



Treatment of Acute Pain in Patients with Opioid Use Disorders

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Disclosures:

Both presenters are fulltime employees of the Federal Government, VA Pittsburgh Healthcare System, and are not representing them in this presentation.

We represent no drug companies.

Objectives

Define	Define pertinent terminology related to substance use
Explore	Explore a few misconceptions about treating acute pain in patients with addiction
Review	Review guidelines and suggestions for the treatment of acute pain in patients with active or remote substance use
Apply	Apply recommendations to patient cases

Patient Case #1

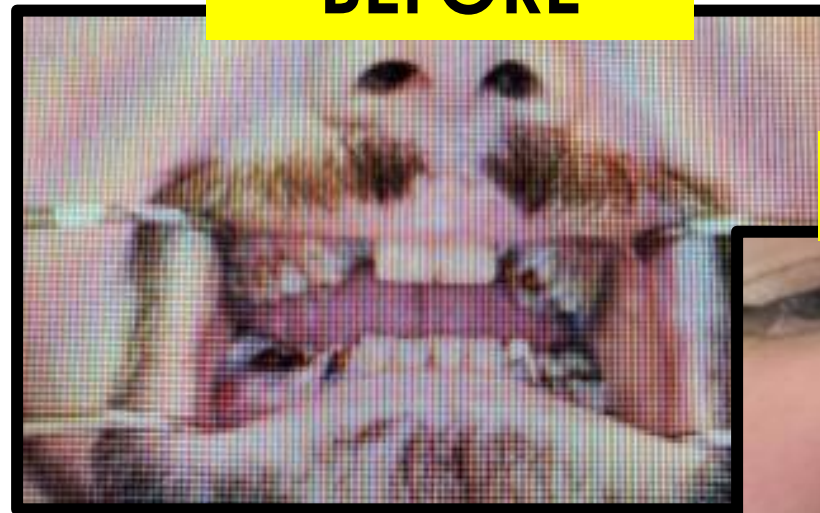
- ▶ 29 y/o male with opioid use disorder (OUD) on buprenorphine 8 mg BID for at least 5 years with no relapses
- ▶ Sustained a workplace injury in which a saw bit dislodged and flung toward his face
 - Avoided major cranium impact
 - Sustained major lower face injury requiring 30 stitches
 - Frightened of taking full agonist opioids
 - Got him in trouble years ago
 - Initially resorted to suffering
- ▶ What are his options?



Patient Case #2

- ▶ 41 y/o male with opioid use disorder (OUD) on buprenorphine 8 mg BID for at least 5 years with no relapses and major anxiety disorder coated with depression and social anxiety over the state of his dentition.
- ▶ Underwent total extractions to get total set of dental implants
- ▶ What are his options?

BEFORE



AFTER

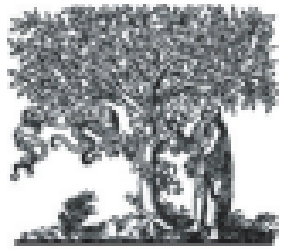


Patient Case #3

- ▶ 31 y/o male with opioid use disorder (OUD) on buprenorphine 8 mg BID for at least 5 years with no relapses
- ▶ Sustained a broken leg subsequent to a motorcycle injury. He was wearing a helmet and sustained no head injury
 - Underwent orthopedic surgery.
 - Inpatient team had difficulty managing his pain post-operatively.
 - He was just about to leave the hospital as he was suffering terribly.
 - He was going to figure this out on his own on the streets.
- ▶ What are his options?

Prescriber Challenges

- ▶ Blamed for creating the opioid epidemic
- ▶ Pressure to address the needs of the patient
- ▶ Pragmatic, ethical and legal issues
- ▶ Evaluating for drug-seeking behaviors
- ▶ Distinguishing true addiction from physical dependence



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Substance use history is associated with lower opioid use for emergency department pain management

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A B S T R A C T

Introduction: In the current national opioid crisis, where 10% of the US population has or has had a substance use disorder (SUD), emergency department (ED) clinicians are challenged when treating pain in the ED and when prescribing pain medications to these patients on discharge as there is concern for contributing to the cycle of addiction. The objective of this study was to examine whether acute pain is treated differently in patients with and without current or past SUD by quantifying the amount of opioid analgesia given in the ED and prescribed on discharge.

Methods: Retrospective cohort study of patients presenting to a 60,000-visit tertiary referral ED with acute fracture between January 1, 2016 and June 30, 2019. The primary exposure was indication of SUD (SUD+) versus those without SUD (SUD-). The primary outcome was receipt of opioids in the ED, and the secondary outcome was opioids prescribed at discharge.

Results: 117 matched pairs ($n = 234$) were included in the sample. Overall, 53.4% and 62.4% of patients received opioids in the ED or a prescription for opioids, respectively. Opioid receipt in the ED was lower among SUD+ patients compared to SUD- patients (48.7% and 58.1%, respectively; aOR: 0.33; 95%CI: 0.14, 0.77). Similarly, receipt of a prescription for opioids was lower among SUD+ patients compared to SUD- patients (56.4% and 68.4%, respectively; aOR: 0.50; 95%CI: 0.26, 0.95).

Conclusions: Overall, ED clinicians gave opioids less frequently to SUD+ patients in the ED and on discharge from the ED compared to SUD- patients with acute pain secondary to acute fracture.

Conclusion Overall, this study quantified how we treat acute pain in patients with and without a history of substance use disorder. This is something clinicians should be aware of so that we do not contribute to addiction or negatively impact recovery but also do not undertreat pain in SUD + patients. In order to address undertreated pain we must address patient and physician attitudes and education, take a multimodal and multidisciplinary approach to pain control, and understand the complexities of pain and pain control. There are currently no specific guidelines outlining if acute pain in SUD+ patients should be managed the same or differently than that of SUD- patients, however, we hope that identifying and quantifying our current practices can be the first step in working toward a better understanding acute pain management in SUD+ patients.

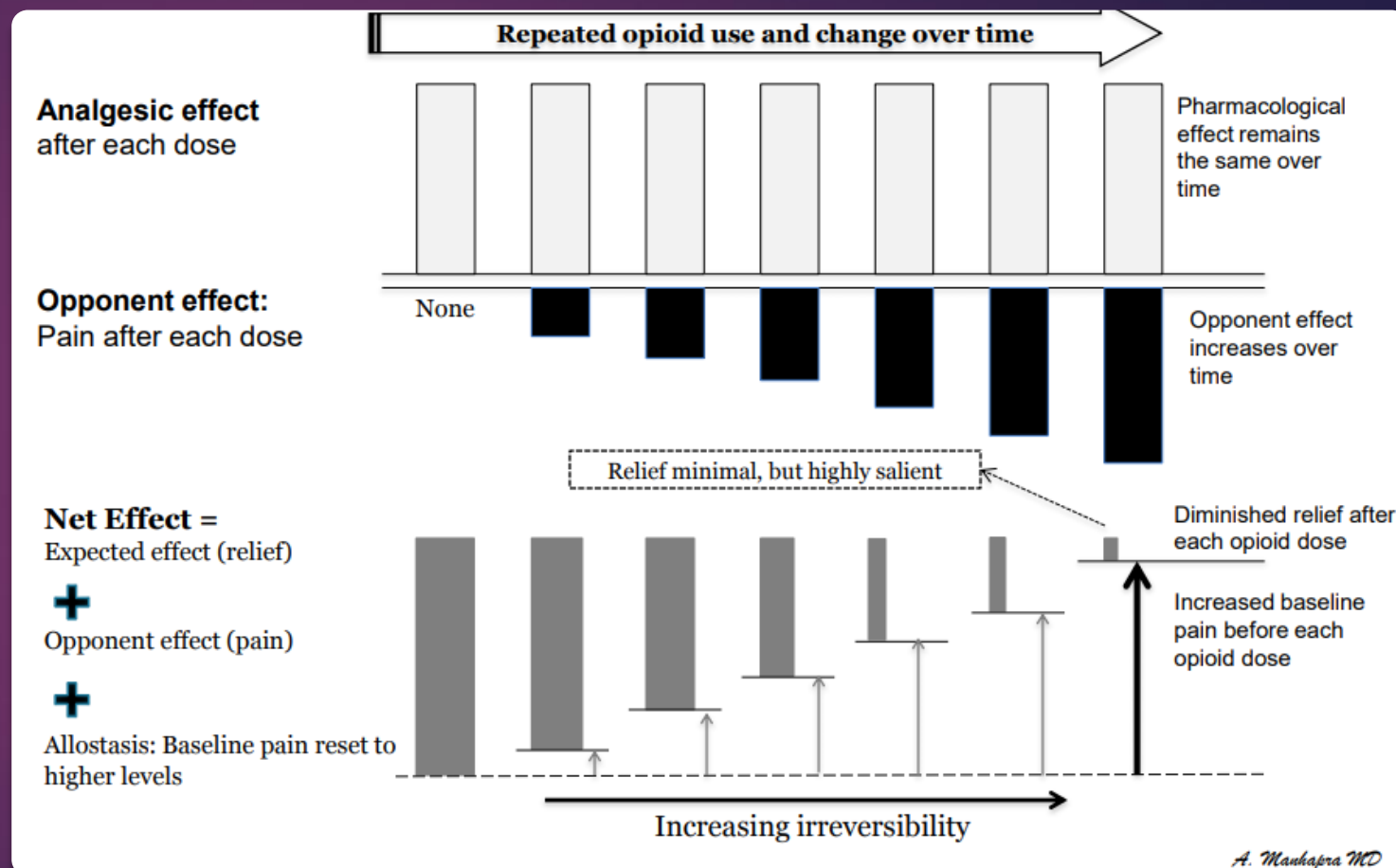
Tolerance

Tolerance is the reduction in response to a drug after its repeated administration, for which there are several mechanisms:

- ▶ Pharmacokinetic - increased metabolism
- ▶ Pharmacodynamic - adaptive changes related to receptors
- ▶ Learned - compensatory mechanisms that are learned
- ▶ Conditioned - learned specific environmental cues paired with drug administration

Opioid Debt - Tolerance

- Tolerance to analgesic effect has to be accounted for and overcome in arriving at an adequate opioid regimen with a net positive analgesic balance, if reliant on opioids.



Physical Dependence

Physical dependence is a state that develops as a result of the adaptation produced by the resetting of homeostatic mechanisms after repeated use.

This adaptation is manifested by a withdrawal syndrome that can be produced by:

- Abrupt cessation
- Rapid dose reduction
- Decreasing blood level
- Administration of an antagonist

} **of an opioid mu receptor agonist**

Withdrawal = Physical Dependence

Opioid Withdrawal

Symptoms of EARLY Withdrawal

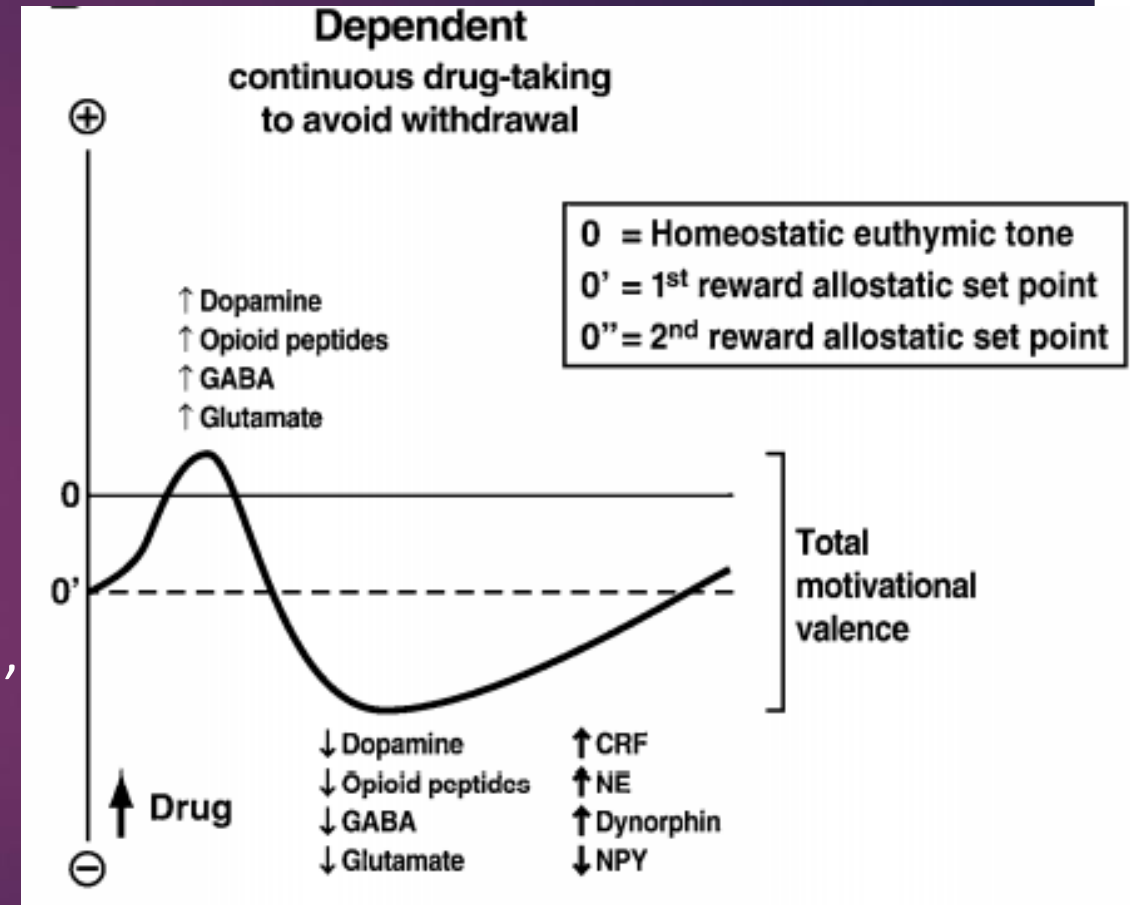
- ▶ Agitation
- ▶ Anxiety
- ▶ Muscle aches
- ▶ Increased tearing
- ▶ Insomnia
- ▶ Runny nose
- ▶ Sweating
- ▶ Yawning

Symptoms of LATE Withdrawal

- ▶ Abdominal cramping
- ▶ Diarrhea
- ▶ Dilated pupils
- ▶ Goosebumps
- ▶ Nausea
- ▶ Vomiting

Opioid Debt – Physical Dependence

- ▶ Allostasis is defined as stability through change.
- ▶ Allostasis involves a feed-forward mechanism rather than the negative feedback mechanisms of homeostasis
- ▶ Allostatic load is the consequence of repeated deviations from homeostasis that take on the form of changed set points that require increasing amounts of energy to defend, and ultimately reach, the level of pathology



Addiction

- ▶ A primary, chronic, neurobiologic disease with genetic, psychosocial and environmental factors influencing its development and manifestations
- ▶ ASAM: 3 Cs
 - ✓ Impaired CONTROL over drug use
 - ✓ COMPULSIVE use (CRAVING)
 - ✓ Continued use despite adverse CONSEQUENCES
- ▶ DSM-V: Substance Use Disorders (SUDs)
 - ▶ Defined by 11 symptoms
 - ▶ Measured on a continuum from mild to severe, based on the number of symptoms the patient endorses (*mild: 2-3; moderate: 4-5; severe: ≥ 6*)

Pain and Addiction

- ▶ The presence of one condition seems to influence the expression of the other
 - Acute pain seems to decrease the euphorogenic qualities of opioids
 - Addiction seems to worsen the experience of pain
- ▶ “Syndrome of Pain Facilitation” **consequence of addictive disease**
 - Pain worsened by:
 - Withdrawal-related sympathetic nervous system arousal
 - Intoxication
 - Sleep disturbances
 - Changes in affect (dual diagnoses quite common)

Treatment Misconceptions



1. Maintenance opioids for OUD provides analgesia
2. Use of opioids for analgesia may result in addiction relapse for MOUD patients on partial agonists
3. Additive effects of opioid analgesics and opioid partial agonist therapy may cause respiratory and CNS depression
4. Reporting pain may be a manipulation to obtain opioid medications, or drug-seeking, because of OUD history

Misconception #1

Maintenance opioids for OUD provides analgesia

- ▶ Maintenance opioids are dosed once daily for the treatment of opioid use disorder
 - ✓ Methadone: up to 80-120mg once daily
 - ✓ Buprenorphine (+/- Naloxone): up to 24mg once daily
- ▶ Duration of action for methadone and buprenorphine
 - ✓ Suppression of withdrawal: 24-48 hours
 - ✓ Analgesic: 4-8 hours



Buprenorphine

- ▶ A partial agonist/ antagonist
 - **Partial agonist activity at mu receptors**
 - Only partially activating (less effective than full opioid agonists)
 - Weak antagonist activity at kappa receptors
 - “Ceiling effect:” Well-documented in regards to non-analgesic effects (i.e., respiratory and CNS depression), but whether this also applies to analgesic effect remains controversial

Misconception #2

Use of opioids for analgesia may result in addiction relapse

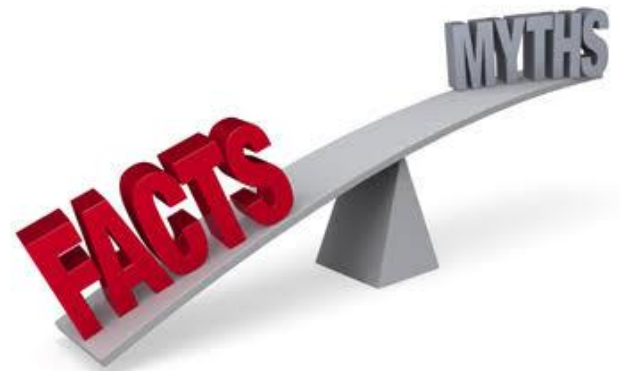
- ▶ There is no evidence that exposure to opioids in the presence of acute pain increases rates of relapse
- ▶ Relapse prevention theories
 - Stress associated with unrelieved pain is more likely to be a trigger for relapse than adequate analgesia



Misconception #3

The additive effects of opioid analgesics and opioid agonist therapy may cause respiratory and CNS depression

- ▶ Additive effect is only theoretical and never actually clinically demonstrated
- ▶ Tolerance to respiratory and CNS depressant effects occurs rapidly and reliably with opioids
- ▶ Acute pain may serve as a natural antagonist to respiratory and CNS depression



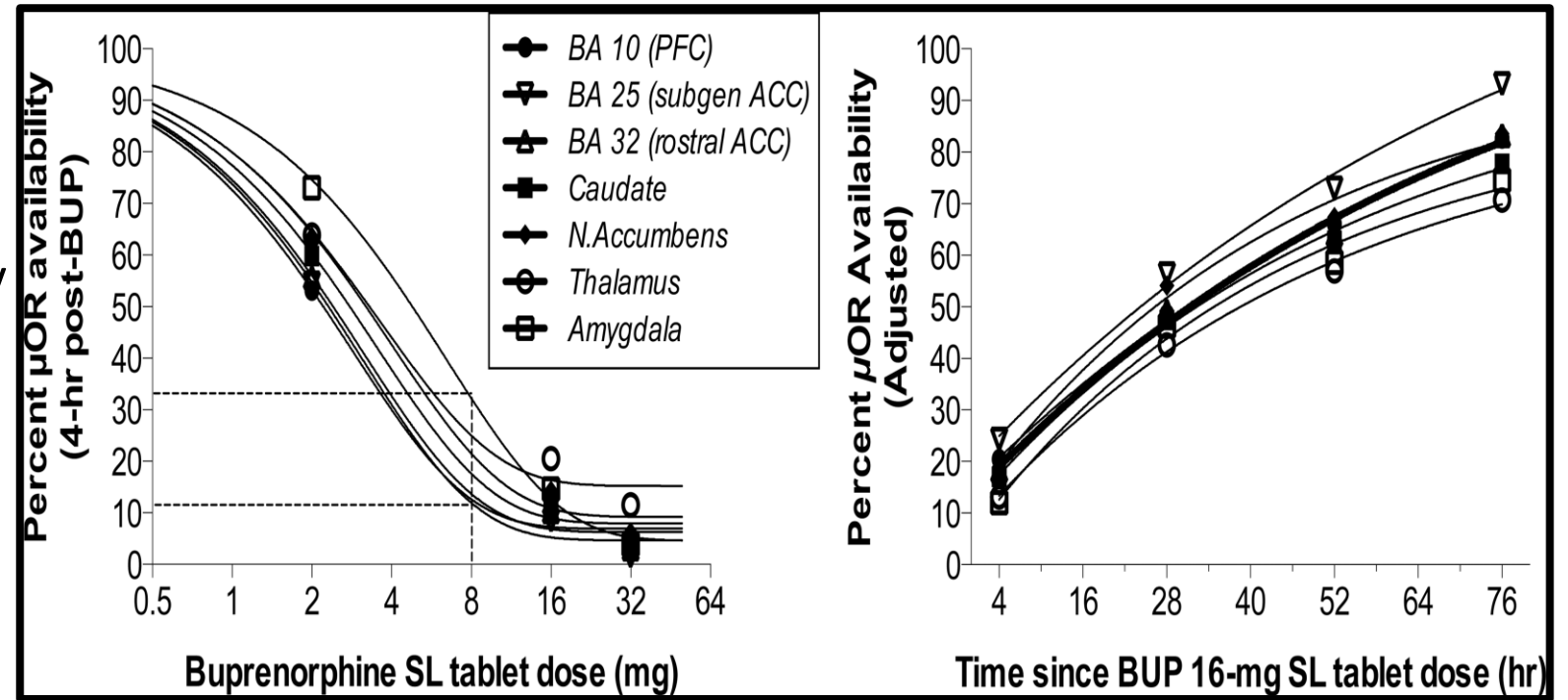
Buprenorphine Co-Administration with Full Agonists

- ▶ **Buprenorphine Initiation with Full Agonist Maintenance**
 - Buprenorphine displaces full agonists from mu receptors
 - To avoid precipitated withdrawal
 - Mild to moderate withdrawal symptoms
 - Micro-dose buprenorphine
- ▶ **Full Agonist Initiation with Buprenorphine Maintenance**
 - Full agonists are not able to displace buprenorphine, so it remains bound to receptors

Mu Opioid Receptor Affinity	
<u>Opioid</u>	<u>K₁ (nM)</u>
Buprenorphine	0.216
Hydromorphone	0.365
Oxymorphone	0.406
Morphine	1.14
Fentanyl	1.35
Methadone	3.38
Oxycodone	25.9
Codeine	734
Tramadol	12,500

Buprenorphine Receptor Occupancy

- ▶ Dependent on buprenorphine dose, time since administration and brain “regions of interest”
- ▶ Buprenorphine $\geq 16\text{mg}$ nears 100% opioid receptor occupancy
- ▶ A small number of receptors remain available for full agonists
- ▶ Higher than normal doses are required to achieve analgesia
- ▶ May require closer monitoring for respiratory depression



Misconception #4

Reporting pain may be a manipulation to obtain opioid medications, or drug-seeking, because of opioid addiction

- ▶ A careful clinical assessment for objective evidence of pain will decrease the chances of being manipulated
- ▶ Patients receiving methadone and buprenorphine typically receive doses that block most euphoric effects of co-administered opioids



Acute Pain Management

**ACTIVE OR REMOTE
OPIOID ADDICTION
OR
OPIOID DEPENDENCE**

Guidance for Clinical Practice

- ▶ SAMHSA Treatment Improvement Protocol (TIP) #54: Managing Chronic Pain in Adults With or In Recovery From Substance Use Disorders (2012)
- ▶ APS/ ASRAPM/ ASACRA Guidelines on the Management of Postoperative Pain (2016)
- ▶ Review Article by St. Marie B and Broglio K (2020)
- ▶ The ASAM Principles of Addiction Medicine

SAMHSA Treatment Improvement Protocol (TIP) #54: Acute Pain

- ▶ Patients dependent on opioids or BZDs should not be withdrawn from these medications
- ▶ Non-pharmacological treatments
 - Stress management, CBT, acupuncture
- ▶ Patient-controlled analgesia (PCA)
 - High bolus doses and short lockout intervals
- ▶ Switch from short- to long-acting agent as quickly as appropriate
- ▶ Do everything you can to bolster recovery support post-operatively

SAMHSA TIP #54: Acute Pain

- ▶ Continue current opioid or equivalent dose of an alternative opioid
 - Should not be expected to control pain
 - Requires supplementation with additional opioids
 - Adjuvant NSAIDs may provide pain relief with reduced opioid dose
- ▶ Consider multimodal analgesia
- ▶ Buprenorphine: decreased benefit from full agonists due to opioid debts
 - Suspend use of buprenorphine if full agonist needed
 - Non-opioid analgesics

APS/ ASRAPM/ ASACRA Guidelines (2016)

- ▶ Collaborative effort of 3 organizations:
 - American Pain Society (APS), American Society of Regional Anesthesia and Pain Medicine (ASRAPM), American Society of Anesthesiologists' Committee on Regional Anesthesia (ASACRA)
- ▶ Consultative expertise might be required in patients with opioid tolerance
 - Particularly those with a history of substance abuse or addiction
- ▶ Adequate pain treatment should not be withheld from patients with active or previous opioid addiction
 - Poorly treated pain can be a trigger for relapse

APS/ ASRAPM/ ASACRA Guidelines (2016)

1. Conduct preoperative evaluation
 - To determine preoperative opioid use and doses
2. Provide education regarding the use of opioids
3. Recognize that
 - Opioid requirements will typically be greater
 - Pain might be more difficult to control
4. Consider consulting pain and/or addiction specialists

APS/ ASRAPM/ ASACRA Guidelines (2016)

5. Consider non-pharmacological interventions
 - ▶ Transcutaneous electrical nerve stimulation
 - 25% less postoperative analgesic use
 - Near incision/ accupoints away from the incision
 - ▶ Cognitive-behavioral therapies
 - Positive effects on postoperative pain, analgesic use and anxiety
 - Inconsistent effects on duration of hospitalization
 - Noninvasive, does not appear to cause harm

APS/ ASRAPM/ ASACRA Guidelines (2016)

6. Consider non-opioid medications

	Pre-Op	Intra-Op	Post-Op
Gabapentin	600mg-1200mg x 1, 1-2 hours prior	---	600mg x 1 or in divided doses, 12 hours after
Pregabalin	150mg-300mg x 1, 1-2 hours prior	---	150mg-300mg x 1, 12 hours after
IV Ketamine	0.5mg/kg bolus	10µg/kg/min infusion	+/- (at lower dose)

APS/ ASRAPM/ ASACRA Guidelines (2016)

7. Consider local anesthetic-based peripheral regional and neuraxial local analgesic techniques
8. Consider PCA with basal infusion of opioids for difficult to manage pain with appropriate monitoring
9. Provide education and instructions on tapering opioids to target dose after discharge

St. Marie and Broglio (2020): Buprenorphine

- ▶ Continue buprenorphine peri-operatively
 1. Plus use PCA and multimodal analgesic approaches
 2. Change buprenorphine dose to every 6–8 hours while using adjuncts such as acetaminophen, non-steroidal anti-inflammatory drugs, and opioids PRN

- ▶ Discontinue buprenorphine
 1. 5 days prior to surgery and add full agonist pre-op
 2. Day of surgery and give single dose extended-release (ER) opioid before surgery
 - ▶ Continue ER opioid via PCA or switch to immediate release opioid

St. Marie and Broglio (2020): Methadone

- ▶ Continue methadone peri-operatively
 1. Patient's usual daily methadone dose during the hospitalization while using multimodal analgesia including opioid and nonopioid analgesics
 2. Divide the total daily methadone dose into 3 times a day dosing and administer additional opioids and nonopioid analgesics for postoperative analgesia

St. Marie and Broglio (2020): Naltrexone

- ✓ Discontinue oral naltrexone 72 hours before surgery
- ✓ Discontinue injectable naltrexone for 30 days prior to surgery
- ✓ In the event of acute pain, 6-20 times the typical opioid dose may be required to overcome the mu receptor blockade!
- ✓ High-potency, full-agonist IV will require close pulse-ox monitoring in hospital setting
- ✓ Naltrexone cannot be re-instated until 7-10 days after the last dose of opioids
- ✓ Potential risk for precipitated opioid withdrawal symptoms upon reinstatement

ASAM Principles of Addiction Medicine

- ▶ Substance use increases the likelihood of developing acute pain
- ▶ Those receiving methadone or buprenorphine should be assumed to receive no analgesic effect from it in the case of surgery or acute trauma
 - Require continuation of methadone/ buprenorphine + greater than usual doses of opioid analgesia

Summary of Recommendations

Buprenorphine

- ▶ Continue daily regimen
- ▶ Continue, but change to Q6-8
- ▶ Discontinue 5 days pre-op or day of surgery

Methadone

- ▶ Continue daily regimen
- ▶ Continue, but change to TID



Either above along with:

- ▶ Consider addition of Patient Controlled Analgesia or short-acting opioids
- ▶ Consider multimodal analgesia
- ▶ Interdisciplinary approach

Multimodal Analgesia

Non-Opioid

1. Acetaminophen
 - ▶ Hepatic Disease: Max 2g/day
2. NSAIDS
 - ▶ *Cochrane Library*. 2013; 6: CD010289
3. Enhanced Recovery Protocol (ERP)
 - ▶ Gabapentin
 - ▶ Ketamine
 - ▶ Lidocaine

Non-Pharmacologic

1. Acupuncture
 - ▶ *Am J Emerg Med*. 2016; 34: 2112- 2116.
2. Cognitive Behavioral Therapy
3. Transcutaneous Electrical Nerve Stimulation

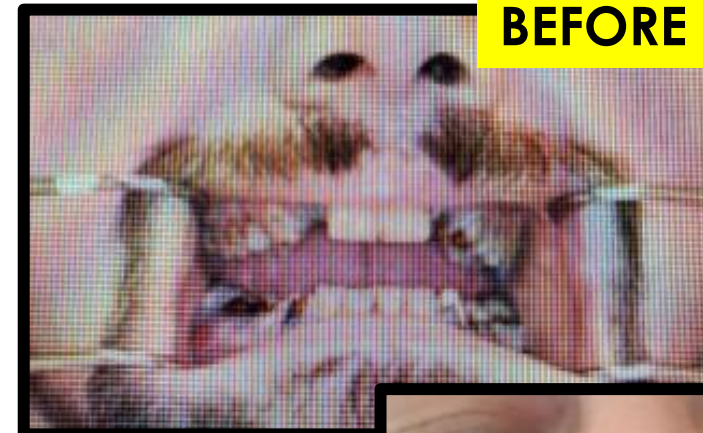
Patient Case #1

- ❖ 29 y/o male with opioid use disorder (OUD) on buprenorphine 8 mg BID for at least 5 years with no relapses
- ❖ Sustained a workplace injury in which a saw bit dislodged and flung toward his face
- ❖ Options exercised:
 - Increased buprenorphine to 8 mg TID for 2 weeks
 - Afterwards, resumed usual regimen, without symptomatic consequence.



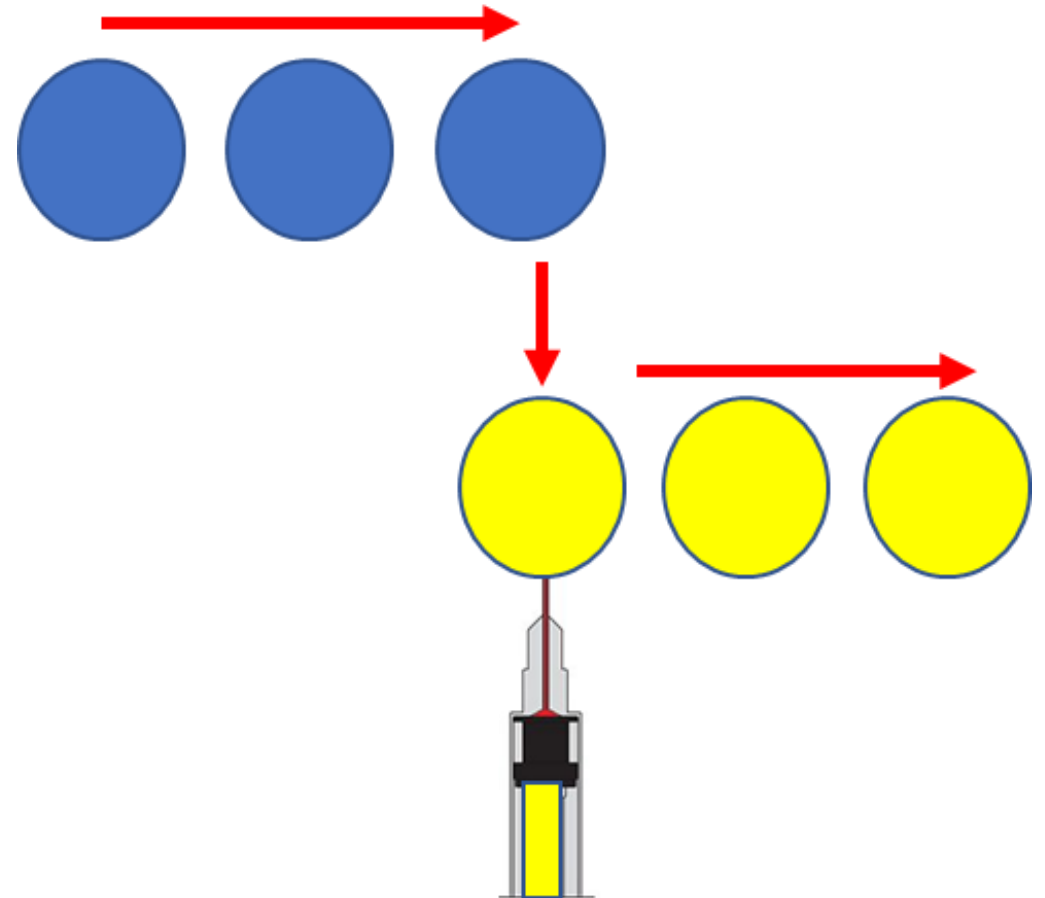
Patient Case #2

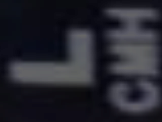
- ❖ 41 y/o male with opioid use disorder (OUD) on buprenorphine 8 mg BID for at least 5 years with no relapses with depression and social anxiety over the state of his dentition.
- ❖ Underwent total extractions to get total set of dental implants.
- ❖ Options exercised:
 - Bupivacaine liposome injectable suspension was employed by the oral surgeon.
 - Buprenorphine regimen was maintained.
 - Patient did quite well from the look of that smile.



Bupivacaine Liposome Injectable Suspension

- ❖ Liposomal bupivacaine is indicated for postsurgical analgesia via single-dose infiltration injection into the surgical site.
- ❖ A single dose reportedly provides analgesia for up to 72 hours.
- ❖ Liposomes are lipid vesicles enclosing aqueous compartments into which a drug can be loaded and are ideally suited to function as carrier vehicles, being biocompatible, biodegradable, and nonimmunogenic.





Patient Case #3

- ❖ 31 y/o male with opioid use disorder (OUD) on buprenorphine 8 mg BID for at least 5 years with no relapses
- ❖ Sustained a broken leg due to a motorcycle injury. He was wearing a helmet and sustained no head injury
- ❖ Option exercised:
 - Ketamine (N-methyl-D-aspartate –NMDA receptor antagonist)
 - Buprenorphine was continued during inpatient stay.

Ketamine

- ❖ Phencyclidine derivative that was developed in the 1960s as an anesthetic agent.
- ❖ Noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, and its analgesic action at sub-anesthetic dose is believed to be primarily due to NMDA receptor antagonism in the brain and spinal cord.
- ❖ NMDA receptor is involved in the amplification of pain signals.
- ❖ There is a large body of literature addressing the use of ketamine in the perioperative setting.

Summary

- ▶ Patients on chronic MOUD require additional analgesia in acute pain situations, likely at higher than usual doses.
- ▶ Pre-op evaluation should include an assessment of the patient's recent opioid use, including the specific opioid, dose, time of last dose.
- ▶ Though methadone continuation has been well-established, it's becoming more common to continue buprenorphine peri-operatively.
- ▶ Multimodal analgesia is likely required.
- ▶ If patients with MOUD are discharged with full agonists
 - ☑ Query the PDMP (excluding methadone maintenance)
 - ☑ Provide naloxone education and kit



Thank You!

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