenorphine & Emergency Surgery

University of Michigan Protocol

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Buprenorphine & Urgent / Emergent Surgery

- No pain to minimal pain procedures
- Buprenorphine is stopped
- How long has patient been off buprenorphine?
 - dose determines length of time → success of perioperative opioids
 - may need doses far in excess of opioid naïve patients
- Contact buprenorphine MD about the case
- Use perioperative opioids
- Post op pain normalizes → MD will restart buprenorphine

Anesthesiology, 2017; 126: 1180-6

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Buprenorphine & Urgent / Emergent Surgery

- No pain to minimal pain
- Patient Still on Buprenorphine
- Contact buprenorphine MD about case
- Continue buprenorphine for post op pain
- Do Not Use Opioids perioperatively
- Multi modal anesthesia with non opioids
 - dexamethasone, ketamine, dexmedetomidine
 - long acting local anesthesia

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Buprenorphine & Urgent / Emergent Surgery

- Moderate to Severe Pain
- Patient stopped buprenorphine
- Use opioids perioperatively
 - use higher doses & more frequent intervals of opioids
- Get follow up with MD post operatively about restarting drug
- Use multi modal therapy for pain

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Buprenorphine & Urgent / Emergent Surgery

- Moderate to Severe Pain
- Patient still using buprenorphine
- **Discontinue** buprenorphine but go to surgery
- Use PCA pump → opioids typically high dose → may need infusion pump therapy
- typical opioid = hydromorphone

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Buprenorphine + Urgent Sx

- Moderate to Severe Pain
- Patient still using buprenorphine
- Want a monitored bed to evaluate hypotension & breathing
- Start gabapentin or pregabalin preoperatively
- Start NSAIDS and/or Tylenol preoperatively
- Intraoperative use of dexmedetomidine & dexamethasone
- Consult pain service

Anesthesiology, 2017; 126: 1180-6

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