Acute and Chronic Pain in Patients with Opioid Use Disorder

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Disclosure Information

- Amy J. Kennedy, MD, MS
  - No Disclosures
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Learning Objectives

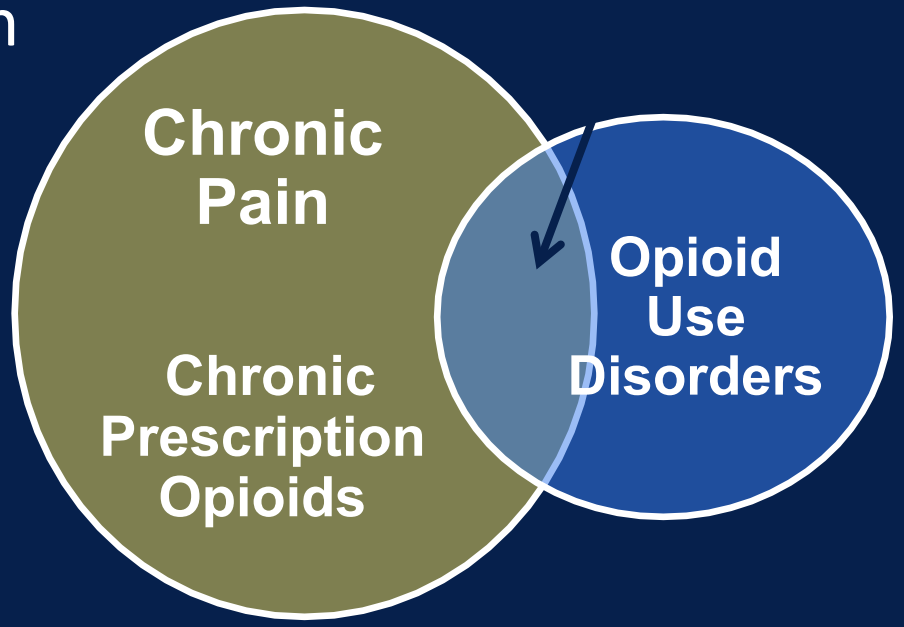
- Develop practical skills to provide person-first care to patients with opioid use disorder and acute and chronic pain
- Recognize how to diagnose opioid use disorder in persons with chronic pain
- Apply evidence-based knowledge on management of buprenorphine induction in patients with acute and chronic pain on full agonist-opioids

Workshop Goals

- Strongly encourage questions/comments via chat throughout the workshop
- Presenters will answer questions in real-time
- 5-10 minutes at the end for additional questions/discussion

Pain and Opioids: By the Numbers

- About 1 in 3 Americans have acute or chronic pain
- In 2014
  - 9.6-11.5 million adults on long-term opioids
  - 2.5 million adults with opioid use disorder (OUD)

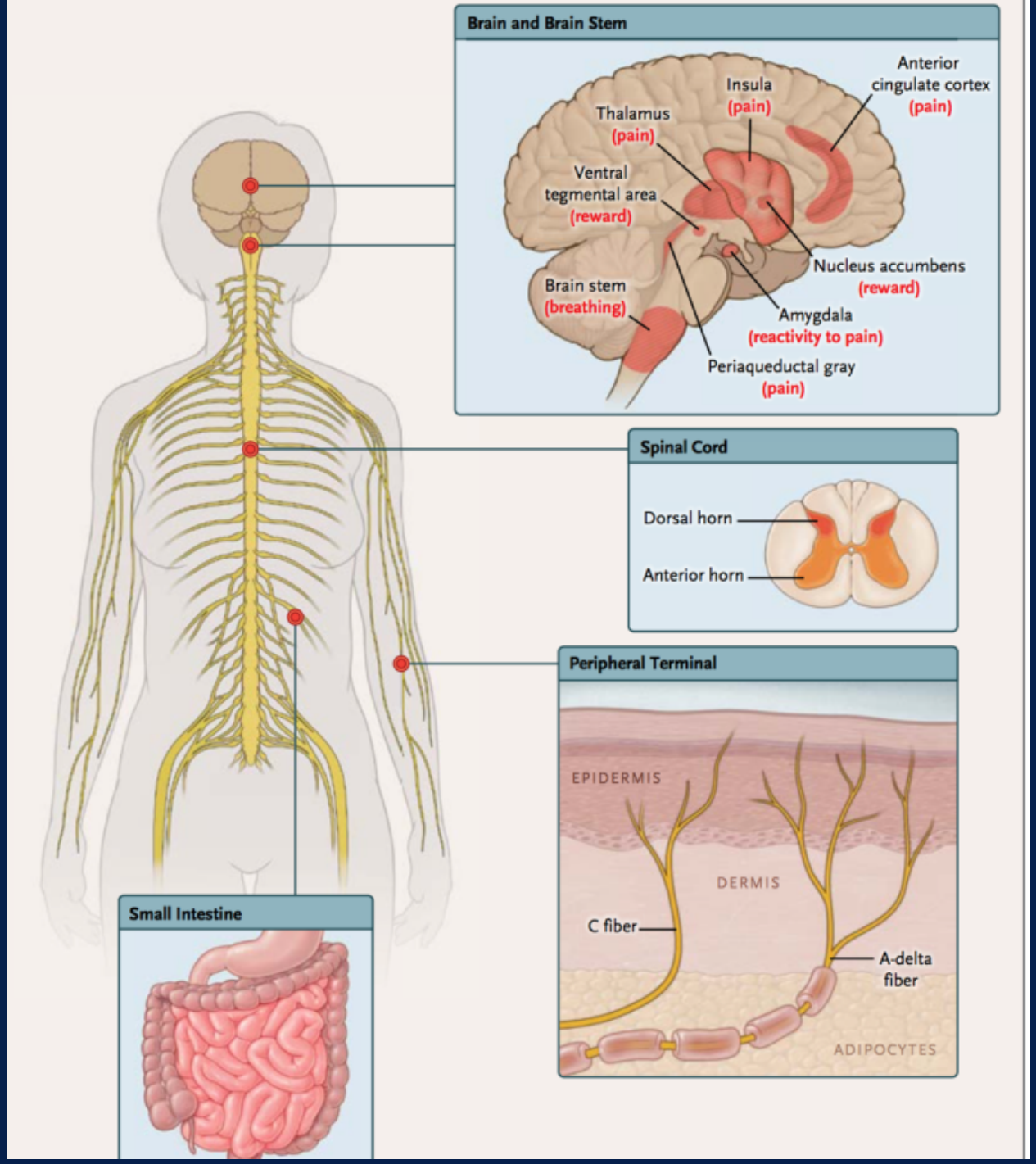


Olsen, State-Journal Register, 2018; Volkow & McLellan, NEJM, 2016

Co-occurrence pain & addiction

- Rates of chronic pain are high in patients in OUD treatment programs
  - Methadone maintenance:
    - >60% any chronic pain
    - 37% severe chronic pain
  - Buprenorphine-naloxone:
    - 36% with chronic pain
- In patients with chronic pain, rates of OUD vary
  - In large health care system, 26% of patients on long-term opioid therapy with OUD
  - In clinic sample, 24% of commercially insured and 20% in Medicaid sample with OUD
  - Rates of addiction 8-12%

Barry, Clin Psychiatry, 2009; Rosenblum, etal, JAMA, 2003; Jamison, et al, J. Pain Symptom Manage, 2000; Barry, et al, Am J Addict, 2013; Boscarino, et al, Addiction, 2010; Sullivan, et al, Pain, 2010; Edlund, et al, Drug Alcohol Depend, 2010; Vowles, Pain, 2015.



Mu-RECEPTORS

- Receptors located areas that regulate:
- Pain perception (e.g. insula, thalamus, cingulate cortex)
- Pain-induced emotional response (amygdala)
- Perception of pleasure and well-being (ventral tegmental area and nucleus accumbens)

Volkow & McLellan, NEJM, 2016

Properties of Opioids

- Directly active brain areas regulating analgesia and reward
- Also, mediate learned association between receipt of drug and physiological and perceptual effects
- Repeat use of opioids strengthens these associations
- Overtime this leads to craving (desire) for the effects of drugs
- IN CHRONIC PAIN: learned association between pain and relief. Relief from even mild pain can lead to early use of opioids outside of schedule.

Volkow & McLellan, NEJM, 2016

Patient Cases

- Laura – Low Back Pain
- Mark – Motor Vehicle Accident
- Elena – New Onset Heart Murmur

Laura

- Laura is a 42 yo woman with a motor vehicle accident (MVA) 14 years ago leading to chronic low back pain, referred to you by a colleague
- She has residual low back pain that failed multiple treatment modalities. She was started on extended-release morphine 10 years ago by prior provider
  - Dose up-titrated to 45 mg extended-release morphine BID and 15 mg QHS (60 mg/day)
- Laura reports after her last provider retired, she has been bouncing to multiple different providers and has struggled to find a provider willing to continue her opioids
- She feels her current regimen is effective at treating her pain and is upset she may not be able to continue it

Audience poll: What would you do?

- Tell patient that you will not prescribe full opioid agonists and offer to taper her off or start buprenorphine
- Refill the prescription for one month
- Ask additional information

Audience poll: Does the patient have an opioid use disorder?

- Yes
- No

Addiction is NOT…

- **Tolerance:** Decrease in opioid potency with repeated administration
  - Tolerance to analgesic and euphoria develops quickly
  - Tolerance to respiratory depression develops more slowly

- **Dependence:** Counter-adaptation in opioid receptors and intracellular signaling leading to physiological adaptations
  - Characterized by withdrawal symptoms with abrupt discontinuation

- Often erroneously equated to addiction

Volkow & McLellan, NEJM, 2016

Make the diagnosis

- Tolerance
- Withdrawal

Loss of control

- Larger amounts and/or longer periods
- Inability to cut down on or control use
- Increased time spent obtaining, using, recovering
- Craving/compulsion

Use despite negative consequences

- Role failure, work, home, school
- Social, interpersonal problems
- Reducing social, work, recreational activity
- Physical hazards
- Physical or psychological harm

American Psychiatric Association, DSM-V, 2013

Opioid misuse

- **Misuse:** Nonmedical use for reasons other than prescribed & can be willful or unintentional use of a substance not consistent with legal or medical guidelines with harmful or potentially harmful consequences

Sehgal, Pain Physician, 2012.

No unique definition of addiction in patients prescribed opioids

- Similar aberrant drug seeking behaviors can be seen in those with uncontrolled pain, anxiety or fear of withdrawal

- Elicit story of:
  - Impaired **control** over drug use
  - **Compulsive** use
  - **Continued** use despite harm
  - **Craving**

Savage, et al, *J Pain Symptom Manage,* 2003*;* Volpe, *Practical Pain Management,* 2020

Does this patient have an OUD?

- She reports that sometimes she runs out of medication early because she has breakthrough pain and has to take an extra dose to "take the edge off"
- She reports she may need a dose increase because she will "watch the clock and count to the minute" when she can take another breakthrough dose of pain medication
- She does not feel she has any problems from the medication, but she did have a recent hospitalization for overdose two months ago (in setting of polypharmacy as she took her opioids plus benzos for anxiety and alcohol)

Audience poll: Does the patient have an opioid use disorder?

- Yes
- No

Make the diagnosis

- Tolerance
- Withdrawal

Loss of control

- Larger amounts and/or longer periods
- Inability to cut down on or control use
- Increased time spent obtaining, using, recovering
- Craving/compulsion

Use despite negative consequences

- Role failure, work, home, school
- Social, interpersonal problems
- Reducing social, work, recreational activity
- ~~Physical hazards~~
- Physical or psychological harm

American Psychiatric Association, DSM-V, 2013

Audience poll: What would you offer Laura?

- Taper her completely off opioids and then offer methadone referral or bup-nx from your practice
- Start bup-nx while she is still receiving oxycodone
- Tell her she is not appropriate for your practice and refer to another provider
- Refill her opioids for another month

We will revisit her case.

Mark

- 32 yo male with history of severe OUD, in sustained remission for past 5 years
  - IV drug use (IDU) with heroin for 3 years
- On long-term maintenance therapy with buprenorphine-naloxone 16 mg SL daily
- Presents to clinic after a MVA with ankle fracture with temporary splint requiring surgical intervention in significant pain (10/10)
- Reports significant anxiety as his surgeon told him he would need to be tapered off of bup for five days before surgery; not prescribed opioids for pain because on bup-nx

Audience poll: How do you treat his pain today?

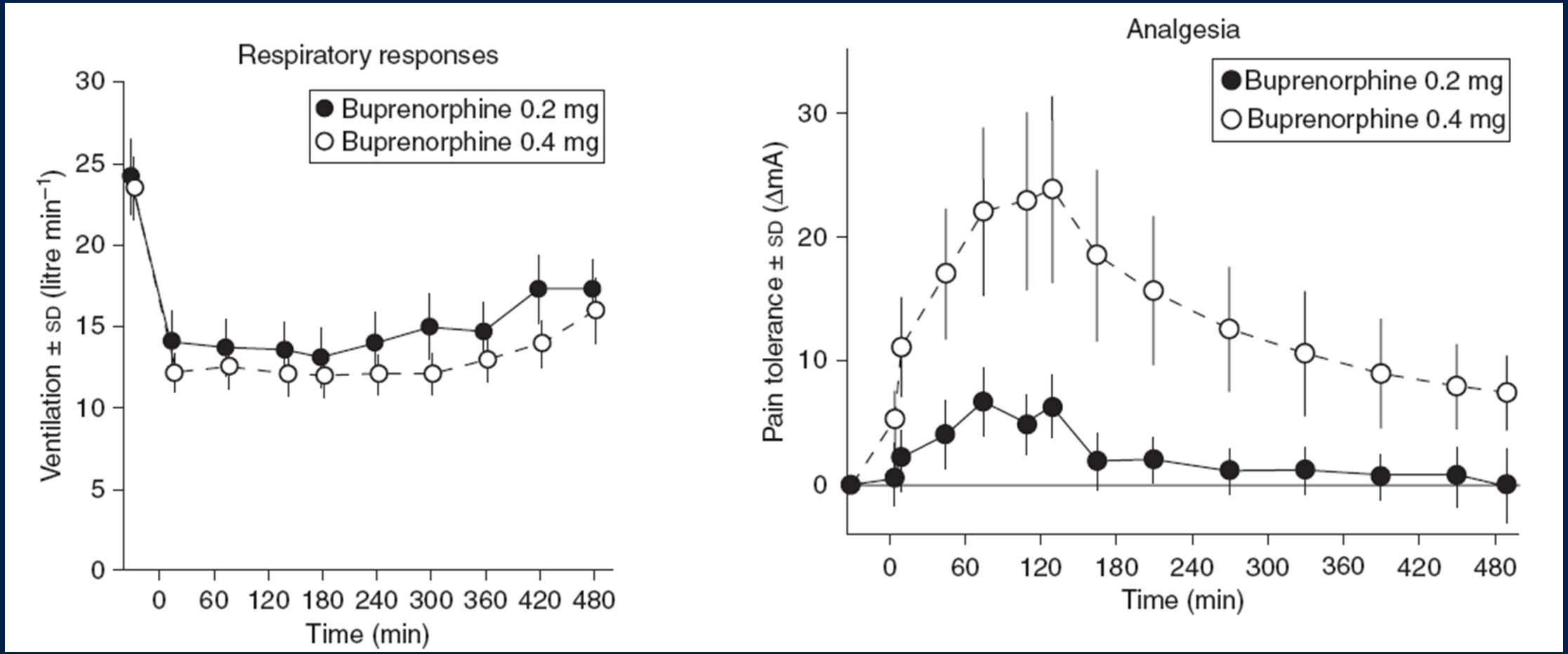
- Keep bup-nx dose the same and divide it up during the day
- Increase bup-nx dose +/- change in the interval
- Give short-course of short-acting opioids

Short-term pain management when on opioid agonist treatment (OAT)

- Analgesic effect ~6-8 hours
- Consider split dosing on TID or QID schedule
- Dose titration is also a possibility
- Ok to give short acting opioids in addition to OAT
  - Patients on OAT will have higher tolerance

Alford DP, Compton P, Samet JH. Ann Intern Med. 2006

Buprenorphine Safety and Pain



Dahan A, et al. Br J Anaesth. 2006

What can we do for this patient?

- Prescribe short opioid script, provide close follow-up, in conjunction with his daily oral buprenorphine dose
- We could increase patient's daily oral dosing of buprenorphine
  - (insurance could be barrier, may need prior auth for increased dose)
- We could split into more frequent daily (TID, QID) doses until surgery, to provide longer pain coverage

Audience poll: What do you tell Mark?

- Hold bup-nx for five days per surgery instructions
- Continue to take bup-nx with no modifications
- Take a smaller dose of bup-nx until surgery

Opioid Debt

- False Assumptions:
  - Often assumed that maintenance OAT treats pain
  - Bup-nx will interfere with pain control in patients undergoing surgery

- Patients physically dependent on OAT need to be maintained on daily equivalence before receiving analgesic effect from other opioids

Alford DP, Compton P, Samet JH. Ann Intern Med. 2006

Peri-Operative Pain Management

- Prior recommendations suggested stopping buprenorphine prior to surgery
- Assumption that buprenorphine blocked the effectiveness of additional opioids
- Limited evidence in perioperative medicine
  - Study found patients on buprenorphine receive higher doses of short acting opioids to achieve adequate analgesia, but experienced similar pain control, length of stay and functional outcomes

Kornfeld H, Manfredi L. Am J Ther. 2010, Hansen LE et al. J Arthroplasty. 2016

Where did 5-day rule come from?

- University of Michigan Protocol
- Stop bup-nx for 5 days before surgery, transition to short-acting full agonist opioids
- Ensure opioid receptor availability for pain management
- MI provider actually took back; no evidence

Stern E. Nurse Anesthesia Capstones. 2015, Ward EN, Quaye AN, Wilens TE. Anesth Analg. 2018

Peri-Operative Pain Management

- Most addiction medicine providers recommend continued use of buprenorphine when possible
  - No consensus on recommendations
  - Study outcomes have been conflicting
  - Some protocols recommend decreasing buprenorphine dose for high-risk surgeries

Elena

- 22 yo woman “found down” under a bridge. She required CPR and naloxone on site and was transferred to the hospital
- Exam notable for loud murmur
- Patient had previous episode of endocarditis at age 20, was treated with 4 weeks of intravenous antibiotics and had a bio-prosthetic valve replacement
- Repeat imaging is suggestive of recurrent prosthetic tricuspid valve endocarditis with septic pulmonary emboli

Elena

- During her first hospitalization she was treated with high dose opioids for “acute pain” and discharged with instructions stating ”do not inject drugs again.”
- Once opioid prescription ended, had residual pain and returned to use
- Using 20-30 bags IV heroin a day prior to admission
  - Last use approximately 36 hours prior
  - Urine drug screen positive for fentanyl and heroin metabolites

Elena

- Primary team currently struggling to manage her pain
- They anticipate repeat tricuspid valve repair tomorrow
  - Other consulting pain teams advised avoiding opioids given “history of OUD”
- Addiction medicine team consulted for recommendations on pain management now and post-operatively

Elena

On physical exam:

- 92% O2 sat; P 135 BP 130/95 T 39.5
- COWS score: 1

- Sweating, grimacing in pain as you walk in the room
- Swollen, erythematous right knee on exam
- Healed sternal incision, pain with inspiration
- 3 left rib fractures (from CPR) with splinting and pain with inspiration

Audience poll:

- How should you approach her pain control?
  - Optimize non-opioid analgesics
  - Use conventional analgesics, including opioids, often at higher doses
  - Offer medications to treat opioid use disorder (e.g. methadone, buprenorphine-naloxone)
  - Consider nerve blocks or other interventional strategies
  - All of the above

Recommendations for pain control

- Acknowledge patient's pain and offer reassurance
- Offer medications to treat opioid use disorder (e.g. buprenorphine-naloxone, methadone) as adjunct
- Optimize non-opioid analgesics for symptomatic management
- Use opioid analgesics, often at higher doses because of cross-tolerance
- Consider injections or other interventions (e.g. nerve blocks, lidocaine patch)

Recommendations for pain control

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Tailor treatment to where people are

"Meet people where they are at, but do not leave them where they are at."

- Have patient-centered conversations
  - What are patient's primary goals
  - Recognize this is just start of conversation for hospitalized patients
- Use motivational interviewing and non-judgmental techniques

Elena

- Does not plan to continue using heroin/fentanyl when she leaves hospital
  - Feels like this was big wake up call
  - Motivated to get back ”on my feet and take care of my daughter”
- Not sure she agrees with medication for OUD (MOUD) as she feels it is “replacing one drug with another”
  - Feels confident she will be successful without MOUD because she is motivated
- Wants to focus on pain control now and after surgery

Recommendations for pain control

- Acknowledge patient's pain and offer reassurance
- Offer medications to treat opioid use disorder (e.g. buprenorphine-naloxone, methadone) as adjunct
- Optimize non-opioid analgesics for symptomatic management
- Use opioid analgesics, often at higher doses because of cross-tolerance
- Consider injections or other interventions (e.g. nerve blocks, lidocaine patch)

Optimizing non-opioid adjuncts

- Perioperative use of gabapentin promotes opioid cessation after surgery and decreases duration of post-operative opioid use
  - 1200 mg preoperatively and 600 mg TID post-operatively
  - Effect via voltage-gated Ca channels in CNS

- Optimize anti-inflammatories and muscle relaxants
  - Ibuprofen/ketorolac and acetaminophen
  - Cyclobenzaprine or methocarbamol
  - Scheduled

Hah, et al, *JAMA Surg*, 2018

Ketamine to treat post-operative pain

- A noncompetitive *N*-methyl-d-aspartate (NMDA) receptor antagonist
- Analgesic action due to NMDA receptor antagonism in the brain and spinal cord
- NMDA receptor involved in amplification of pain signals, the development of central sensitization, and opioid tolerance

Bell and Kalso, Pain Rep, 2018: Haller, et al, Anethes, 2002; Balzer, et al,Acad Emer Med, 2020

Ketamine to treat post-operative pain

- Anti-inflammatory effects (reducing IL-6 in surgical patients)
- Side-effects: high doses can cause dissociation, transient tachycardia and hypertension
- Dosing range:
  - Bolus: up to 0.35 mg/kg IV push
  - Initial infusion: 0.1 mg/kg to 0.5 mg/kg per hour
  - Maintenance: Not to exceed 1 mg/kg per hour

Bell and Kalso, Pain Rep, 2018: Haller, et al, Anethes, 2002; Balzer, et al,Acad Emer Med, 2020

Recommendations for pain control

- Acknowledge patient's pain and offer reassurance
- Offer medications to treat opioid use disorder (e.g. buprenorphine-naloxone, methadone) as adjunct
- Optimize non-opioid analgesics for symptomatic management
- Use opioid analgesics, often at higher doses because of cross-tolerance
- Interventional pain injections (nerve blocks, lidocaine, etc)

"It just hurts"

- Opioid-induced tolerance
  - Lack of response to a drug
  - Need higher doses of drugs to receive same effect
  - Cross-tolerance

- Opioid-induced hyperalgesia
  - Paradoxical increase in sensitivity to painful stimuli
  - Driven by neuro-plastic changes to pain perception→ sensitivity

Grider & Ackerman, Exp Rev of Clinical Pharm, 2008

General principles for opioid tx in patient with OUD

- Use more potent opioids with shorter dosing intervals compared to opioid-naïve patients
- Schedule continuous opioids for better long-acting pain control
- Recognize maintenance agonist does not provide adequate analgesia

Alford , Compton, Samet, Ann Intern Med, 2006

Elena

- Had been getting 5-10 mg of oxycodone q4h with untreated 10/10 pain plus opioid withdrawal symptoms
- Started on 20 mg q4h of oxycodone with 0.5 mg IV hydromorphone q3h prn severe pain
  - Feels this takes the edge off her pain and lets her get some. sleep
- Scheduled for surgery at 8 AM tomorrow

Recommendations for pain control

- Acknowledge patient's pain and offer reassurance
- Offer medications to treat opioid use disorder (e.g. buprenorphine-naloxone, methadone) as adjunct
- Optimize non-opioid analgesics for symptomatic management
- Use opioid analgesics, often at higher doses because of cross-tolerance
- Consider injections or other interventions (e.g. nerve blocks, lidocaine patch)

Elena

- She received a nerve block along her sternal incision for 48 hours
- She received ketamine for a total of 72 hours
- Her acetaminophen 1g QID was continued
- Her opioid regimen was increased to 20 mg q3h RTC plus 1 mg hydromorphone q3h prn severe pain post-operatively
- 3 days later, her opioid regimen was tapered to 20 mg q4h RTC and she reported improvement in pain
- You re-introduce the idea of MOUD

Hospitalization as window of opportunity

- Patients describe hospitalization as a time of high motivation because of concerns related to mortality and interruption in regular substance use
- MOUD is efficacious in retaining people in treatment, suppressing illicit opioid use and decreasing craving
- MOUD initiation in hospital is feasible and increases engagement in treatment after hospitalization
- Use as part of broader patient-centered conversations

Velez, et al, J Gen Intern Med, 2017; Mattick, et al, Coch Data Syst Rev, 2014; Liebschutz, et al, JAMA Intern Med, 2014

Elena

- Expresses interest in starting buprenorphine-naloxone
- Concerned about ”getting super sick” but also wants to avoid untreated pain or opioid withdrawal
- What strategies to safely start buprenorphine-naloxone?

Terminology

- Induction
  - Find lowest effective dose that controls withdrawals symptoms and limits cravings
  - Not necessarily opioid-free during this time

- Maintenance
  - Optimal dose that supports patients being free of illicit opioids
  - Prevents withdrawal and controls cravings
  - Safe for long-term use

Our typical buprenorphine induction

- Hold full opioid agonists—monitor for signs of withdrawal
  - Clinical opioid withdrawal scale (COWS) 12-16
  - Typically 12 hours after short-acting opioid (heroin) and 18 hours after long -acting opioid (oxycodone); methadone hold 48-72 hrs.
- When mild-moderate withdrawal symptoms present, give 4 mg buprenorphine dose
- Re-dose 4mg q3-4 hr

Barriers with traditional induction approaches in hospitalized patients

- Requires frequent reassessment and dosing based on symptoms
  - Challenging on medicine floors
- Need to experience withdrawal symptoms prior to first dose
  - Hard to sit with withdrawal in hospital setting even with comfort meds
  - Difficult if also experiencing acute or chronic pain in addition to withdrawal
- Can be challenging for patients who are ambivalent to commit to induction process

GOAL of induction: avoid precipitating acute withdrawal

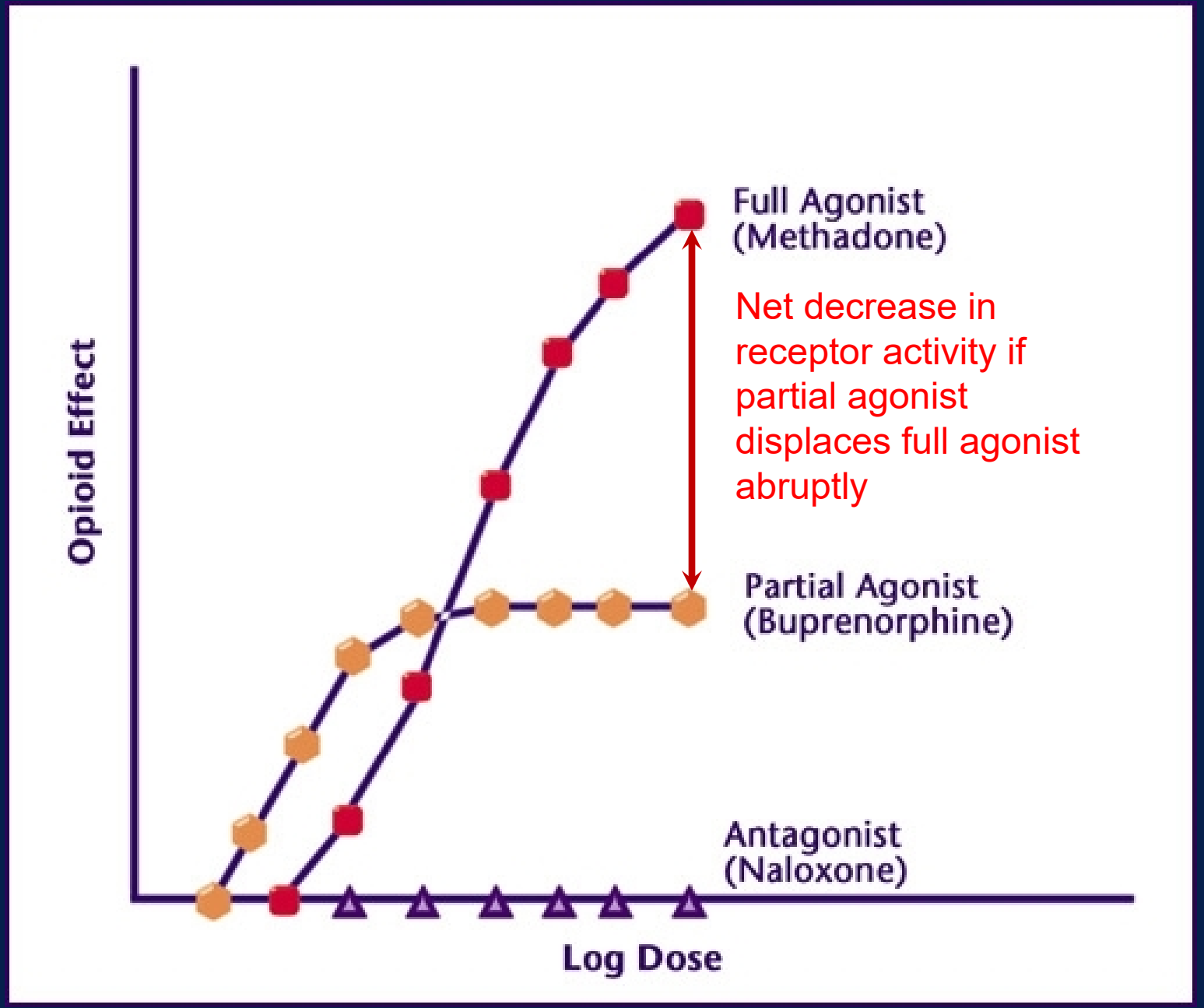

Figure from: https://www.naabt.org/education/technical_explanation_buprenorphine.cfm

General principles of micro-dosing induction

- Allow patients to continue full opioid agonists as starting small doses of buprenorphine
- Start with small doses of buprenorphine to gradually displace full opioid agonist
  - Monitor for signs of opioid withdrawal during induction
- Gradually increase the amount of buprenorphine patients receive
- Continue full opioid agonist during induction period
- Start to wean full opioid agonists as tolerated after buprenorphine maintenance dose achieved
- Limited evidence: no comparative-effectiveness trials comparing traditional induction to micro-dosing induction protocols; small case-series reporting protocols

Terasaki, Smith, Calcaterra, Pharmacotherapy, 2019

SELECT BUPRENORPHINE MICRODOSING REGIMENS PREVIOUSLY PRESENTED OR PUBLISHED[a]

	Case 1 (outpatient setting)[8]		Case 1 (inpatient setting)[12]		Case 2 (inpatient setting)[12]		>80 MME protocol (unspecified setting)[15]		Vancouver area (unspecified setting)[17]		18-day protocol (outpatient setting)[24]	
Day	Buprenorphine	Full agonist: heroin	Buprenorphine	Full agonist: hydromorphone	Buprenorphine	Full agonist: hydromorphone	Buprenorphine	Full agonist	Buprenorphine	Full agonist	Buprenorphine	Full agonist
1	0.2 mg SL	2.5 g IN	0.25 mg SL every 4 hrs (1 mg total)	11 mg IV total	0.5 mg SL every 3 hrs (2.5 mg total)	26 mg PO	20 μg/hr patch	Full dose	0.5 mg	Full dose	0.2 mg SL	Full dose
2	0.2 mg SL	2.0 g IN	0.5 mg SL every 4 hrs (2.5 mg total)	15 mg IV	1.0 mg SL every 3 hrs (8 mg total)	24 mg PO	Remove patch, give 2 mg SL every 2 hrs up to 8 mg	Full dose	0.5 mg	Full dose	0.2 mg × 2 SL	Full dose
3	0.8 + 2.0 mg SL	0.5 g IN	1.0 mg SL every 4 hrs (5 mg total)	15 mg IV	12 mg/day	Stop	Can titrate up to 16 mg SL	Full dose	1.0 mg	Full dose	0.2 mg × 3 SL	Full dose
4	2.0 + 2.5 mg SL	1.5 g IN	2.0 mg SL every 4 hrs (8 mg total)	4 mg IV			Can titrate up to 24 mg SL	Full dose	1.0 mg	Full dose	0.8 mg SL	Full dose
5	2.5 + 2.5 mg SL	0.5 g IN	16.0 mg/day	Stop			Continue	Taper or stop	1.5 mg	Full dose	1.2 mg SL	Full dose
6	2.5 + 4.0 mg SL	Stop							1.5 mg	Full dose	1.6 mg SL	Full dose
7	4.0 + 4.0 mg SL								2 mg	Full dose	2 mg SL	Full dose
8	4.0 + 4.0 mg SL								4 mg	Full dose	2.8 mg SL	Full dose
9	8.0 + 4.0 mg SL								6 mg	Full dose	3.6 mg SL	Full dose
10									8–12 mg	Full dose	4.4 mg SL	Full dose
11									16 mg	Stop	5.2 mg SL	Full dose
12											6.4 mg SL	Full dose
13											8 mg SL	Full dose
14											10 mg SL	Full dose
15											12 mg SL	Stop
16											16 mg SL[b]	
17											20 mg SL[b]	
18											24 mg SL[b]	

IN = intranasally; MME = morphine milligram equivalent; PO = orally; SL = sublingually.

Permission was obtained from the corresponding authors of each cited protocol to publish or republish their work.

[a]Buprenorphine was either administered as monotherapy or as a combination product with naloxone.

[b]Suggested up-titration

Terasaki, Smith, Calcaterra, Pharmacotherapy, 2019

For Elena:

- Day 1: Started 20 mcg buprenorphine patch
  - Continued on 20 mg oxycodone q4h (but made prn)
- Day 2: 24 hours after patch placed, given 2 mg of SL buprenorphine—no withdrawal
  - Given total of 6 mg (dosed as 2 mg q4h--holding for over sedation or withdrawal)
  - Remove patch at 48 hours
- Day 3: Received 8 mg BID buprenorphine-nx
- Day 4: Patient-centered discussion on opioid wean
  - Tapered off all opioids prior to discharge to SNF on Day 9

Elena

- Patient successfully transitioned to 8 mg BID buprenorphine-nx prior to hospital discharge
- Currently in sustained remission 8 months following hospital discharge

Back to our first case….

Laura

- 42 yo woman with residual low back pain that failed multiple treatment modalities. She was started on extended-release morphine 10 years ago by prior provider
  - Dose up-titrated to 45 mg extended-release morphine BID and 15 mg QHS (60 mg/day)
- She feels her current regimen is effective at treating her pain and is upset she may not be able to continue it
- Endorsing concerning behaviors suggestive of OUD

SELECT BUPRENORPHINE MICRODOSING REGIMENS PREVIOUSLY PRESENTED OR PUBLISHED[a]

	Case 1 (outpatient setting)[8]		Case 1 (inpatient setting)[12]		Case 2 (inpatient setting)[12]		>80 MME protocol (unspecified setting)[15]		Vancouver area (unspecified setting)[17]		18-day protocol (outpatient setting)[24]	
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9	8.0 + 4.0 mg SL								6 mg	Full dose	3.6 mg SL	Full dose
10									8–12 mg	Full dose	4.4 mg SL	Full dose
11									16 mg	Stop	5.2 mg SL	Full dose
12											6.4 mg SL	Full dose
13											8 mg SL	Full dose
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[b]Suggested up-titration

Terasaki, Smith, Calcaterra, Pharmacotherapy, 2019

Outpatient microdosing induction

- Utilized COWS assessments in office
- Set expectations: 7-12 day process
- Slowly up-titrate bup-nx film or tablet (0.5mg daily -> BID)
- Can consider buprenorphine patch for mcg dosing
  - Insurance can be a barrier
  - Place patch on patient two days prior to provider visit
- After induction complete, can titrate medication using flexible dosing, address pain and cravings

Brar R et al. Drug Alcohol Rev. 2020,
Randhawa PA et al. CMAJ. 2020

Example Micro-Dosing

Box 1: Outpatient microdosing induction schedule for buprenorphine–naloxone

- Day 1: 0.5 mg once a day
- Day 2: 0.5 mg twice a day
- Day 3: 1 mg twice a day
- Day 4: 2 mg twice a day
- Day 5: 3 mg twice a day
- Day 6: 4 mg twice a day
- Day 7: 12 mg (stop other opioids)

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Final Takeaways/Summary

- Opioid use disorder is diagnosed the same way in patients with and without chronic pain
- Buprenorphine split dosing/titration can be helpful for patients on maintenance treatment with acute pain
- Inpatient and outpatient bup microdosing are novel strategies to prevent withdrawal and manage pain in patients starting buprenorphine treatment

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