PERIOPERATIVE MANAGEMENT OF MEDICATIONS FOR OPIOID USE DISORDER

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OVERVIEW

- Introduction
- Management of MOUD
  - Buprenorphine
  - Methadone
  - Naltrexone
- Summary

OPIOID USE DISORDER

- The disorder includes the desire to obtain and take opioids despite social and professional consequences.
- It affects 16 million people worldwide and 2.1 million in the US
- Houston has about 50-100 reports monthly
  - -1/3 are fatal
- Diagnosis is based on the American Psychiatric Association DSM 5

Box 1 American Psychiatric Association criteria for OUD

Impaired control:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.

Social impairment:

5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.

Risky use:

8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

Pharmacological criteria:

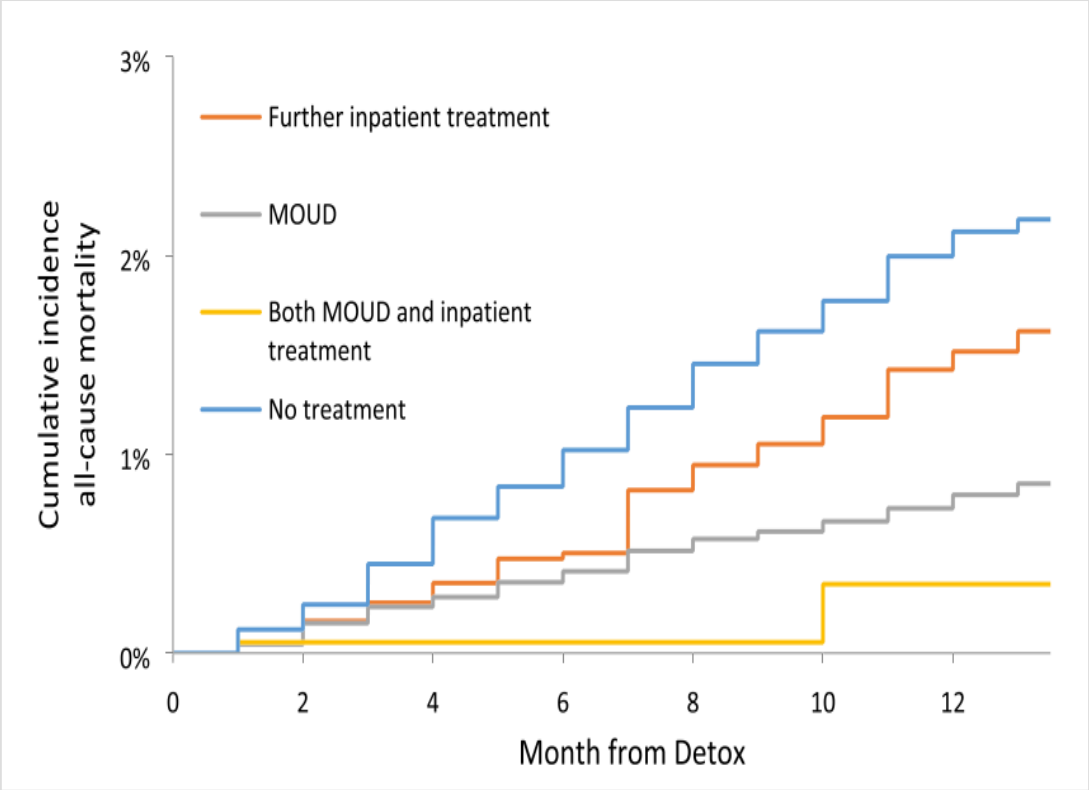
10. Exhibits symptoms of tolerance (reducing effect with increasing dose).*
11. Exhibits symptoms of withdrawal (physiological symptoms due to absence of a substance typically used repeatedly).*

*10 and 11 do not apply to individuals taking chronic opioids under medical supervision.

Kohan L, et al. Reg Anesth Pain Med 2021;46:840–859. doi:10.1136/rapm-2021-103007

MEDICAL MANAGEMENT OF OUD

- Treatment is a combination of medical management and psychosocial support
- Medication for opioid use disorder (MOUD): Methadone, buprenorphine, naltrexone
- Significant decrease in all cause mortality
- Meta analysis by Sorto et al
  - 19 cohort studies, > 140,000 patients
  - Increased mortality during times of induction and immediately after discontinuation
  - Do not disrupt treatment unless necessary



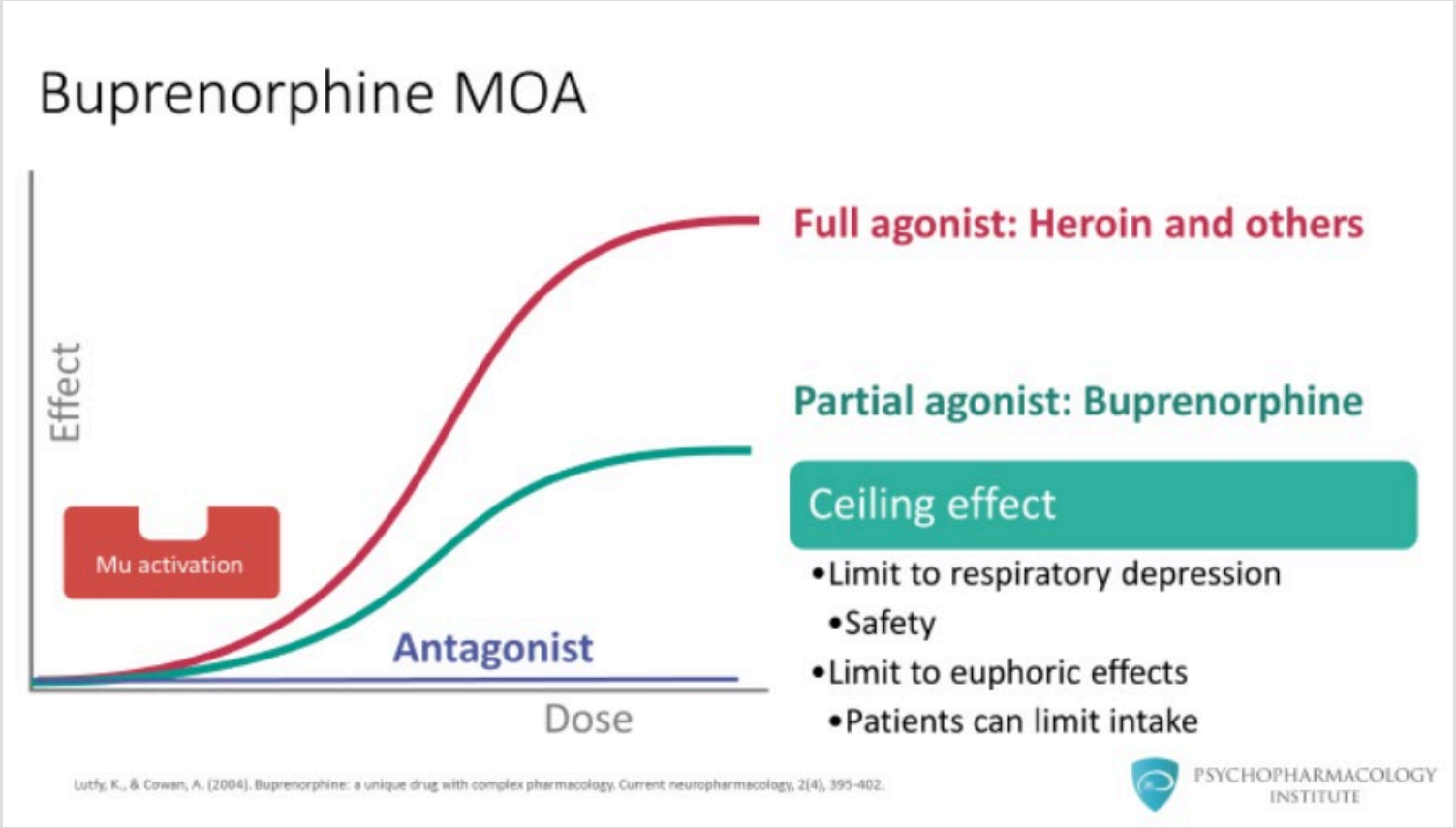
BUPRENORPHINE

- 45M with PMH of HTN, heroine abuse on maintenance buprenorphine, and RCC
- Pre-op evaluation for partial nephrectomy
- Has never had surgery
- Currently takes 16 mg of sublingual buprenorphine

- Can buprenorphine be continued?
- Does the dosage need to be adjusted?
- When can buprenorphine be restarted?
- How to optimize pain control in patients taking buprenorphine?

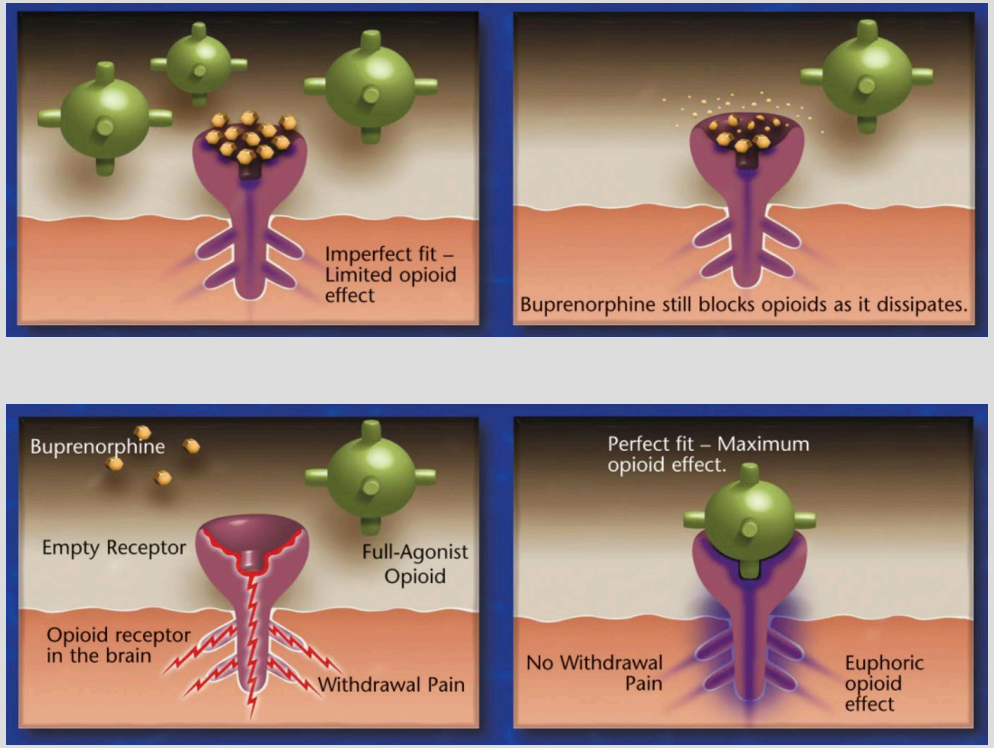
BUPRENORPHINE

- Mechanism of Action
  - Partial mu agonist, weak kappa antagonist, and weak delta agonist
- Mode of delivery
  - Single agent or combined with naloxone
  - Available as ER SQ injection, sublingual tablet or buccal film
  - Half life is up 24-42 hours for sublingual, up to 60 days for ER SQ injection



INDUCTION AND MAINTENANCE OF BUPRENORPHINE FOR OUD

- Patient is started on buprenorphine 2-8 mg
- Can alleviate opioid withdrawals within 20-40 minutes
- Titrated based on symptoms
- Optimal dose normally is between 8-16 mg daily, but can go as high as 32mg
- Can be dosed one to three times daily
- Daily dosing has the best adherence to therapy



Naabt. The National Alliance of Advocates for Buprenorphine Treatment. 2011.

PERIOPERATIVE CONCERNS ABOUT BUPRENORPHINE

- Perioperative concerns about buprenorphine
  - Buprenorphine has high affinity to mu receptors
  - Can displace full agonists
  - Has extremely long half life
  - 2004 Treatment Improvement Protocol released by the US Center for Substance Abuse treatment now obsolete

PERIOPERATIVE MANAGEMENT OF BUPRENORPHINE

- New guidelines were released in 2021
- Expert panel involved in the new development of the guidelines are from pain medicine, addiction medicine, and pharmacy health science
- Based on 10 case reports, 2 case series, 5 cohort studies, 12 Systematic review, 5 Guidelines.
- There were 100% consensus among the expert panels.

Consensus: "Buprenorphine is a potent analgesic despite being a partial mu-opioid receptor agonist. While buprenorphine has a strong affinity for the mu-opioid receptor, opioid receptors remain free for binding by full mu agonists even at standard doses of buprenorphine….effective analgesia may be obtained both with buprenorphine and with concomitant use of full mu agonists…."

PERIOPERATIVE MANAGEMENT OF BUPRENORPHINE

- Greenwald et al. Carfentanil PET study
- Average Buprenorphine maintenance dose 8-12 mg/daily
- Only 20% of receptor availability is needed for pain control
- It is recommended to continue home dose
- Reasonable to taper to 16 mg/daily if inadequate pain control is encountered

Maintenance Dose	Percent of Available Mu Receptors
1 mg	71-85%
2 mg	53-72%
4 mg	36-55%
8 mg	20-35%
12 mg	13-24%
16 mg	9-20%
24 mg	4-15%
32 mg	2-12%

μ-Opioid Receptor Binding Affinities (Ki)

Medication	Ki (nM)
Sufentanil	0.1380
Buprenorphine	0.2157
Hydromorphone	0.3654
Oxymorphone	0.4055
Butorphanol (mixed)	0.7622
Morphine	1.168
Fentanyl	1.346
Naloxone (antagonist)	1.518
Nalbuphine (mixed)	2.118
Methadone	3.378
Remifentanil	21.1
Oxycodone	25.87
Hydrocodone	41.58
Meperidine	450.1

D.A. Volpe et al. Regulatory Toxicology and Pharmacology 59 (2011).

PERIOPERATIVE MANAGEMENT OF BUPRENORPHINE

Preoperative	Intraoperative	Postoperative
❖ Have a clear discussion about management of buprenorphine and acute pain management ❖ Determine if home dose is >16 mg daily or not ❖ Review old patient records for previous surgeries ❖ Continue Buprenorphine on the day of surgery	❖ Consider non-opioid pain medications that can target different pain receptors (i.e. ketamine, precedex, NSAIDS, acetaminophen, precedex, lidocaine gtt, Magnesium) ❖ Regional Anesthesia	❖ Restart buprenorphine as soon as possible ❖ Split home dose into 2-3 doses to provide analgesic advantages ❖ Sufentanil or Hydromorphone 1st line ❖ Regional or neuraxial blocks ❖ Continue multimodal medications ❖ Opioid Taper plan

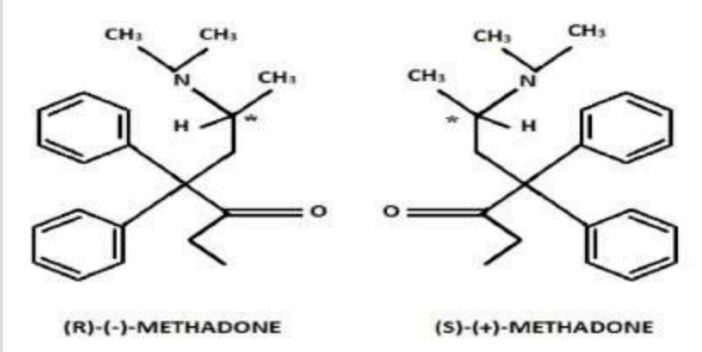
METHADONE

- 35F PMH of OUD presents after MVC
- GCS 15, Primary survey intact
- Secondary Survey: open fx of RLE
- Orthopedic team posted patient for urgent ORIF

- Should you take methadone the day of surgery?
- When should you restart methadone?
- Does the home dose of methadone need to be adjusted
- Can I combine methadone with other opioids?

METHADONE

- Basic Mechanism of Action
  - Administered as a racemic mixture: levomethadone and dextromethadone
  - Full opioid agonist binds mainly to mu receptors and somewhat to kappa and delta
  - NDMA antagonist
  - Inhibits reuptake of serotonin and norepinephrine
  - Analgesic effect is 6-8 hours
  - Reduction of cravings and withdrawal symptoms last for 24-36 hours



Ahmad T, Valentovic MA, Rankin GO. *Biochem Pharmacol.* 2018;153:196-204.

METHADONE

- Benefits
  - blocks the euphoric effects of another full agonist
  - Suppression of withdrawals and cravings
  - Reduces CNS sensitization to pain/hyperalgesia
  - Reduces tolerance to opioids
    - Internalization of mu receptors
- Adverse effects
  - QT prolongation
  - Respiratory depression
  - Hypoglycemia
  - Nausea
  - Constipation, lethargy
  - Serotonin syndrome

Codeine Withdrawal Timeline, Symptoms, and Treatment - PAX Memphis. https://paxmemphis.com/codeine-withdrawal-timeline/.

INDUCTION AND MAINTENANCE OF METHADONE

- Initial dose 10-20 mg
- Observed for 2-3 hours and additional 5-10 mg given based on symptoms
- Aim to reach a dose that prevent sedation and withdrawal
- Subsequently, the next aim is to to titrate to reduce cravings and the use of illicit drugs
- Average effective dose is 60-120 mg daily
- Administered as a one-time daily dose

PERIOPERATIVE MANAGEMENT OF METHADONE

Preoperative	Intraoperative	Postoperative
❖ Have a clear discussion about management of home dose methadone and pain management post-op ❖ Detailed hx on dose, frequency, and time of last dose. ❖ Review old patient records for previous surgeries ❖ EKG to assess QT interval ❖ Continue Methadone on the day of surgery	❖ Consider non-opioid pain medications that can target different pain receptors (i.e. ketamine, precedex, NSAIDS, acetaminophen) ❖ Regional Anesthesia ❖ Opiods for pain control	❖ Restart PO methadone as soon as possible ❖ If PO is not possible, IV, IM, SQ administration. Split home daily dose to 2-4 doses ❖ Opioid requirement is expected to be higher ❖ Regional or neuraxial blocks ❖ Continue multimodal medications ❖ Opioid tapering plan

NALTREXONE

- 55M hospitalized and needs a BKA
- PMH: htn, hld, peripheral neuropathy, DMII, Vicodin abuse
- Taking naltrexone 50 mg daily
- Vitals wnl

- Should naltrexone be continued preoperatively?
- Should naltrexone be restarted post op?
- Is the dose of naltrexone adjusted for elective surgery?
- Can he receive opioids for pain control?

NALTREXONE

- Mechanism of action
  - Pure antagonist at the opioid mu receptor
  - No intrinsic agonist effects
  - Long term antagonism will increase opioid receptors within central nervous system
- Formulation
  - Oral Naltrexone: 14 hour half life
    - Stop 72 hours before elective surgery
  - Intramuscular ER: 5 day half life
    - Stop 25 days before surgery

PERIOPERATIVE MANAGEMENT OF NALTREXONE

Preoperative	Intraoperative	Postoperative
❖ Stop for 72 hours if taking PO ❖ Stop ER IM formula for 25 days and transition to PO ❖ Some patients come in for unplanned surgery and is unable to stop naltrexone prior to surgery	❖ Regional Anesthesia ❖ Consider non-opioid pain medications that can target different pain receptors	❖ Treat with opioids if necessary ❖ Watch for an exaggerated or attenuated response to opioids ❖ Continue regional or neuraxial blocks ❖ Continue multimodal medications ❖ Acute Pain Management consult ❖ Do not restart Naltrexone until off opioids for at least 7 days

SUMMARY

Buprenoprhine	Methadone	Naltrexone
Continue perioperatively	Continue perioperatively	Stop perioperatively
Assess if home dose exceeds 16 mg daily	Expect high opioid requirement	Nonelective surgery patients will need 6-20 times the typical dose of opioids
Use opioids with high Affinity for pain control		Do not restart until 7 days since last opioid use

Promote calm and comfort

Anxiety, fear, depression are common: Instill sense of control, provide education on self-management techniques such as mindfulness meditation. Reduce noise, uncertainty, confusion. Positioning, splinting, and physical comfort should be maximized. Minimize unnecessary NPO status.

TREAT UNPLEASANT SYMPTOMS:

Diphenhydramine 25-50mg PO q8h prn insomnia/anxiety
Tizanidine 2-4mg q6h prn muscle spasms
Ondansetron 4mg PO q6h prn nausea
Trazadone 50mg PO qhs prn insomnia
Melatonin 3mg PO qhs prn insomnia
Lorazepam 0.5-1mg PO prn anxiety
Antipsychotics prn psychotic disorder symptom control
Nicotine replacement prn tobacco dependence

Regional Anesthesia

Peripheral nerve blocks: superficial cervical plexus, brachial plexus, radial/median/ulnar, PECS, erratus plane, TAP, femoral, sciatic, posterior tibial.
Spinal and Epidural anesthesia

Acetaminophen and NSAIDs

Acetaminophen and **NSAIDs,** when not contrainidicated, should are the foundation of a multimodal analgesic strategy.

Gabapentinoids

In opioid depenent patients, the calcium channel inhibitors, gabapentin and pregabalin reduce postoperative pain and reduce opioid consumption. Gabapentin 300-600mg PO TID.

Alpha-2 agonists

Clonidine and Dexmedetomidine are anxiolytic and analgesic with significant opioid sparing affects. e.g. **Clonidine** 0.1-0.3mg PO q6-8h prn pain or anxiety (NTE 1.2mg/day, hold if BP <100/70).

Ketamine & Magnesium (NMDAR antagonists)

Ketamine is the most potent non-opioid analgesic for opioid tolerant patients. A brief infusion of 0.3mg/kg IV over 15min is followed by 0.3-1mg/kg/hr as needed.
Magnesium is also an NMDAR with analgesic and opioid sparing effect. eg. 30-50mg/kg bolus followed by 10-mg/kg/hr.

IV Lidocaine (Na channel antagonist)

Opioid sparing analgesic. A bolus of 1-1.5mg/kg is followed by 1.5-3 mg/kg/h. Contraindications include cardiac dysrthymias. Must monitor serum levels after 24hrs.

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