# Treating Pain in Hospitalized Patients on Medications for Opioid Use Disorder (MOUD)

**Emily Casey, PharmD, Bridget Durkin, MD, MBE, Erik Saka, MD, MBE, Steven Tate, MD, MSc**

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# Disclosure Information

- Emily Casey, PharmD: Clinical Pharmacy Specialist Pain Management and Substance Use at Hospital of the University of Pennsylvania
  - No disclosures
- Bridget R. Durkin, MD, MBE: Assistant Professor of Clinical Medicine, Palliative Care, Internal Medicine, Hospital of the University of Pennsylvania
  - No disclosures
- Erik O. Saka, MD, MBE: Assistant Professor of Anesthesiology and Critical Care, Hospital of the University of Pennsylvania
  - No disclosures
- Steven Tate, MD MSc: Clinical Assistant Professor of Psychiatry & Behavioral Sciences, Stanford University School of Medicine
  - No disclosures

# Learning Objectives

- Pain Management in the Fentanyl Era
- Understanding and Evaluating Pain
- Multi-modal Analgesia
- MOUD Overview
- Optimizing MOUD for Pain
- Role of Opioids
- Perioperative Pain

# Case

HA is a 36 y/o man with history of OUD on buprenorphine, cocaine use disorder, CKD, chronic back pain, presenting with chills, nausea, and poorly controlled acute pain due to necrotic lower extremity wounds.

In the ED, he is noted by physical exam and imaging to have tendon and muscular involvement with purulent drainage of his wounds. Labs are notable for leukocytosis, anemia, and AKI.

He is prescribed buprenorphine 8mg daily which he last took yesterday. He has had ongoing cravings with daily IV fentanyl use (~10 bags daily; last used 12 hours to presentation). COWS 13 and in 10 out 10 pain.

# Why Prioritize Pain Management?

- "Engagement with the medical system as a ‘last resort’, with admission to hospital in a critical or a 'near death' condition common."
- "Severe physical pain and debility were normalized, incorporated into the day to day.” (Harris 2020)

- Hospitalization is a reachable moment
  - Build trust in healthcare system
  - Introduce MOUD
  - Provide harm-reduction education
  - Offer social support and resources (SW, CM, peer-recovery, specialists)
  - Ease suffering

Harris M. Normalised pain and severe health care delay among people who inject drugs in London: Adapting cultural safety principles to promote care. Soc Sci Med. 2020 Sep;260:113183. doi: 10.1016/j.socscimed.2020.113183. Epub 2020 Jul 9. PMID: 32682207; PMCID: PMC7441308.

# Why Prioritize Pain Management?

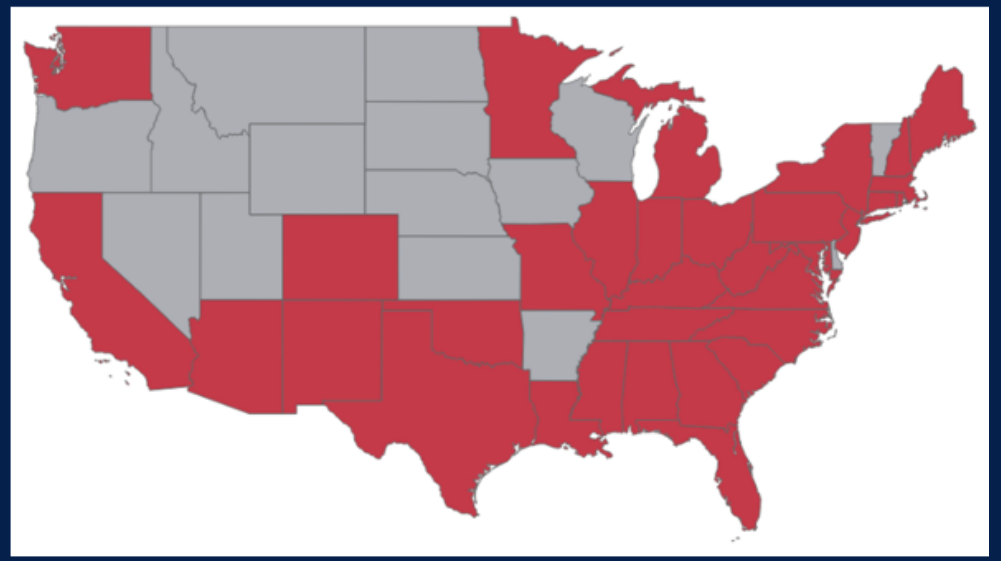
- 25-30% of PWID leave hospital in self-directed discharge (Ti)
  - undertreated pain and withdrawal (Simon)
- Over 40% hospitalized for IVDU-related infections, use their own supply (Barnett, Fanucchi)

- Good pain management is standard of care for all patients
  - MOUD + short-acting opioids
  - *ASAM National Practice Guideline for Treatment of OUD 2020 Focused Update*
  - Permitted by federal guidelines (21 C.F.R. § 1306.07)


Ti L, Ti L. Leaving the Hospital Against Medical Advice Among People Who Use Illicit Drugs: A Systematic Review. Am J Public Health. 2015 Dec;105(12):e53-9. doi: 10.2105/AJPH.2015.302885. Epub 2015 Oct 15. PMID: 26469651; PMCID: PMC4638247.
Simon R, Snow R, Wakeman S. Understanding why patients with substance use disorders leave the hospital against medical advice: A qualitative study. Subst Abus. 2020;41(4):519-525. doi: 10.1080/08897077.2019.1671942. Epub 2019 Oct 22. PMID: 31638862.
Fanucchi LC, Lofwall MR, Nuzzo PA, Walsh SL, In-hospital illicit drug use, substance use disorders, and acceptance of residential treatment in a prospective pilot needs assessment of hospitalized adults with severe infections from injecting drugs, Journal of Substance Abuse Treatment, Volume 92, 2018, Pages 64-69, ISSN 0740-5472, https://doi.org/10.1016/j.jsat.2018.06.011.
Barnett B, Morris NP, Suzuki J, Addressing in-hospital illicit substance use, The Lancet Psychiatry, Volume 8, Issue 1, 2021, Pages 17-18, ISSN 2215-0366, https://doi.org/10.1016/S2215-0366(20)30487-9.

# Pain Management in the Era of Fentanyl

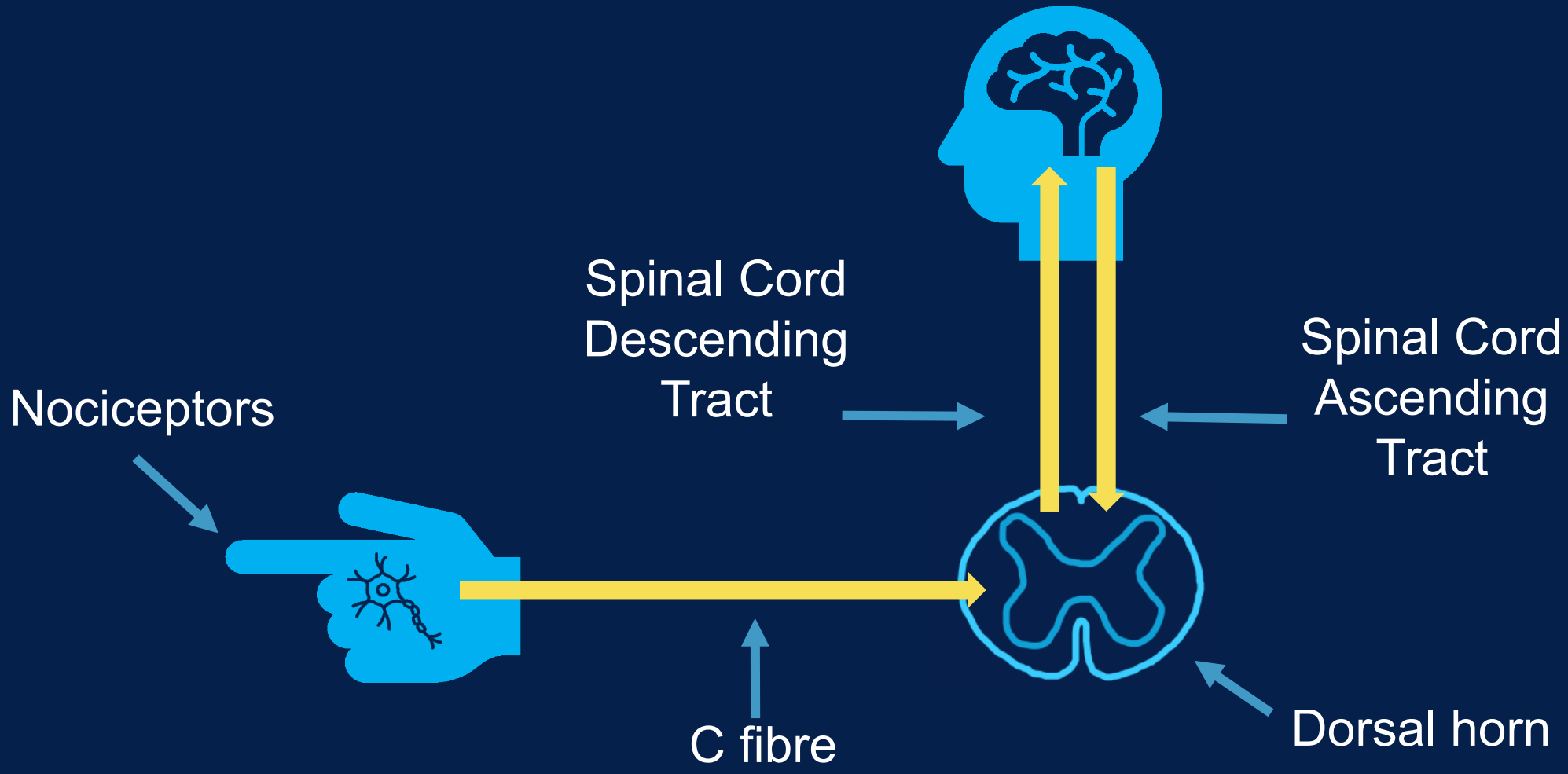
- Fentanyl purity averaged 11.9% in 2021 nationally
  - Increased from 2.8% 5 years ago
- Estimated fentanyl per bag
  - 500 OME (6-4500 OME)
- Tablets averaged 2.2 mg of fentanyl
  - Estimated Lethal dose = 2 mg when opioid-naïve
- Increase in potent fentanyl analogues
  - 14% with fluorofentanyl
- Increase in xylazine adulterant
  - 14% with xylazine

Fentanyl Profiling Program Report CY 2021, Drug Enforcement Administration, Special Testing and Research Laboratory, 2022. https://www.dea.gov/sites/default/files/2022-08/FPP%20Report%20CY%202021_DEA.gov_.pdf

# Understanding & Evaluating Pain

# Pain Pathophysiology




Fong A, Schug S. Pathophysiology of Pain. (2014). Plastic and Reconstructive Surgery. 134(4S02):82-14S.

# Pain Classifications

Nociceptive

Somatic

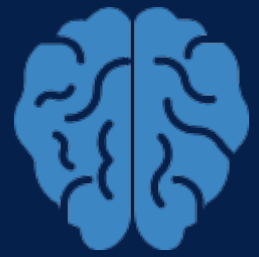
- Tissue damage
- Arthritis, trauma, bone metastases
- Sharp, aching, dull; well-localized

Visceral

- Damage to internal organ
- Colon cancer, cholecystitis
- Cramping, dull, aching; poorly localized, referred

Neuropathic

- Nerve damage
- Neuropathy, post-injury, nerve compression
- Burning, stabbing, itching, tingling



Central sensitization

- CNS dysfunction
- CRPS, OIH, fibromyalgia
- Quality variable

# Pain Assessment

## OPQRST

Onset
Provocation/Palliation
Quality
Radiation
Severity
Timing

## Old Carts

Onset
Location
Duration
Characteristic
Alleviating/ Aggravating Factors
Timing
Severity

# Total Pain

## A Concept Borrow from Palliative Care

Injury
Cancer
Treatment related
Withdrawal
Comorbidities (chronic pain)
Opioid central sensitization


Anxiety
Depression
Fear of suffering
Past experiences of pain (trauma, bias)
Helplessness

Loss of role
Loss of social status
Financial worries
Worries about family
Relying on others
Loss of self-worth

"Why me?"
Anger at God/fate
Loss of faith
Fear of the unknown
Loss of meaning

Kubler-Ross, E., On death and dying. 1969, London: Routledge, 1989.

# Patient Education

- Goals
  - Reduce pain enough to stay for treatment
  - Improve function: e.g. PT/OT
- Expectation setting
  - Will not entirely take away pain
  - Do not use your own supply of opioids
- Share decision-making
  - Will continue to adjust medications
  - Offer choices when able

Briggs E. Br J Pain. 2012;6(2):85-91. PMID: 2651647

# Approach to Pain Management

# Multimodal Analgesia

The key to adequate analgesia is a balanced regimen!

- Non-pharmacologic Interventions
- Nonopioid oral and topical medications
- Interventional procedures
- Opioid agonists

Schwenk ES, Mariana ER. (2018). Designing the ideal perioperative pain management plan starts with multimodal analgesia. Korean Journal of Anesthesiology. 71(5):345-352. DOI:10.4097/kja.d.18.00217. PMID:30139215

St Marie B. Broglio K. (2021). Managing Pain in the Setting of Opioid Use Disorder. Pain Management Nursing. 21(1):26-34. DOI: 10.1016/j.pmn.2019.08.003. PMID: 31648905

# Non-Pharmacologic Treatment

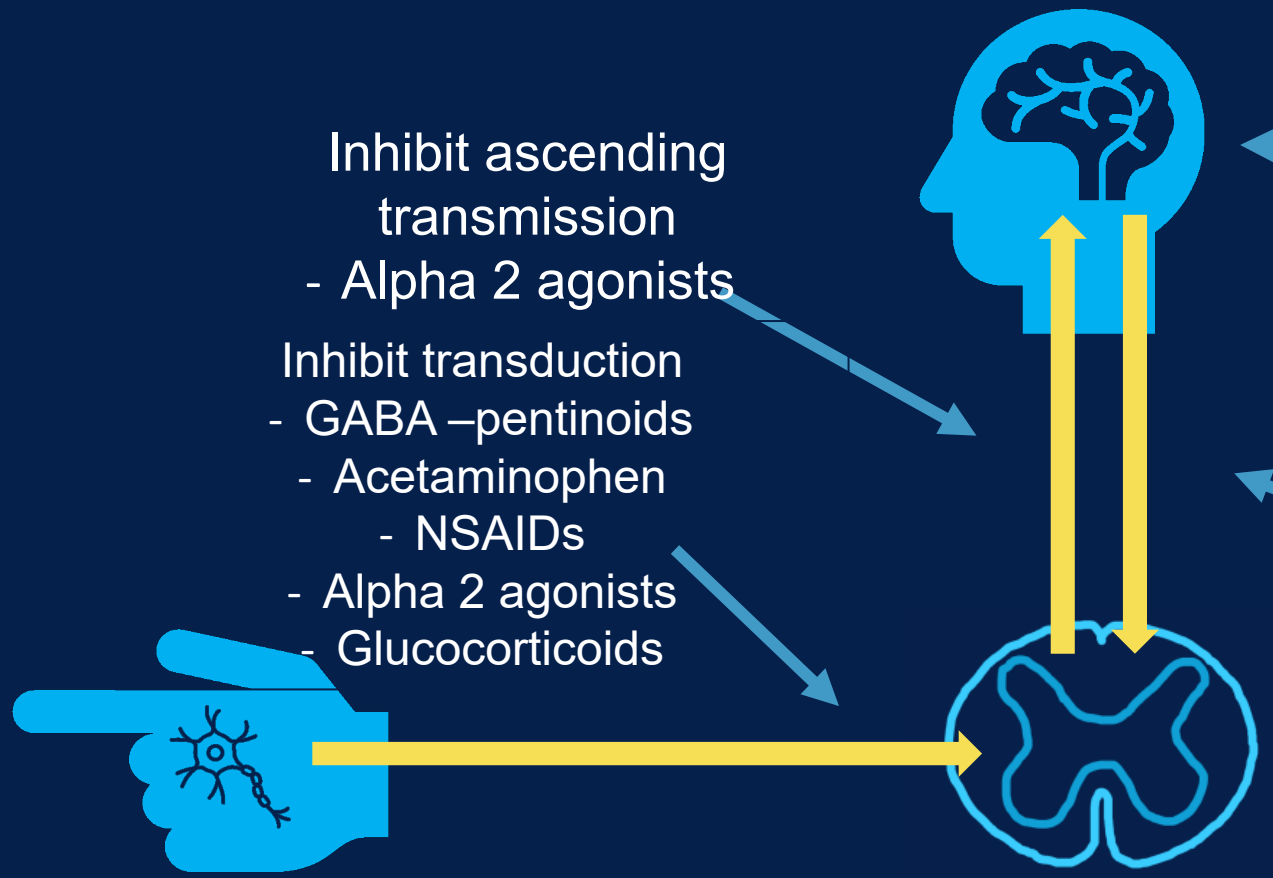
Heat/ice
Exercise/Physical therapy
Procedures:
- Radiation therapy (onco)
- Nerve block
- Neurolysis


Treatment of:
anxiety, depression, insomnia, PTSD
With medications and/or therapy

Social support (food, housing)
Peer recovery support
Therapy/counseling

Meditation / mindfulness
Motivational Interviewing
Supportive listening
Chaplain support

# Pain Pathophysiology



Inhibit ascending transmission
- Alpha 2 agonists

Inhibit transduction
- GABA –pentinoids
- Acetaminophen
- NSAIDs
- Alpha 2 agonists
- Glucocorticoids

Inhibit perception
-SNRIs
-TCAs
- Alpha 2 agonists
- Ketamine

Interrupt descending modulation
- SNRIs
- TCAs
- GABA –pentinoids
- Ketamine

Obata H. (2017) Analgesic Mechanisms of Antidepressants for Neuropathic Pain. International Journal of Molecular Sciences. 18(11):2483. DOI:10.3390/ijms18112483. PMID: 29160850

Chincholkar C. (2018). Analgesic mechanisms of gabapentinoids and effects in experimental pain models: a narrative review. British Journal of Anaesthesia. 120(6):1315-1334

# Opioid-Sparing Medications

| Nociceptive Pain | Neuropathic Pain | Severe Acute Pain |
| --- | --- | --- |
| • Acetaminophen<br>• NSAIDs<br>• Steroids<br>• Topicals | • SNRIs<br>• TCAs<br>• Gabapentinoids<br>• Topicals<br>• Carbamazepine | • Ketamine (PO/IV)<br>• Lidocaine (IV) |

# Opioid-Sparing Medications - Topicals

- Little systemic absorption
  - Can use in hepatic and renal dysfunction

| Drug | Use | Dosing Tips |
|---|---|---|
| **Lidocaine cream & patch** | Postherpetic neuralgia, allodynia, chronic neuropathic pain | Patch can left on > 12h |
| **Diclofenac** | most helpful in osteoarthritis | 4g four x / day |
| **Capsaicin** | Postherpetic neuralgia (itching/dermatitis can limit use) | 3-4 x / day |

Maloney J, Pew S, Wie C, Gupta R, Freeman J, Natalie S.(2021). Comprehensive Review of Topical Analgesics for Chronic Pain. Current Pain Headache Rep. 25,7. 9 PMID: 33534003

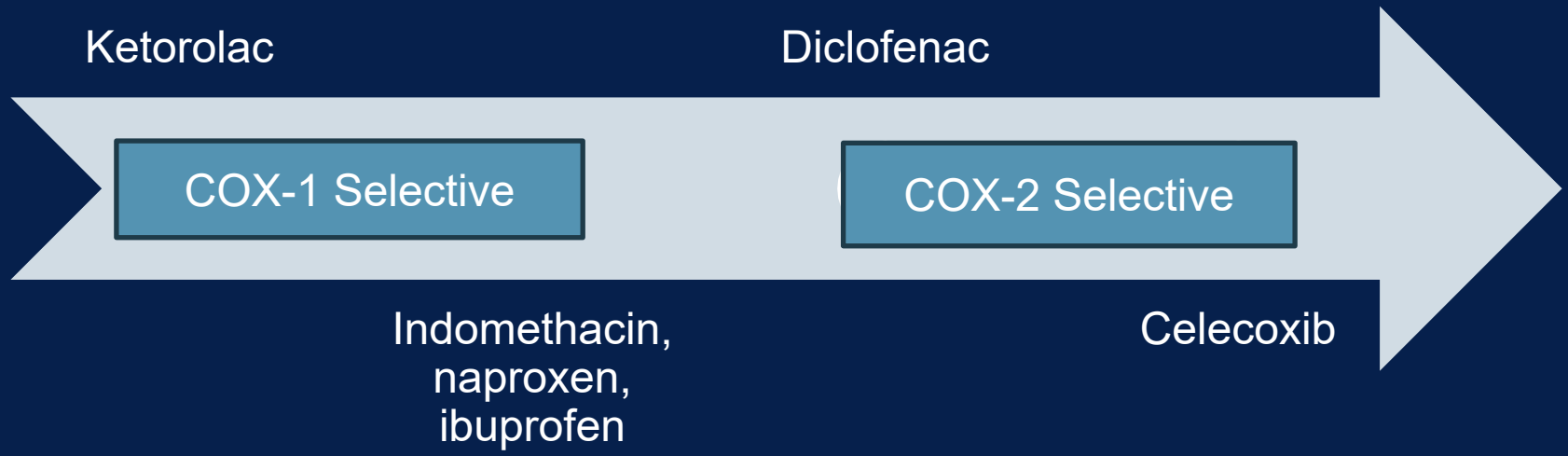
# Opioid-Sparing Medications - Acetaminophen

- Complex MOA (CNS & spinal cord)
- Available IV and PO
  - Same efficacy in RCTs
  - 1:1 dosing ratio
- Schedule 1000mg every 6 hours
  - Max 4g/24 hours
- Hepatically cleared
  - Limit to 2g/ day in liver disease

Ohashi N, Kohno.(2020). Analgesic Effect of Acetaminophen. Frontiers in Pharmacology. 11:580289. DOI:10.3389/fphar.2020.580289 PMID: 33328986

Jibril F, (2015). Intravenous versus Oral Acetaminophen for Pain: Systematic Review of Current Evidence to Support Clinical Decision Making. Can J Hosp Pharm. 68(3):238-247. DOI:10.4212/cjho.v68i3.1458

# Opioid-Sparing Medications - NSAIDs




- Renally cleared!
  - Caution in renal impairment, avoid in renal failure
- Ketorolac 15mg IV q6h effective as 30mg IV q6h

Schjerning A-M, McGettigan P, Gislason G. (2020). Cardiovascualr effects and safety of (non aspriin) NSAIDs. Nature Reviews Cardiology. 17:574-584.

# Opioid-Sparing Medications - Gabapentinoids

| Drug | Starting Dose | Bioavailablity |
|---|---|---|
| **Gabapentin** | 300 mg TID | Drops (66% to 33%) as dose increases > 1200mg/d<br>due to saturable absorption |
| **Pregabalin** | 50-100mg TID | > 90% |

- Renally cleared – dose adjust with poor renal function
- Patients may benefit from a switch from gabapentin to pregabalin!

Kbrader HN, Wesche D, Miller R, CHapel S, Janiczek N, Burger P. (2010). A Comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clin PHarmacokinet. 49(10):661-9. PMID:20818832

# Opioid-Sparing Medications - SNRIs

- Venlafaxine (IR and ER)
  - IR with short half-life; risk of withdrawal
- Duloxetine
  - Doses > 60mg not more effective

- Renally cleared – dose adjust with poor renal function
- Most effective when used with gabapentin and/or TCAs
- Consider in concomitant anxiety/depression

Faye S, et al. Lancet. 2022;400(10353):680-690. PMID: 36007534
Aiyer R, et al. Pain Med. 2017;18(10):1999-2012. PMID: 27837032
Marks DM, et al. Current Neuropharmacology. 2009;7(4):331-336. PMID: 20514212

# Opioid-Sparing Medications - Lidocaine

- MOA poorly understood
- Studies shown ?benefit in acute perioperative pain
  - Decreases opioid use
  - No clear benefits in treating/preventing chronic pain
- Use limited to 24hrs
  - Local anesthetic systemic toxicity (LAST) risk increases
  - LAST: worsening CNS SE, e.g. AMS, anxiety, seizures, cardiac arrest, death
- Contraindications: extremes of age, pregnancy, metabolic disturbances
- Dosing: (1.5mg/kg bolus) 1.0-2.0mg/kg/hr infusion

Meg E. Carley, Luis E. Chaparro, Manon Choinière, Henrik Kehlet, R. Andrew Moore, Elizabeth Van Den Kerkhof, Ian Gilron; Pharmacotherapy for the Prevention of Chronic Pain after Surgery in Adults: An Updated Systematic Review and Meta-analysis. *Anesthesiology* 2021; 135:304–325 doi: https://doi.org/10.1097/ALN.0000000000003837

Weinberg G, Barron G. Local Anesthetic Systemic Toxicity (LAST): Not Gone, Hopefully Not Forgotten. Reg Anesth Pain Med. 2016 Jan-Feb;41(1):1-2. doi: 10.1097/AAP.0000000000000334. PMID: 26678759.

Moller RA, Datta S, Fox J, Johnson M, Covino BG. Effects of progesterone on the cardiac electrophysiologic action of bupivacaine and lidocaine. Anesthesiology. 1992 Apr;76(4):604-8. doi: 10.1097/00000542-199204000-00018. PMID: 1550285.

# Withdrawal Management: Ketamine

- N-methyl-D-aspartate (NMDA) receptor antagonist
  - Activity at serotonin, dopamine, K-opioid, norepi and other receptors
- Dose-dependent effect

- Oral
  - Undergoes first pass metabolism with active metabolite
  - Starting dose 10-20mg q6h
  - Peak 30m
  - Increase by 10mg per dose every 12-24h
  - Usual max 50mg q6h
  - Typical effective dose: 1.5-3mg/kg/day

- IV infusion
  - Bolus: 0.1-0.5mg/kg over 2-15 minutes
  - Starting infusion: 0.1-0.2mg/kg/hr (or higher)
  - Can increase q30-60 min
  - Usual effective dose 0.1-0.5mg/kg/hr


Gupta A, Devi LA, Gomes I. Potentiation of μ-opioid receptor-mediated signaling by ketamine. J Neurochem. 2011 Oct;119(2):294-302. doi: 10.1111/j.1471-4159.2011.07361.x

Hailozian C, Luftig J, Liang A, et al. Synergistic Effect of Ketamine and Buprenorphine Observed in the Treatment of Buprenorphine Precipitated Opioid Withdrawal in a Patient With Fentanyl Use. J Addict Med. 2022 Jul-Aug 01;16(4):483-487. doi: 10.1097/ADM.0000000000000929

Christian NJ, Butner JL, Evarts MS, Weimer MB. Precipitated Opioid Withdrawal Treated With Ketamine in a Hospitalized Patient: A Case Report. J Addict Med. 2023 Jul-Aug 01;17(4):488-490. doi: 10.1097/ADM.0000000000001151

# Opioid-Sparing Medications - Others

- TCAs: Amitriptyline, imipramine, desipramine, nortriptyline
  - Anticholinergic side effects
  - Avoid > 60 years old
- Muscle relaxers: Baclofen, tizanidine, cyclobenzaprine
  - Cyclobenzaprine resembles TCA
  - Tizanidine helpful in xylazine withdrawal
- Carbamazepine
  - Useful for trigeminal neuralgia at 200-400mg/day
  - Blood dyscrasias, hepatotoxicity, hyponatremia

Sindrup SH, et al. Basic Clin Pharmacol Toxicol. 2005;96(6):399-409
Al-Quliti KW. Neurosciences. 2015;20(2):107-114 PMID:25864062
Van Tukder MW, et al. Cochrane Database Syst Rev. 2003;2:CD004252. PMID:12804507

# Case

HA is admitted to surgical services for wound management, and is started on IV antibiotics.  Labs are notable for leukocytosis, anemia, and AKI on CKD (GFR 33). His COWS is 13 and he is in 10 out 10 pain. He describes his pain as a constant, sharp and burning, worse with movement.

Which of the following non-opioid medications do you start? (you may choose more than one)

A. Acetaminophen 1g q6h
B. Ketorolac 30mg q4h
C. Gabapentin 900mg q8h
D. Ketamine PO 10mg q6h

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# Medications for Opioid Use Disorder

# MOUD as Backbone of Pain Management

- MOUD is Life-Saving (NNT 53)
  - Reduce overdose deaths
  - Increase treatment retention
- "Medication first" treatment
  - Benefit, regardless of additional counseling
  - Benefit even if patients don’t plan to continue treatment
- Methadone & buprenorphine are time-proven analgesics

Englander H, Davis CS. Hospital Standards of Care for People with Substance Use Disorder. N Engl J Med. 2022 Aug 25;387(8):672-675. doi: 10.1056/NEJMp2204687. Epub 2022 Aug 20. PMID: 35984354.
Wakeman SE, Larochelle MR, Ameli O, et al. Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder. JAMA Netw Open. 2020;3(2):e1920622. doi:10.1001/jamanetworkopen.2019.20622
Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, Bagley SM, Liebschutz JM, Walley AY. Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality: A Cohort Study. Ann Intern Med. 2018 Aug 7;169(3):137-145. doi: 10.7326/M17-3107. Epub 2018 Jun 19. PMID: 29913516; PMCID: PMC6387681.

# Properties of MOUD

## Methadone

Full μ-agonist
Strong affinity at μ-receptor

Safe in renal failure

## Buprenorphine

Partial μ-agonist
Very strong affinity at μ-receptor

Safe in renal failure

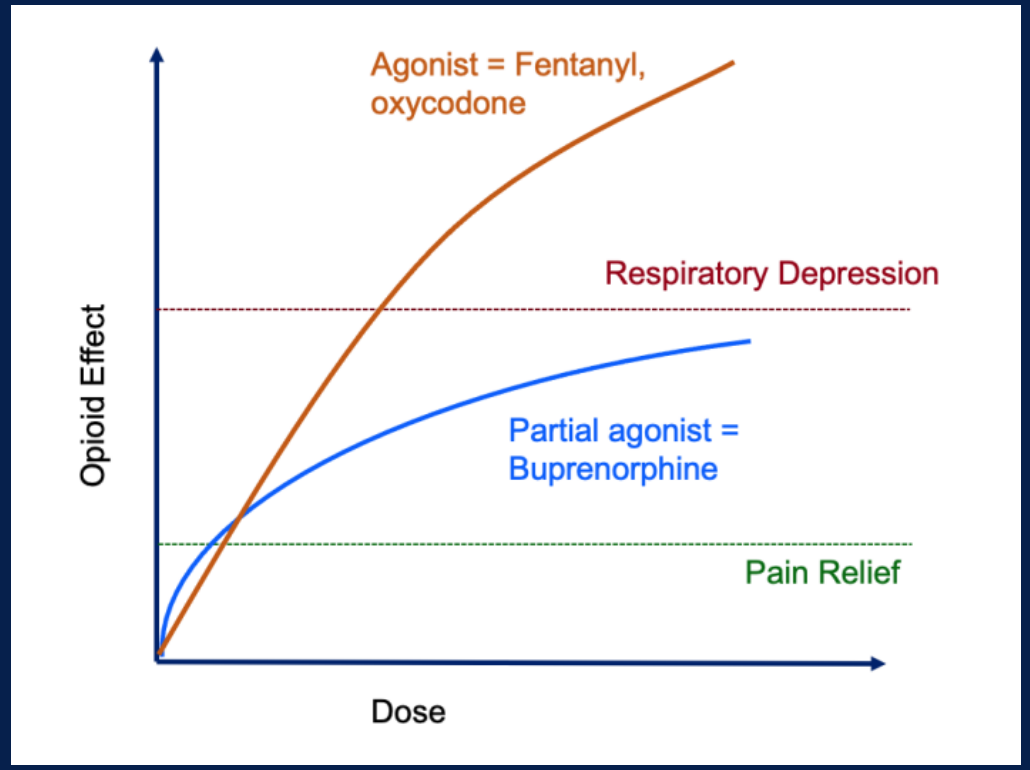
## Naltrexone

Full μ-antagonist
Strong affinity at μ-receptor

Primarily renally cleared

# Buprenorphine

- μ-opioid partial agonist; κ-antagonist
  - Low risk of overdose, respiratory depression, tolerance
  - Anti-depressant, anti-craving effects
- Developed as analgesic
  - Duration 6-8 hours
- Approved for OUD in 1992
  - Benefit at ≥ 16mg daily
- Strong binding to receptor
  - Blocks other opioids
  - Can cause precipitated withdrawal




*Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, Bagley SM, Liebschutz JM, Walley AY. Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality: A Cohort Study. Ann Intern Med. 2018 Aug 7;169(3):137-145. doi: 10.7326/M17-3107. Epub 2018 Jun 19. PMID: 29913516; PMCID: PMC6387681.*

# Formulations of Buprenorphine

1 mg Suboxone™
(bupe/nal SL film)

≈


0.25 mg
IV bupe

≈

450 mcg Belbuca™
(bupe buccal film)

| Formulation | Product (Brand Name) | Onset | Bioavailability (Relative to IV) |
|---|---|---|---|
| Intravenous | Buprenorphine (Buprenex™) | 10-15 minutes | 100% |
| Buccal film | Buprenorphine (Belbuca™) | 30-60 minutes | 45-65% |
| Transdermal Patch | Buprenorphine (Butrans™) | 18-24 hours | 10-15% |
| Sublingual (SL) film<br>Tablet (SL) | Buprenorphine/Naloxone (Suboxone™)<br>Buprenorphine (Subutex™) | 30-60 minutes | 25-50% |

Slide adapted from Tanya J. Uritsky, PharmD, BCPP

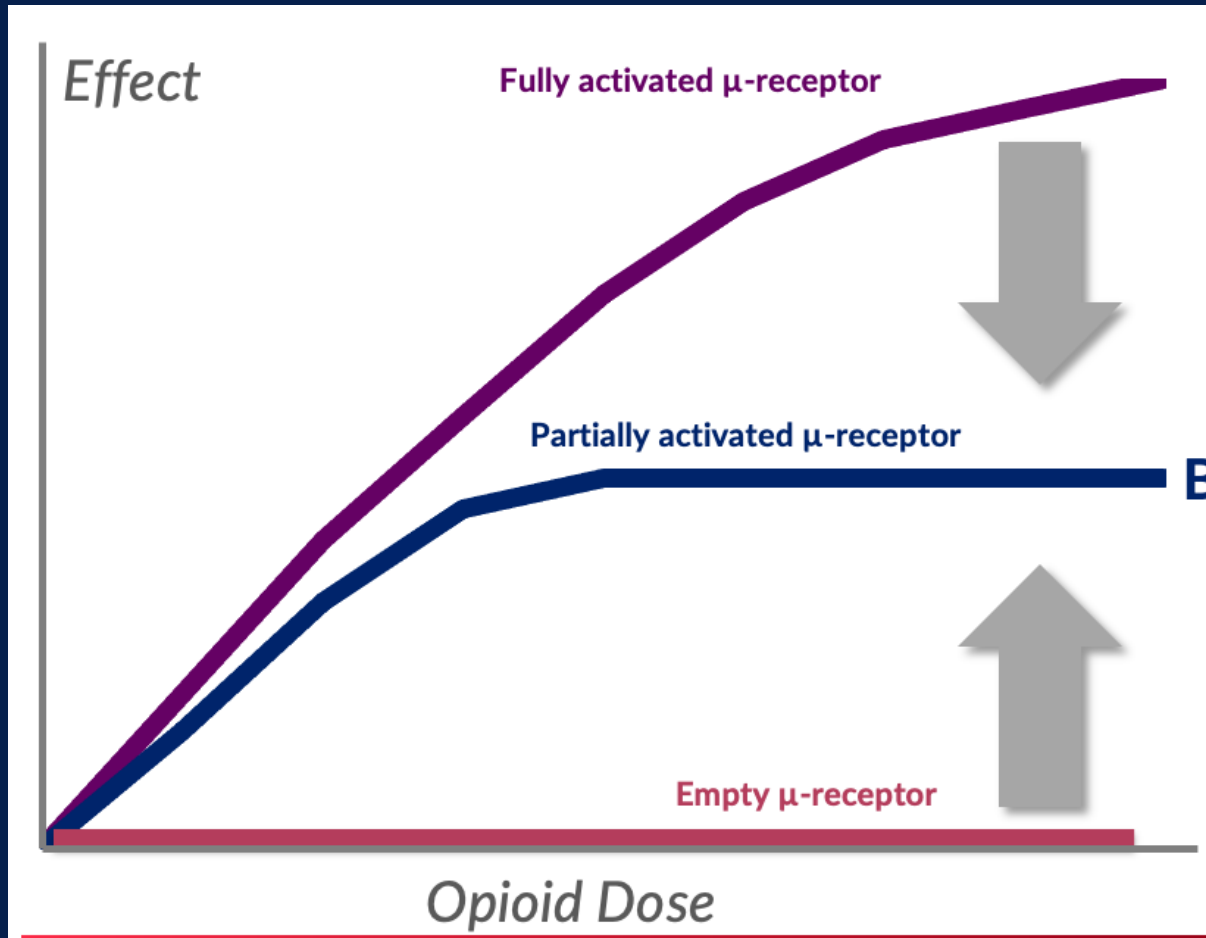
Mendelson J, Upton RA, Everhart ET, Jacob P 3rd, Jones RT. Bioavailability of sublingual buprenorphine. J Clin Pharmacol. 1997;37(1):31-37.
Case AA, Kullgren J, Anwar S, Pedraza S, Davis MP. Treating Chronic Pain with Buprenorphine-The Practical Guide. Curr Treat Options Oncol. 2021;22(12):116. Published 2021 Nov 18.

# MOUD Buprenorphine Products

- Buprenorphine-naloxone SL (tabs & films)
  - 2-0.5mg
  - 8-2mg
  - also 4-1mg, 12-3mg
- Buprenorphine (monoproduct) (tabs only)
  - 2mg
  - 8mg

- Available in 2 long-acting injectable formulations
  - Sublocade® 2 dosing levels (~8-24mg SL bupe); monthly sub-Q depot
  - Brixadi® 3-4 dosing levels (equiv 6-24mg SL bup); weekly & monthly
  - Requires REMS-certified pharmacy

# Precipitated Withdrawal




Precipitated Withdrawal = sudden reduction in receptor activation

**Buprenorphine (high affinity)**

Relief of withdrawal = increase in receptor activation

# Buprenorphine can be Effective Analgesia

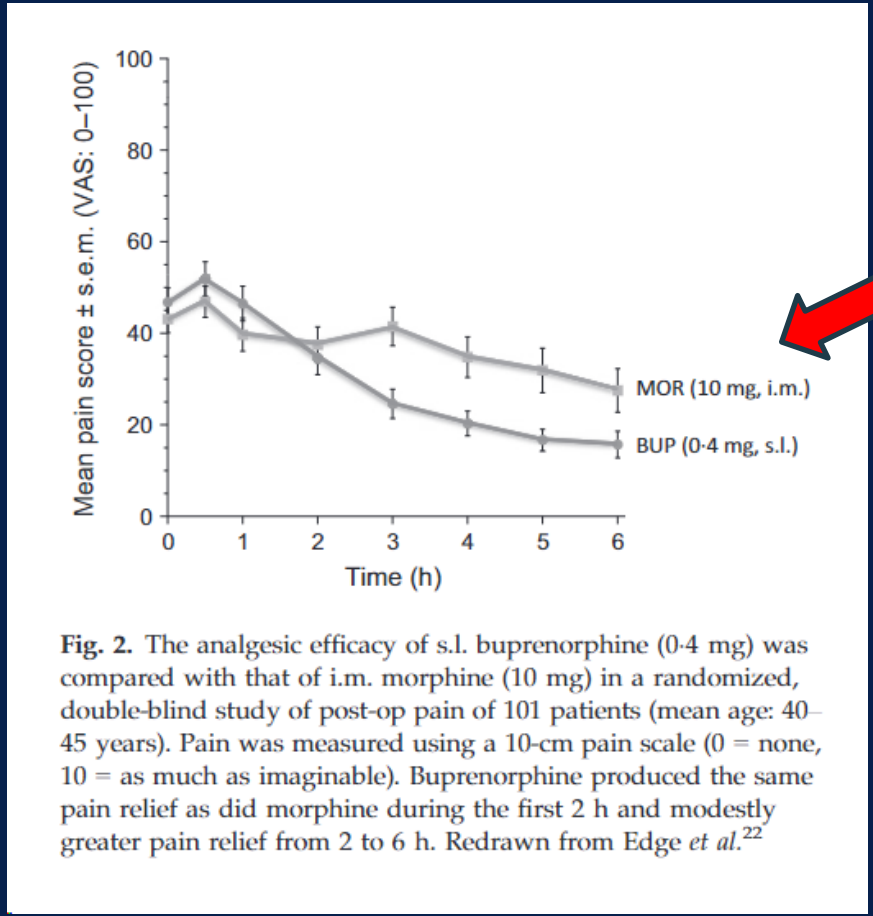



**Fig. 2.** The analgesic efficacy of s.l. buprenorphine (0·4 mg) was compared with that of i.m. morphine (10 mg) in a randomized, double-blind study of post-op pain of 101 patients (mean age: 40–45 years). Pain was measured using a 10-cm pain scale (0 = none, 10 = as much as imaginable). Buprenorphine produced the same pain relief as did morphine during the first 2 h and modestly greater pain relief from 2 to 6 h. Redrawn from Edge *et al.*[22]

Double blind RCT of sl bupe vs morphine for post operative pain

Raffa, R.B., Haidery, M., Huang, H.-.-M., Kalladeen, K., Lockstein, D.E., Ono, H., Shope, M.J., Sowunmi, O.A., Tran, J.K. and Pergolizzi, J.V., Jr (2014), The clinical analgesic efficacy of buprenorphine. J Clin Pharm Ther, 39: 577-583. https://doi.org/10.1111/jcpt.12196

# Methadone

- μ-opioid agonist
  - NMDA receptor antagonist
  - Serotonin and norepinephrine reuptake inhibition
- Developed as an analgesic
  - Pain control: 4-8 hours
- Oldest, most proven medication for OUD
- Strong binding to receptor
  - Competitively blocks other opioids at high doses
- Complex pharmacology
  - Long half-life
  - 5-7 days to steady state
- Risks
  - QTc prolongation
  - Respiratory depression /overdose

Larochelle MR, Bernson D, Land T, Stopka TJ, Wang N, Xuan Z, Bagley SM, Liebschutz JM, Walley AY. Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality: A Cohort Study. Ann Intern Med. 2018 Aug 7;169(3):137-145. doi: 10.7326/M17-3107. Epub 2018 Jun 19. PMID: 29913516; PMCID: PMC6387681.

Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2003;(2):CD002207. doi: 10.1002/14651858.CD002207. Update in: Cochrane Database Syst Rev. 2004;(3):CD002207. PMID: 12804429.

# Methadone & QTc

**ACP Consensus Guidelines on Methadone:**

- **EKG recommended**
  - Before starting
  - 30-day follow-up
  - Annually
  - More often if > 100mg/day

- QTc > 500 ms, consider:
  - discontinuing / reducing dose
  - eliminating contributing factors
  - using an alternative (e.g. buprenorphine)

- QTc 450-500 ms:
  - discuss risks and benefits
  - monitor more frequently

Mori J. Krantz, Judith Martin, Barry Stimmel, et al. QTc Interval Screening in Methadone Treatment. Ann Intern Med.2009;150:387-395. [Epub 17 March 2009]. doi:10.7326/0003-4819-150-6-200903170-00103

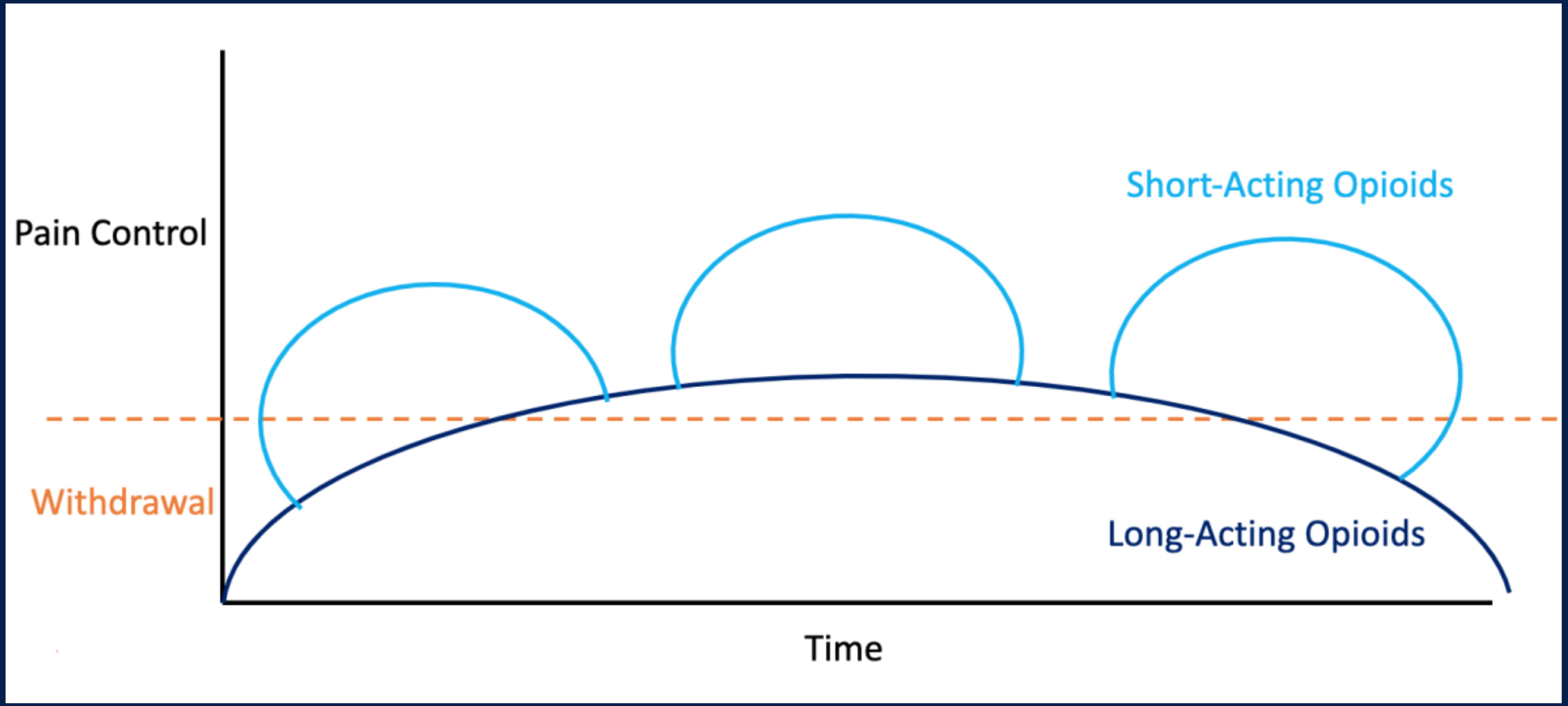
# Extended Release Naltrexone

- μ-opioid antagonist
- Monthly IM injection
- Less robust evidence as MOUD than methadone & buprenorphine
- Approved for use in Alcohol Use Disorder

Adam Rupp, Erin Young, Andrea L Chadwick, Low-dose naltrexone's utility for non-cancer centralized pain conditions: a scoping review, Pain Medicine, Volume 24, Issue 11, November 2023, Pages 1270–1281, https://doi.org/10.1093/pm/pnad074

# MOUD and Pain Management

# Approach to Pain Management

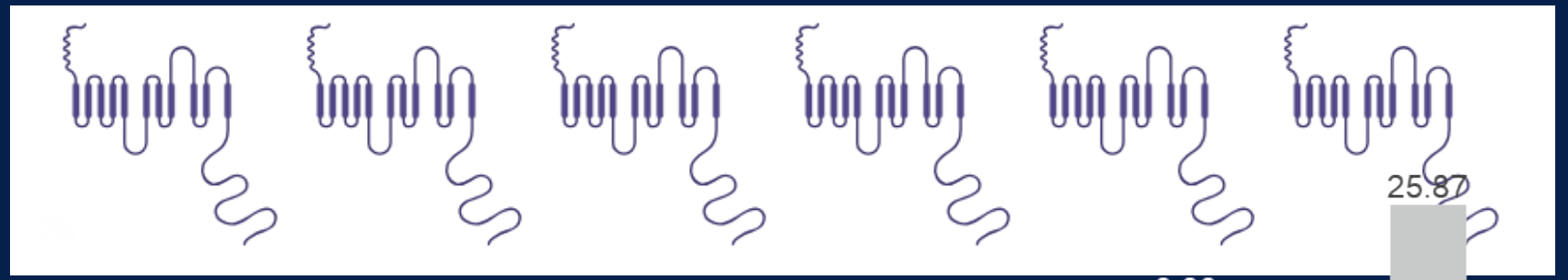


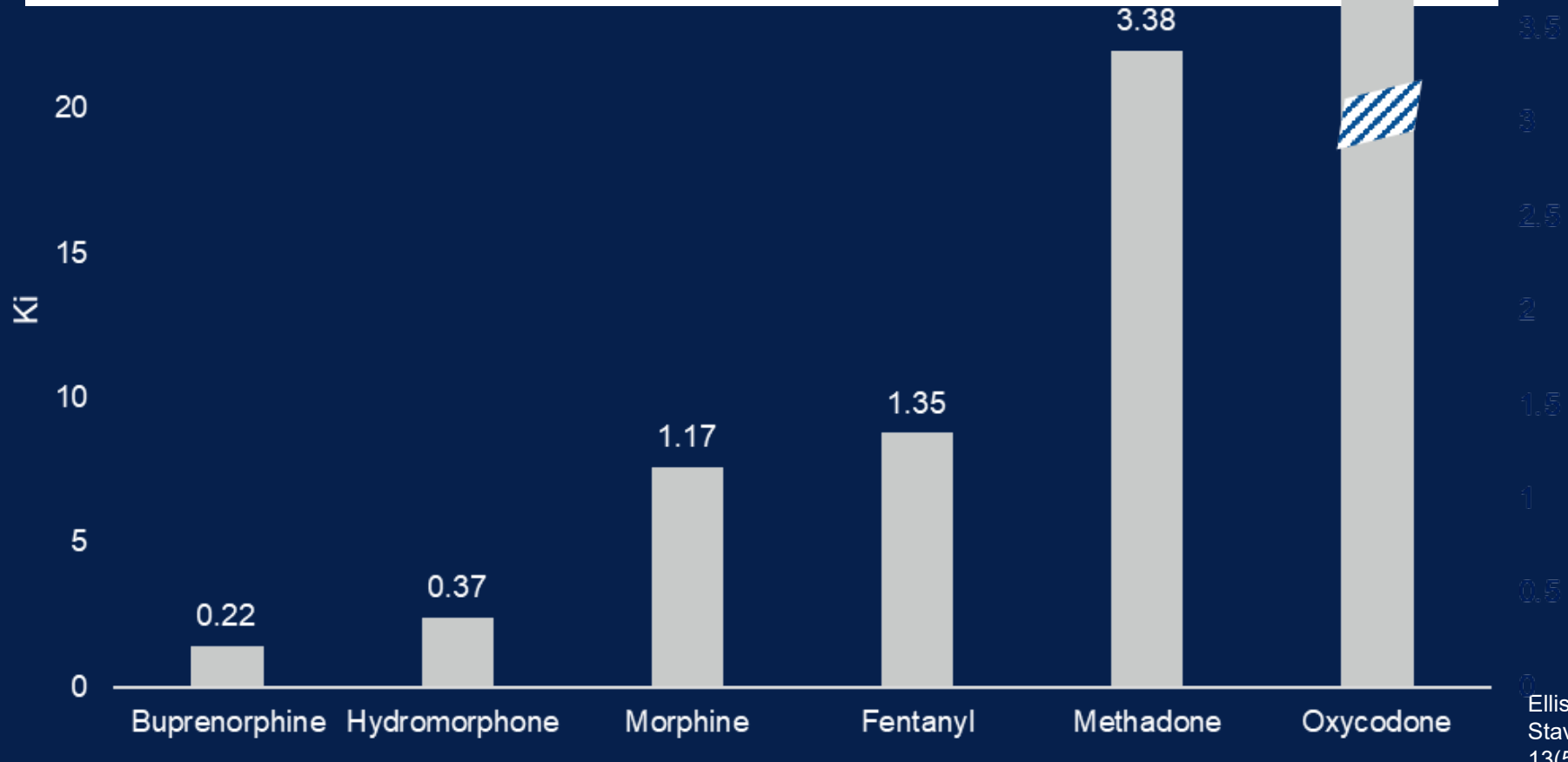
# Properties of Opioid Agonists

| Drug | Equianalgesic Oral Dose (mg) | Equianalgesic I V Dose (mg) | Use in Renal Failure | Starting Dose – Opioid Naïve (PO/IV) | Starting Dose – Opioid Tolerant (PO/IV ) |
|---|---|---|---|---|---|
| Morphine | 30 | 10 | No | 5 mg / 2mg | 15mg / 5mg |
| Oxycodone | 20 | --------- | Caution | 5mg / --- | 10mg/ --- |
| Hydromorphone | 7.5 | 1.5 | Caution | 2mg / 0.2mg | 4mg / 0.4 mg |
| Fentanyl | --------- | 0.01 | Yes | --- / 25mcg | ---- / 100mcg |

Codeine & tramadol are prodrugs, not recommended due to variable metabolism & effects

# Properties of Opioid Agonists






Lower Ki = stronger affinity

Ellis CR, Kruhlak LN, Kim MT, Hawkins EG, Stavitskaya. (2018). PLoS ONE. 13(5):e0197734.. PMID: 29795628

# Patients on Methadone

- Split dosing for analgesic effect (q8h)
  - Discuss with patient
  - Anticipate discharge / reconsolidation plan
- For patient unable to take PO
  - IV methadone (PO:IV is 2:1 conversion)
- Consider PRN methadone dose
  - 10% of total daily dose
  - Administered at least 4 hours after scheduled dose

# Patients on Buprenorphine

- Continue buprenorphine (home dose or ≥ 8mg daily)
- Consider
  - Split dosing (TID/QID) for analgesic effect
  - Increasing to a total daily dose of 24-32 mg
  - Use of PRN dosing
- When using full opioid agonists
  - Higher doses may be needed
  - Prefer opioids with high affinity for the mu-opioid receptor
- For intubated/sedated patients
  - Use SL or IV buprenorphine

# Patients on Extended-Release Naltrexone

- When using full opioid agonists
  - Higher doses may be needed to overcome some blocking effects
  - Use opioids with high affinity for the mu-opioid receptor

# Case

HA is receiving acetaminophen 1g q6h, and his ketamine PO is uptitrated to 20mg q6h. His AKI has improved with IV fluids (GFR 66) and he is started on ketorolac 15mg q6h and gabapentin 300mg q8h. He is experiencing ongoing 9 out of 10 pain.

Which of the following strategies do you consider for his buprenorphine management? (you may choose more than one)

A. Stop buprenorphine and start scheduled full agonist opioid for pain

B. Increase buprenorphine to 8mg q8h with additional PRN buprenorphine for pain

C. Continue buprenorphine 8mg and add full agonist opioid PRN for pain

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# Starting Buprenorphine

- "Traditional" induction = wait until opioid receptor is empty, based on
  - timing of last opioid dose
  - withdrawal symptoms/COWS score

Conservatively:

- 8-12 hours after short-acting (oxycodone IR, hydromorphone)
- 24 hours after long-acting (oxycodone ER)
- Fentanyl after 1-5 days (depending on usage)
- Methadone after 3-5 days (depending on dose)

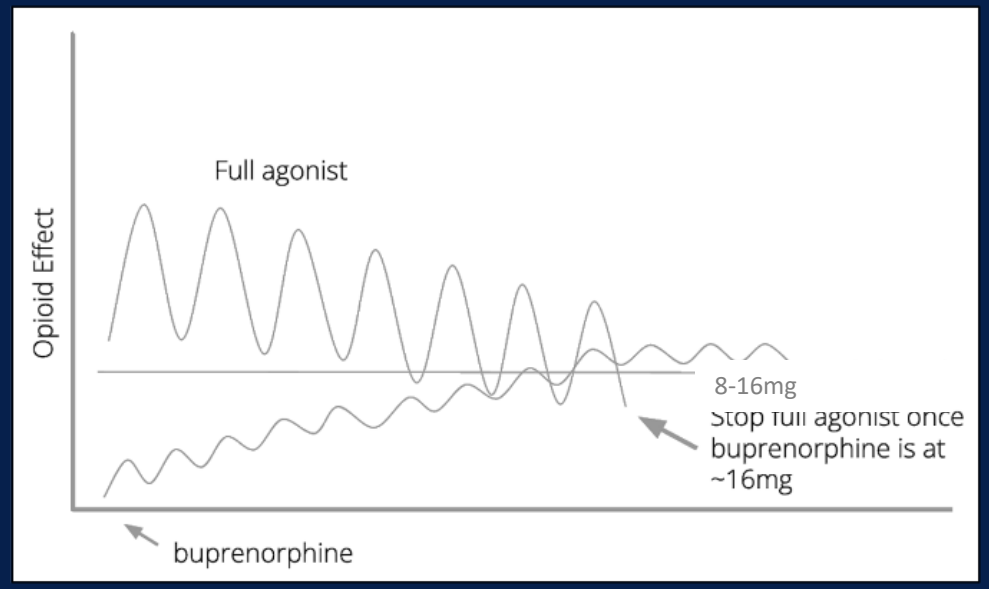
# Starting Buprenorphine

If patient is on ≥ 8mg bup, can add agonist without risk of "precip"

- Patients at risk include patients not yet on buprenorphine...
  - Requiring ongoing full-dose agonists for pain
  - On methadone (due to long half-life)
  - Using fentanyl (due to accumulation in fat tissue)

# Avoiding Precipitated Withdrawal

- Low-dose or micro-induction can avoid precipitated withdrawal
  - Cross titration over 4-7 days
  - Continuing full-agonist opioids
  - Frequent dosing of low-dose bupe (~0.5mg SL), gradually overtaking opioid receptors
  - Taper or stop full-agonist opioids once bupe ≥ 8-16mg




Various effective low-dose protocols exist

One Example:
Day 1: 150 mcg buccal film q6h
Day 2: 450 mcg buccal film q6h
Day 3: Buprenorphine/naloxone 2 mg SL q6h
Day 4: Buprenorphine/naloxone 4 mg SL q6-8h

# Additional Opioid Agonists

Example protocol (Penn Medicine)

1. Use long-acting opioid
   - methadone, buprenorphine, or oxycodone ER
2. Start a short-acting opioid
   - **e.g. oxycodone 20mg q4h or hydromorphone 8mg q4h** (for patients using fentanyl)
   - uptitrate to effect
   - For poorly controlled pain, can add
     - IV PRN (e.g. hydromorphone IV 1.5-2mg)
     - or PCA (e.g. hydromorphone IV 0.5mg basal/0.5mg q15m bolus)
3. Use non-opioid adjuvants
4. Transition to MOUD
   - methadone or buprenorphine
   - taper off short-acting opioids

Thakrar, A. P., Uritsky, T. J., Christopher, C., Winston, A., Ronning, K., Sigueza, A. L., Caputo, A., McFadden, R., Olenik, J. M., Perrone, J., Delgado, M. K., Lowenstein, M., & Compton, P. (2023). Safety and preliminary outcomes of short-acting opioid agonist treatment (sOAT) for hospitalized patients with opioid use disorder. *Addiction science & clinical practice*, *18*(1), 13. https://doi.org/10.1186/s13722-023-00368-z

https://penncamp.org/clinical/pain-and-opioid-withdrawal-in-hospitalized-patients/

# Risks & Benefits of Full Agonists

- At Penn, review of outcomes
  - 23 high-risk patients with fentanyl dependence
  - Received median doses 20-35mg oxycodone q4h
  - Guided by expert pharmacist
  - No evidence of iatrogenic overdose
  - 65% left on methadone/buprenorphine, self-discharge rate fell


Thakrar, A. P., Uritsky, T. J., Christopher, C., Winston, A., Ronning, K., Sigueza, A. L., Caputo, A., McFadden, R., Olenik, J. M., Perrone, J., Delgado, M. K., Lowenstein, M., & Compton, P. (2023). Safety and preliminary outcomes of short-acting opioid agonist treatment (sOAT) for hospitalized patients with opioid use disorder. *Addiction science & clinical practice*, *18*(1), 13. https://doi.org/10.1186/s13722-023-00368-z

https://penncamp.org/clinical/pain-and-opioid-withdrawal-in-hospitalized-patients/

# Dosing Opioid Agonists

| Formulation | Time to Peak Effect | Duration of Analgesia |
|---|---|---|
| IV (morphine, hydromorphone) | 8-15 min | 2-3 hours |
| Short-acting oral (oxycodone, hydromorphone, morphine) | 30-60 min | 3-4 hours |
| Long-acting oral (oxycodone ER, morphine SR) | 3-5 hours | 8-24 hours |

- Rule of thumb = PRN dose ~10% of total daily OME
- Monitor for changes in renal & liver function, clinical condition (sepsis, hypercalcemia)

Lexicomp Online. Waltham, MA: UpToDate, Inc. 2024. Accessed February 22, 2024.

# Converting from One Agonist to Another

® Add up 24-hour usage
- IV Hydromorphone (HM) 2mg x 5 doses = 10mg IV HM
- Oxycodone IR 40mg x 4 doses = 160mg oxycodone

® Convert to Oral Morphine Equivalents (OME)
- 10mg IV HM x $\frac{30\ \text{OME}}{1.5\text{mg IV HM}}$ = 200 OME = 420 OME / day
- 160mg oxycodone x $\frac{30\ \text{OME}}{20\ \text{oxycodone}}$ = 240 OME

| Drug | Oral Dose (mg) | IV Dose (mg) |
|---|---|---|
| Morphine | 30 | 10 |
| Oxycodone | 20 | --------- |
| Hydromorphone | 7.5 | 1.5 |

✸ Convert from OME to new agonist (traditionally dose-reduce 25%, not recommended in OUD)
- 420 OME x $\frac{7.5\ \text{PO HM}}{30\ \text{OME}}$ = 105mg PO HM / day

✸ Divide by # of doses per day
- 105 mg PO HM / 6 doses = 17.6mg q4h
- Round based on available tabs = Hydromorphone PO 16mg q4h

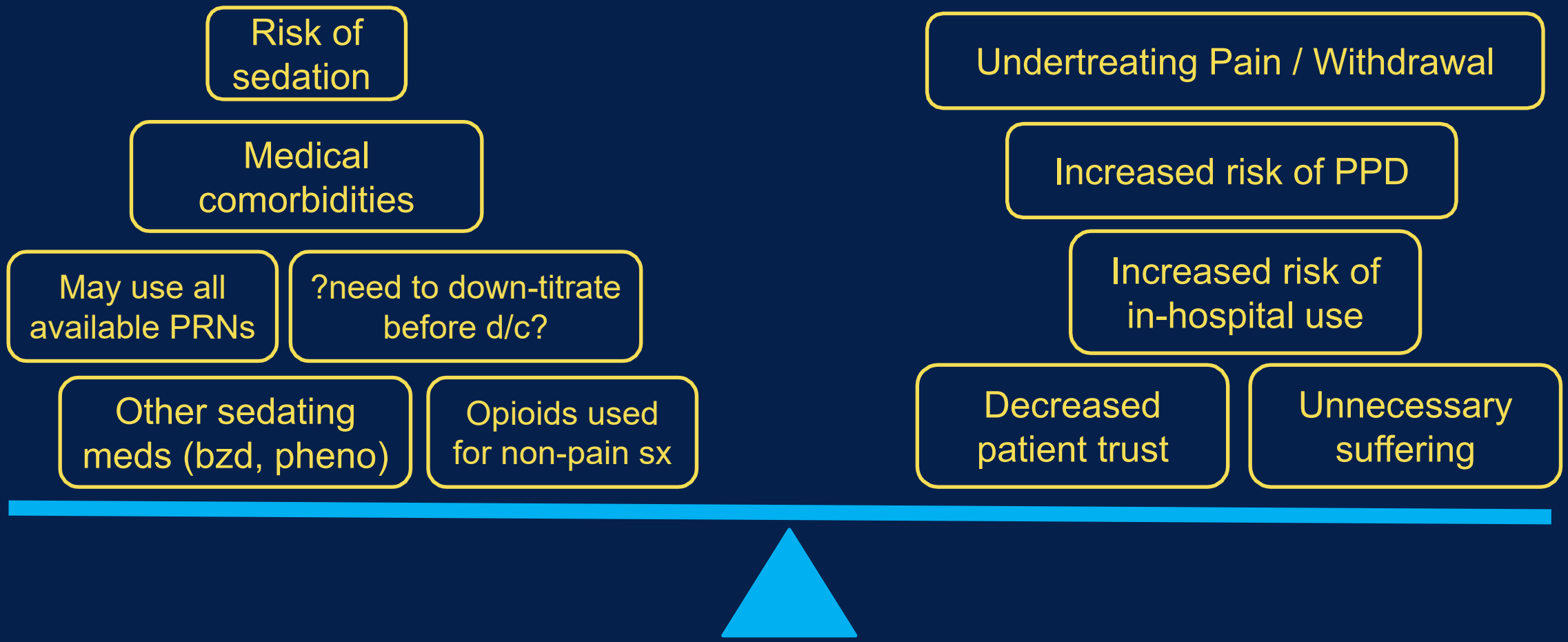
# How to Order a PCA

| | Penn Pathway for patient with OUD | **Options** |
|---|---|---|
| Opioid | Hydromorphone | Hydromorphone (also morphine, fentanyl) |
| Basal rate | 0.5mg | 0-1mg (based on previous use) |
| Bolus (demand) dose | 0.5mg | 0.5-2mg (based on previous use and lock-out) |
| Lock-out | q15m | Q10-30 min (consider total max hourly dose available) |
| Loading dose | 2mg | 0-2mg |
| 4-hour lock-out | NONE | NONE |
| Additional nurse-given PRN | | at least 2x demand dose |

# The "Art" of Opioid Management

- Oral and scheduled dosing > to high-dose IV PRNs
  - Collaboration for down-titration
- Consider scheduling rather than PRN
  - Prior to dressing changes or PT/OT
  - Bedtime/morning
  - Focus on function
- Ensure treating other symptoms
  - e.g. anxiety, insomnia
- Don't forget bowel regimen (scheduled senna & PEG)
- Consider prognosis and discharge plans

# Dosing as a Balancing Act



# Case

HA is continued on buprenorphine 8mg daily. His pain is controlled (5 out of 10) with PO hydromorphone 16mg q4 and additional PO HM q4h PRN (used total of 10 doses in past 24-h). He has had post-operative nausea/vomiting previously. Anesthesia is planning to place a popliteal/saphenous nerve block.

Which of the following strategies do you consider for pain management post-op? (you may choose more than one)

A. 3mg IV hydromorphone scheduled q4h with additional breakthrough doses q3h PRN
B. 1.5mg IV hydromorphone scheduled q4h with additional breakthrough doses q3h PRN
C. PCA of IV hydromorphone 0mg basal rate, 0.5mg demand-dose q30m
D. PCA of IV hydromorphone 0.5mg basal rate, 1mg demand-dose q15m

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C. PCA of IV hydromorphone 0mg basal rate, 0.5mg demand-dose q30m
D. PCA of IV hydromorphone 0.5mg basal rate, 1mg demand-dose q15m

# Perioperative Management

# Peri-operative Management

- Continue MOUD in perioperative period
  - Including buprenorphine (home dose or ≥ 8mg / day)
- Methadone
  - Dose can be supplemented by Anesthesia perioperatively
  - Can be split-dosed postoperatively for improved pain control
- Consider long-acting and short-acting agents
  - or PCA with basal rate
- Consider nerve blocks


Burns SL, Majdak P, Urman RD. Perioperative and Periprocedural anesthetic management of opioid tolerant patients and patients with active and medically treated opioid use disorder. Curr Opin Anaesthesiol. 2022 Aug 1;35(4):514-520. doi: 10.1097/ACO.0000000000001157. Epub 2022 Jul 5. PMID: 35788122; PMCID: PMC9308736.

Kohan L, Potru S, Barreveld AM, *et al*

Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel

*Regional Anesthesia & Pain Medicine* 2021;**46:**840-859.

# Perioperative Buprenorphine Management

- Historical concern that opioid agonist is unable to displace buprenorphine
- Resulting in inadequate pain control

- Multiple case series supporting continuation of buprenorphine
- MOUD is life-saving

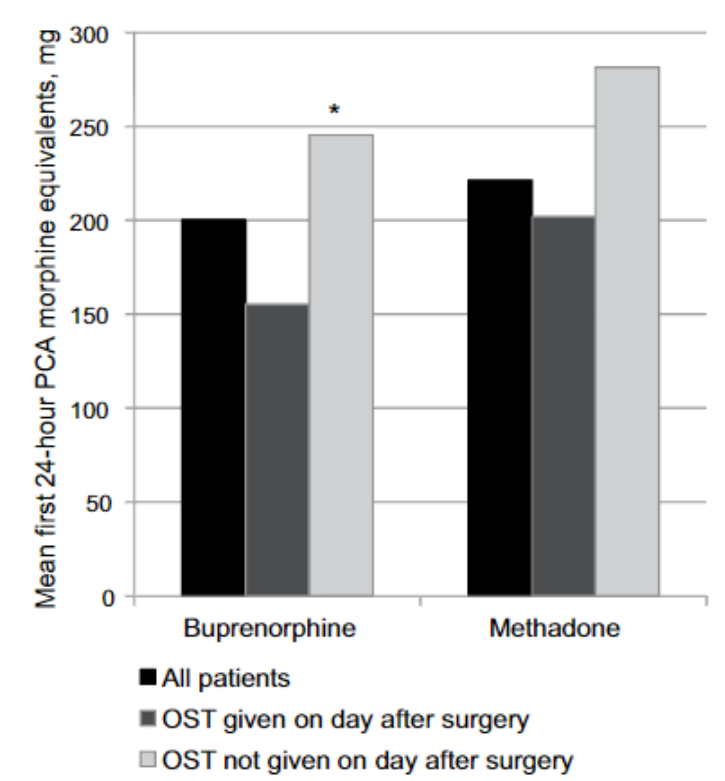



Figure 1: Comparison of PCA opioid requirements in buprenorphine and methadone opioid substitution therapy patients. * The mean PCA morphine equivalent dose was significantly higher ($P$=0.02) in patients who did not receive buprenorphine the first day after surgery compared with those who did. PCA=patient-controlled analgesia, OST=opiod substitution therapy.


Kohan L, Potru S, Barreveld AM, *et al* Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel*Regional Anesthesia & Pain Medicine* 2021;**46:**840-859.

*Pain Relief and Opioid Requirements in the First 24 Hours after Surgery in Patients Taking Buprenorphine and Methadone Opioid Substitution Therapy* P. E. Macintyre, R. A. Russell, K. A. N. Usher, M. Gaughwin, and C. A. Huxtable Anaesthesia and Intensive Care 2013 41:2, 222-230

# Perioperative Management - Naltrexone

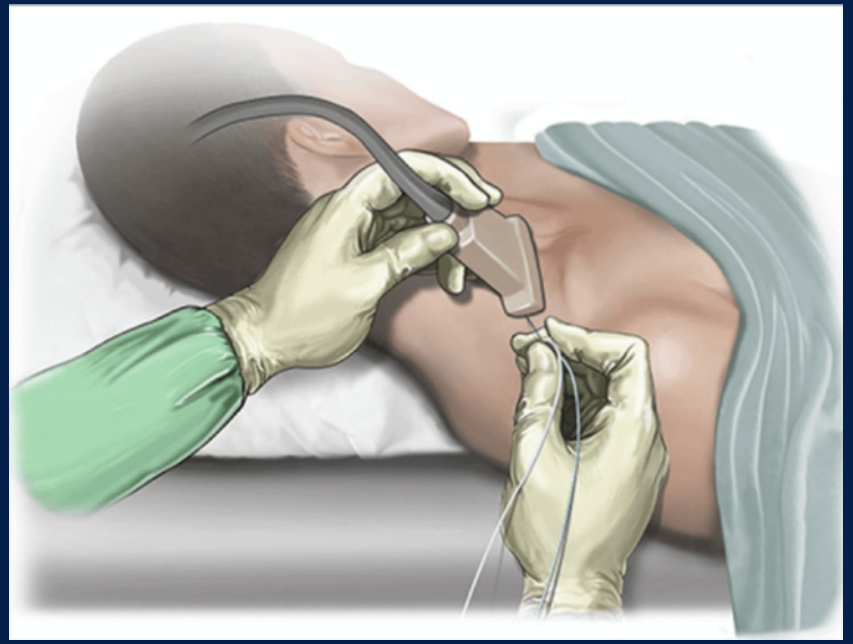
- "Standard" recommendation: Wait < 4 weeks after dose of extended-release IM naltrexone and 72-h after oral naltrexone
  - May have increased response due to opioid receptor upregulation
  - If surgery earlier, may require higher full opioid agonist dosing

- Patients are at high risk of relapse and overdose while MOUD is being held
  - Discuss risk and benefits of holding naltrexone with patient and anesthesiologist
  - Consider alternatives
    - Buprenorphine
    - Treating through naltrexone

Ward EN, Quaye AN, Wilens TE. Opioid Use Disorders: Perioperative Management of a Special Population. Anesth Analg. 2018 Aug;127(2):539-547. doi: 10.1213/ANE.0000000000003477. PMID: 29847389; PMCID: PMC6523021.

# Nerve Block Basics

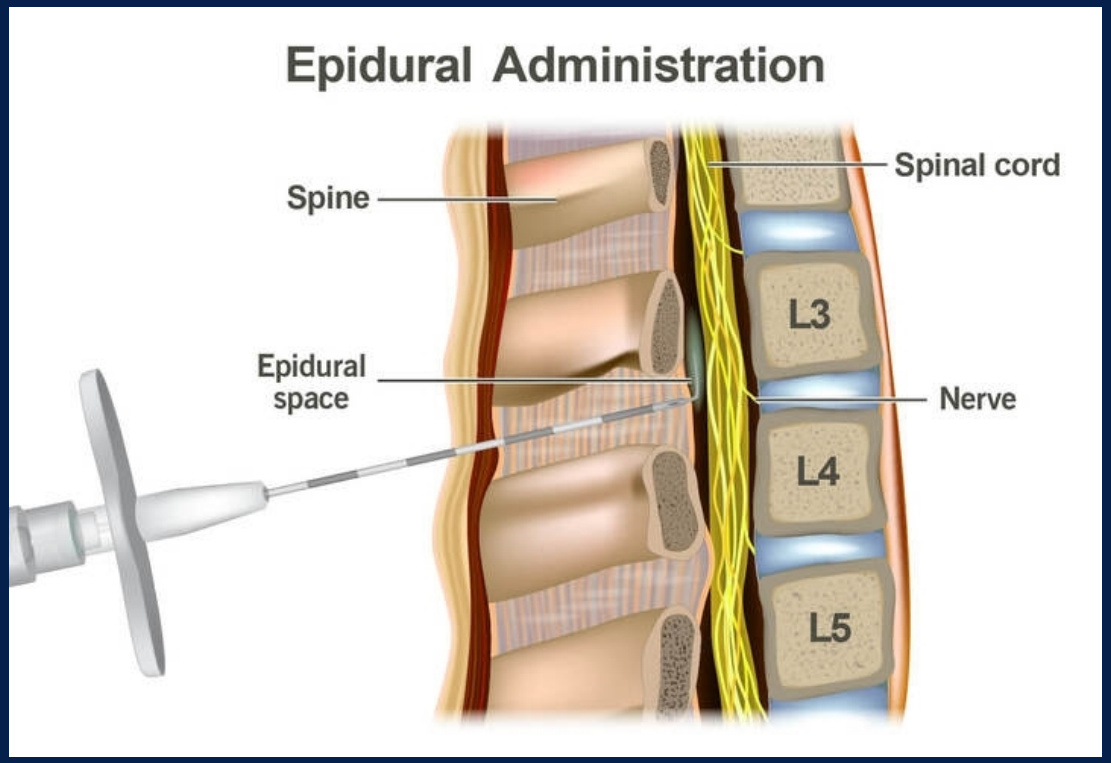
- Duration: 1-12 hours
- Local anesthetics: lidocaine, bupivacaine, ropivacaine
  - Additives to enhance and/or extend the duration of block
  - Nerve block catheters



Gola W, Zając M, Cugowski A. Adjuvants in peripheral nerve blocks - the current state of knowledge. Anaesthesiol Intensive Ther. 2020;52(4):323-329. doi: 10.5114/ait.2020.98213. PMID: 33165883; PMCID: PMC10183787.

https://www.healthdirect.gov.au/surgery/peripheral-nerve-block-upper-limb

# Nerve Block Targets




- Thorax/abdomen
  - Epidural/spinal and erector spinae
  - Quadratus lumborum and TAP blocks
- Extremities
  - Interscalene/supraclavicular/infraclavicular
  - Femoral/adductor canal/saphenous/popliteal and fascia iliaca

https://www.nysora.com/
https://my.clevelandclinic.org/health/treatments/21896-epidural

# Case

Following surgery, HA is switched back to oral analgesia. His infection and pain are improving. He is receiving peer support and visits from hospital chaplain. He decides to leave in patient-directed discharge. He is provided with PO antibiotics, wound-care supplies, naloxone, and clinic follow-up.

Which of the following approaches do you recommend for his buprenorphine at discharge? (you may choose more than one)

A. Resume previous dose of 8mg buprenorphine
B. Resume previous dose of 8mg buprenorphine and continue PO hydromorphone 16mg q4h
C. Increase buprenorphine to 8mg TID
D. Start long-acting injectable buprenorphine

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# Final Takeaways/Summary

| Treat Pain | | | |
|---|---|---|---|
| Optimize non-opioid strategies (medications and nonpharmacologic) | Continue MOUD as they can be effective analgesia | Full opioid agonists can be added to MOUD | Continue MOUD in the perioperative period |

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