Evidence-Based Use of Buprenorphine

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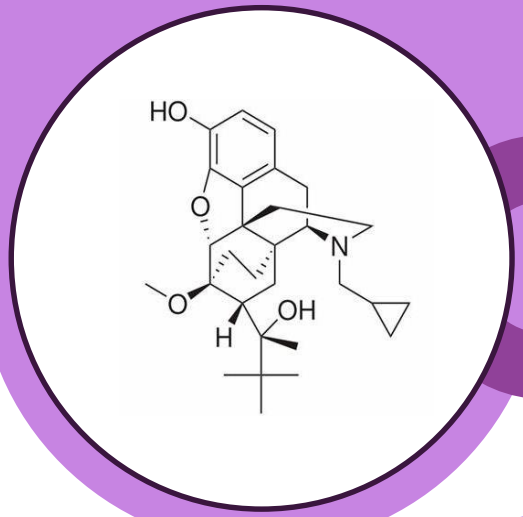
01

Objectives & Introduction to Buprenorphine

Objectives

- Describe a framework for acute pain management for patients on BUP
- Compare available strategies for starting BUP in patients with OUD
- Identify patients who may beneft from chronic pain management with BUP
- Integrate evidence-based use of BUP into everyday clinical practice

Buprenorphine



Buprenorphine is an opioid used to treat opioid use disorder, acute pain, and chronic pain

Buprenorphine's receptor activity includes:

- **Partial agonism** with very high binding affinity for the μ-opioid receptor
- **Antagonism** with high binding affinity for the δ- and κ-opioid receptors
- **Agonism** with low binding affinity for the opioid receptor-like 1 receptor

Gudin J, Fudin J. A Narrative Pharmacological Review of Buprenorphine. *Pain Ther*. 2020;9(1):41-54.

02

A Case-Based Approach to Buprenorphine

Case 1: BUP & Acute Pain

Barb Dwyer (26/F)

Chief Complaint: MVC w/ multiple fractures requiring ORIF

PMH: HTN, OUD

Home Medications

- Lisinopril 20 mg, daily
- Norethindrone/Ethinyl Estradiol 1/0.02 mg, daily
- Suboxone Sublingual Film® 8-2 mg, twice daily

Why is this patient on Buprenorphine?

Should the Buprenorphine be continued in the hospital?

How should her acute pain be managed?

What about perioperative pain management?

Opioid Use Disorder

A problematic pattern of opioids use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

Impaired Control	1. Larger amounts or over a longer period than intended 2. 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, use, or recover from opioids
Social Impairment	4. Craving, or a strong desire or urge to use opioids 5. Failure to fulfill major role obligations at work, school, or home 6. Continued opioid use despite social or interpersonal problems 7. Social, occupational, or recreational activities are given up or reduced because of opioid use.
Risky Use	8. Use in situations in which it is physically hazardous 9. Continued use despite harm
Physical Dependence	10. Tolerance 11. Withdrawal

Buprenorphine for OUD

Treatment Retention

- BUP, compared to placebo, improves retention in treatment at low, medium, and high doses
- Compared to methadone, BUP has lower retention rates but similar rates of abstinence among those retained

Drug Use

- BUP, compared to placebo, decreases the number of morphine-positive UDS
- Patients with BUP-positive UDS are less likley to be positve for other opioids like heroin or fentanyl

Overdose

- BUP, compared to no MOUD, decreases rates of all-cause mortality, with continued benefit after discontinuation
- BUP provides some risk mitigation against full agonist opioid overdose including fentanyl

Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane database of systematic reviews. 2014. (2).
Schwartz, R. P., et al. (2013). Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995-2009. American journal of public health, 103(5), 917–922.
Saloner, B., Whitley, P., LaRue, L., Dawson, E., & Huskey, A. (2021). Polysubstance Use Among Patients Treated With Buprenorphine From a National Urine Drug Test Database. JAMA network open, 4(9), e2123019.
Ma, J., et al.. (2019). Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. *Molecular psychiatry*, *24*(12), 1868–1883.

BUP and Mortality

Mortality Risk During And After Opioid Substitution Treatment:

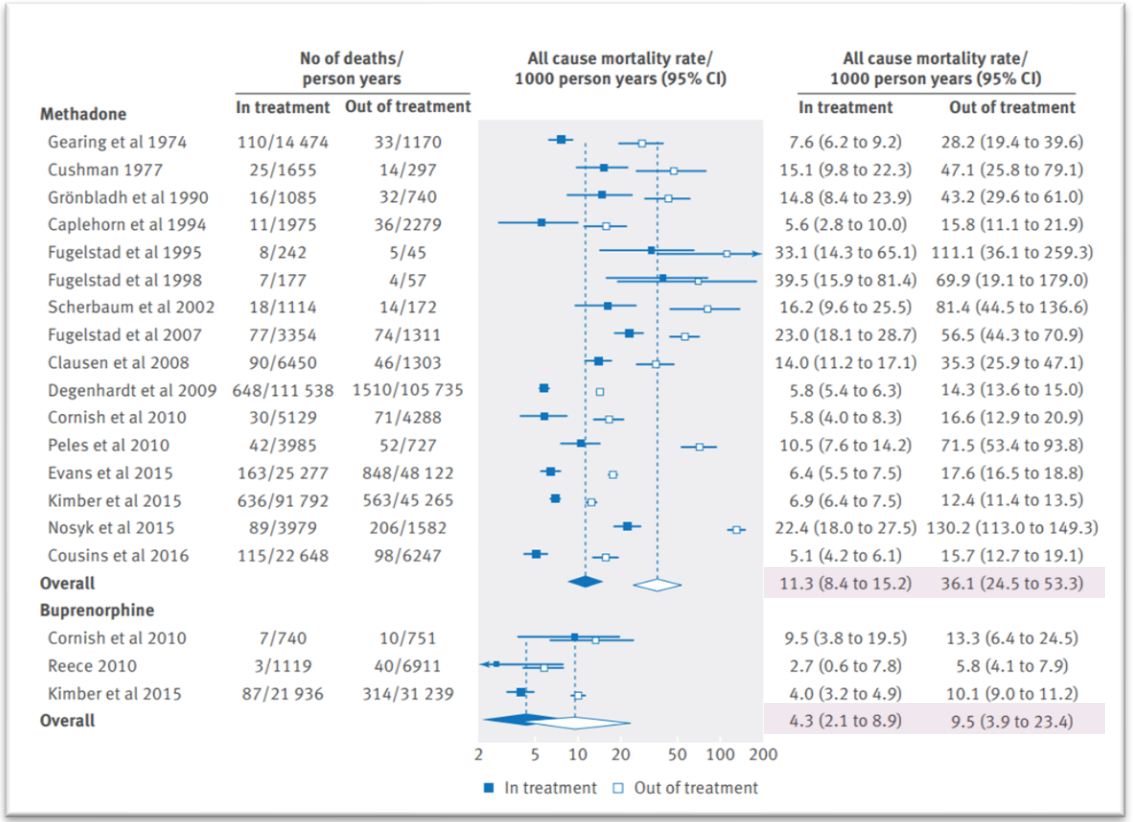
Systematic Review and Meta-analysis of Cohort Studies

Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L., Ferri, M., & Pastor-Barriuso, R. (2017). *BMJ (Clinical research ed.)*, *357*, j1550.

Pooled All Cause Mortality Rates Per 1000 Person Years

Methadone *vs.* No Rx:
11.3 *vs.* 36.1

Buprenorphine *vs.* No Rx:
4.3 *vs.* 9.5



BUP for OUD: Formulations

Monoproduct

Contain only Buprenorphine, which *may* increase risk of diversion or misuse

Idea:
Monoproduct Buprenorphine will be used recreationally

Reality:
The majority of non-prescribed Buprenorphine use is for therapeutic indications

Examples:
Subutex®

Combination

Contain BUP and Naloxone which is thought to act as a *deterrent* for misuse

Idea:
Naloxone will only be absorbed if used IV, not when taken by mouth

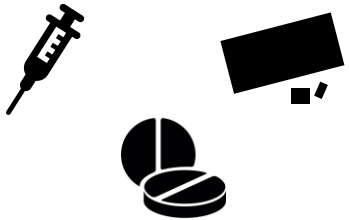
Reality:
A small portion of Naloxone is absorbed when taken by mouth *(Intolerance, Liver Disease)*

Examples:
Suboxone®, Zubsolv®

Injectables

Contain only Buprenorphine with goal of increasing medication adherence and decrease risk of diversion

Examples:
Sublocade®, Brixadi®



Poliwoda, S., Noor, N., Jenkins, J. S., Stark, C. W., Steib, M., Hasoon, J., Varrassi, G., Urits, I., Viswanath, O., Kaye, A. M., & Kaye, A. D. (2022). Buprenorphine and its formulations: a comprehensive review. Health psychology research, 10(3), 37517.

Management for Surgical Patients

Options

1. **Discontinue BUP**
   - Due to concern for ceiling effect of BUP's analgesic properties and high receptor affinity leading to potential competition with full agonists

2. **Reduce BUP Dose** *(8-16 mg)*
   - Potential to increase number of opioid receptors available to full agonits

3. **Continue BUP without Dose Reduction**
   - Assumes analgesic benefit of BUP in addition to use of full opioid agonists

Considerations

Predisposes patients with OUD to an increased risk of relapse and overdose with BUP discontinuation

May benefit patients receiving high-dose BUP who are undergoing MAJOR procedures

Emerging evidence supports ability to achieve sufficient analgesia despite BUP

Perioperative BUP Management

Treating Perioperative & Acute Pain in Patients on BUP: Narrative Literature Review & Practice Recommendations

Buresh, M., et al. (2020). Journal of general internal medicine, 35(12), 3635–3643.

- In 12 of the 15 cases where buprenorphine was continued (5 case reports, plus 8 cases from case series), **adequate pain control was achieved**

American Society of Anesthesiologists

AAPM American Academy of Pain Medicine

ASRA

U.S. Department of Veterans Affairs

ashp

ASAM American Society of Addiction Medicine

*"Buprenorphine **should not be** routinely **discontinued** in the perioperative setting"*

Kohan, L., et al. (2021). BUP management in the perioperative period: educational review and recommendations from a multisociety expert panel. Regional anesthesia and pain medicine, 46(10), 840–859.

Acute Pain Management

Buprenorphine

Consider splitting BUP dose into **Q6-8h** dosing or increasing total daily dose up to **32 mg**

Non-Opioid Medications	
NSAIDs	Ketamine
Acetaminophen	IV Lidocaine
Duloxetine	Alpha-Agonists
Gabapentinoids	Dexmedetomidine
Diclofenac	Regional or Neuraxial Blocks

Buresh, et al. (2020). Treating Perioperative and Acute Pain in Patients on Buprenorphine: Narrative Literature Review and Practice Recommendations. *Journal of general internal medicine*, *35*(12), 3635–3643.

Opioid Agonists

Patients with moderate to severe pain (pain score 5+) will likely need short-acting full agonist opioids to address acute and/or immediate postoperative pain

- In these cases, continue the patient's home BUP dose and select **one short-acting full agonist** (PO/IV) → reassess and titrate!
    - Starting doses **will be higher** than opioid-naive patients
- Consider transition to **IV PCA** if pain cannot be controlled with PO or IV options (PCA with boluses only)

Discharge regimens should be individualized, with consideration of expected duration of pain, patient stability, and ability to take opioids safely

Buresh, et al. (2020). Treating Perioperative and Acute Pain in Patients on BUP: Narrative Literature Review and Practice Recommendations. Journal of general internal medicine, 35(12), 3635–3643.

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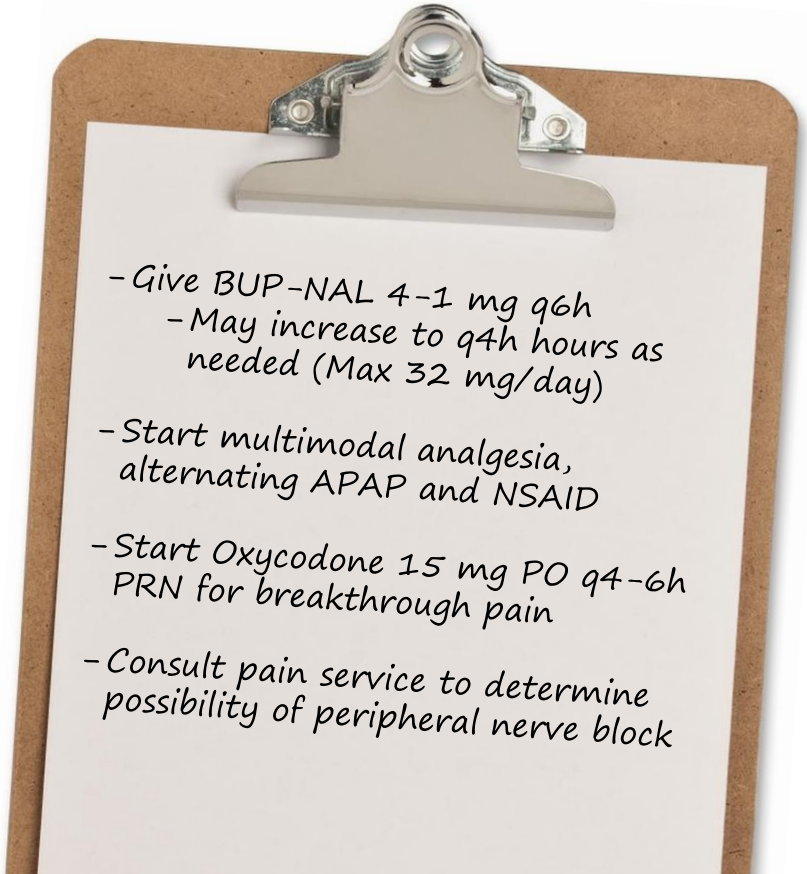


Key Points for Acute Pain

BUP Works for OUD

BUP improves treatment retention, decreases drug use, and reduces the risk of drug overdose deaths

Continuation as a Priority

Primary literature and major medical organizations support continuation of BUP whenever possible

Pain Management

In addition to adjusting BUP dose and frequency, using a multimodal approach (*including full-agonist opioids*) is best

Case 2: Starting BUP

Justin Time (35/M)

Chief Complaint: Level 1 trauma w/ thermal injuries after house fire. Interested in starting BUP

PMH: HIV, OUD, Hypothyroidism

Inpatient Medications

- Levothyroxine 88 mcg, daily
- Biktarvy® 50 mg/200 mg/25 mg, daily
- Hydromorphone PCA (0.2 mg q10 minutes)
- Acetaminophen 650 mg every 4 hours PRN
- Enoxaparin 40 mg SC, daily

Does he need to be in opioid withdrawal before starting BUP?

Is the patient at risk for precipitated withdrawal?

How do I choose which induction method to use?

What dose of BUP should the patient be discharged on?

BUP Initiation Strategies

"Micro"- dosing

"Micro"- dosing refers to the use of low-dose BUP while opioids are continued

Continuing full opioid agonists supports BUP initiation by maintaining the level of opioid receptor activation needed to match a patient's baseline

Patients are administered or self-administer full agonist opioids during a multiday dose escalation of low-dose BUP

Standard

Standard induction dosing refers to the use of typical BUP doses after opioid discontinuation

Waiting for the development of withdrawal symptoms and administering standard doses aims to minimize the risk of precipitated withdrawal

After a period of abstinence leading to mild-moderate withdrawal, BUP is started at 2-8 mg and increased over several days

"Macro"- dosing

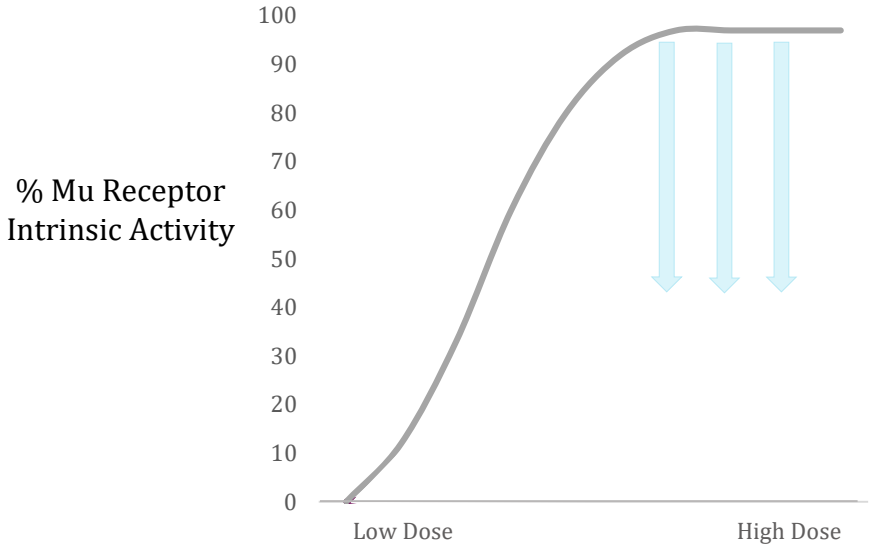
"Macro"- dosing refers to the use of rapid high-dose BUP after opioid discontinuation

Increasing initial doses of BUP beyond 8 mg will result in increased agonist opioid receptor activation and strengthened opioid blockade

After a period of abstinence leading to mild withdrawal, BUP is escalated rapidly to 16–32 mg 1 or 2 initial doses

Weimer, M. B., et al. (2023). ASAM Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-potency Synthetic Opioids. *Journal of addiction medicine*, 10.1097/ADM.0000000000001202.

Precipitated Withdrawal



Full Opioid Agonist

*Results in a **net decrease** in receptor activity if a partial agonist displaces full agonist*

Partial Opioid Agonist

Drug	K_i (nM)	Drug	K_i (nM)	Drug	K_i (nM)
Tramadol	12,486	Hydrocodone	41.58	Butorphanol	0.7622
Codeine	734.2	Oxycodone	25.87	Levorphanol	0.4194
Meperidine	450.1	Diphenoxylate	12.37	Oxymorphone	0.4055
Propoxyphene	120.2	Alfentanil	7.391	Hydromorphone	0.3654
Pentazocine	117.8	Methadone	3.378	Buprenorphine	0.2157
		Nalbuphine	2.118	Sufentanil	0.1380
		Fentanyl	1.346		
		Morphine	1.168		

Volpe, D. A., et al. (2011). selected opioid drugs. *Reg*

Managing Precipitated Withdrawal

There are **three** potential responses to severe precipitated withdrawal:

1. **Reassurance and Symptomatic Medication**
   - Symptomatic medications can be added based on the symptom that occur
     - Examples: Nausea (*Ondansetron*), Anxiety (*Clonidine*)

2. **Adding Further Buprenorphine**
   - Goal is to increase opioid agonist effect by escalating BUP dose
   - Typically achieved by administering 8-16 mg of additional BUP

3. **Abandoning Buprenorphine Treatment**
   - Considered based on patient preference and failure of alternative methods to alleviate withdrawal symptoms

Precipitated Withdrawal is characterized by the rapid onset of opioid withdrawal symptoms (*aches, nausea vomiting, diarrhea abdominal cramps, dilated pupils, runny nose, yawning*) within 1–2 hours following the first dose of BUP, and gradually subsiding over the subsequent 6–24 h

Oakley, B., Wilson, H., Hayes, V., & Lintzeris, N. (2021). Managing opioid withdrawal precipitated by buprenorphine with buprenorphine. *Drug and alcohol review*, *40*(4), 567–571.
Spadaro, A., Long, B., Koyfman, A., & Perrone, J. (2022). Buprenorphine precipitated opioid withdrawal: Prevention and management in the ED setting. *The American journal of emergency medicine*, *58*, 22–26.

Justin Time (35/M) Hydromorphone PCA 0.2 mg q10 minutes

Standard Induction

The main objective is to wait for enough of the full-opioid agonist to be cleared that the patient begins to experience mild-moderate withdrawal

1. **Day 1:** Significantly decrease or discontinue the hydromorphone
2. **Day 2:** Start Suboxone® 2 mg-0.5 mg every 2 hours PRN for COWS ≥8
    - Change to Suboxone® 8 mg-2 mg BID when PRN doses tolerated

Buprenorphine should not be expected to cover acute pain needs in addition to the patients known opioid debt so **resuming a full-agonist** is reasonable

Inpatient or Outpatient

Need for Opioid Withdrawal

Suboxone®, Subutex®

1-3 Days for Stabilization

Justin Time (35/M) Hydromorphone PCA 0.2 mg q10 minutes

"Micro"-dosing

The main objective is to slowly displace hydromorphone from opioid receptors by introducing small amounts of buprenorphine

1. **Day 1:** Start Butrans® 20-40 mcg patch
2. **Day 2:** Start Suboxone® 2 mg-0.5 mg films every 4 hours x 4 doses
3. **Day 3:** Start Suboxone® 8 mg-2 mg film BID and *remove* Butrans® patch

Buprenorphine should not be expected to cover acute pain needs in addition to the patients known opioid debt so **continuing a full-agonist** is reasonable

Karavolis, Z. A., & Roy, P. J. (2022). Adapting Low-dose Buprenorphine Induction To Meet Patient Needs: A Pilot Study. *Drug And Alcohol Dependence Reports*, *5*, 100104.
Tang, V. Et Al. (2020). Case Series: Limited Opioid Withdrawal With Use Of TD BUP To Bridge To SL BUP In Hospitalized Patients. The American Journal On Addictions, 29(1), 73–

Inpatient or Outpatient

No Need for Opioid Withdrawal

Butrans®, Belbuca®, Suboxone® (*Cut*), Subutex® (*Split*)

3-10 Days for Stabilization

Justin Time (35/M) Hydromorphone PCA 0.2 mg q10 minutes

"Macro"-dosing

The main objective is to minimize the amount of time that a patient will be experiencing mild-moderate withdrawal by administering high BUP doses

1. **Day 1:** Significantly decrease or discontinue the hydromorphone
2. **Day 2:** Give Suboxone® 4 mg-1 mg once COWS ≥8
   - Administer 8 to 24 mg of Suboxone ® every 30-60 minutes with a maximum total BUP dose of ≤32 mg

Buprenorphine should not be expected to cover acute pain needs in addition to the patients known opioid debt so **resuming a full-agonist** is reasonable

Herring, A. A et al. (2021). High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder. *JAMA network open*, *4*(7), e2117128.

Inpatient or ED

Need for Opioid Withdrawal

Suboxone®, Subutex ®

≤2 hours for Stabilization

Choosing an Induction Method

"*Micro*"-dosing

Advantages

Opioid abstinence is not required before starting

Disadvantages

Most time-consuming method (3-10+ days to complete)

Standard Induction

Advantages

Most common and well-described technique

Disadvantages

Significant amount of time in opioid withdrawal

"*Macro*"-dosing

Advantages

Quick stabilization and limits amount of time in withdrawal

Disadvantages

Concerns with excess sedation or respiratory depression

Discharge Planning

Buprenorphine

The patient can be discharged on Suboxone® 8-2 mg films BID or transition to a long-acting injectable formulation

Follow-Up Care

The patient should be provided with a follow-up appointment with a person who can continue their BUP prescription

Harm Reduction

The patient should ideally leave the hospital with naloxone in hand in order as they have a high risk of overdose

Pain Regimen

Discharge regimens should consider expected pain duration, patient's stability, and their ability to take opioids safely

Case 2: Starting BUP

Justin Time (35/M)

Chief Complaint: Level 1 trauma w/ thermal injuries after house fire. Interested in starting BUP

PMH: HIV, OUD, Hypothyroidism

Inpatient Medications

- Levothyroxine 88 mcg, daily
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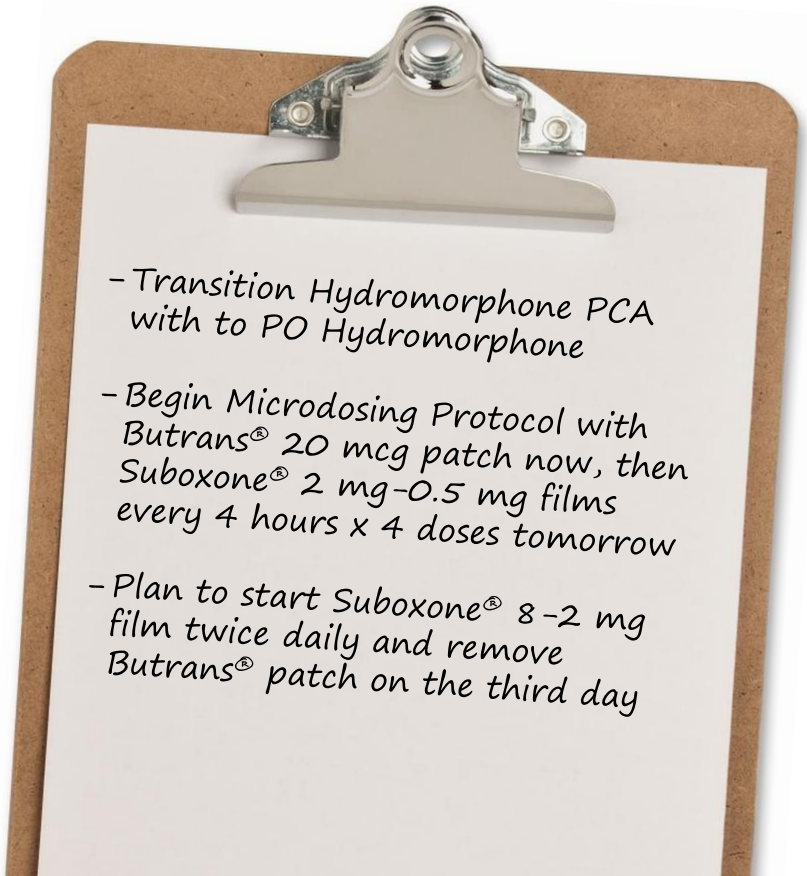


Key Points for Induction

Precipitated Withdrawal

While usually avoidable, precipitated withdrawal can be managed with additional BUP and comfort medications

Induction Strategies

Three main strategies exist for BUP induction, each with unique advantages and disadvantages

Discharge Planning

Patients who are newly initiated on BUP may require additional resources and support upon discharge

Case 3: BUP & Chronic Pain

Will Power (58/M)

Chief Complaint: Back pain

PMH: DM, HTN, COPD, CAD s/p stent, GERD, Gout, HCV-cirrhosis, DJD, spinal stenosis, neuropathy

Substance use History: 1 ppd x 55 years, Heroin, IDU, Cocaine, Alcohol- last use 1999

Home Medications

- Lisinopril
- Atenolol
- Metformin
- Inhalers
- Gabapentin
- Duloxetine
- Aspirin
- APAP
- Omeprazole

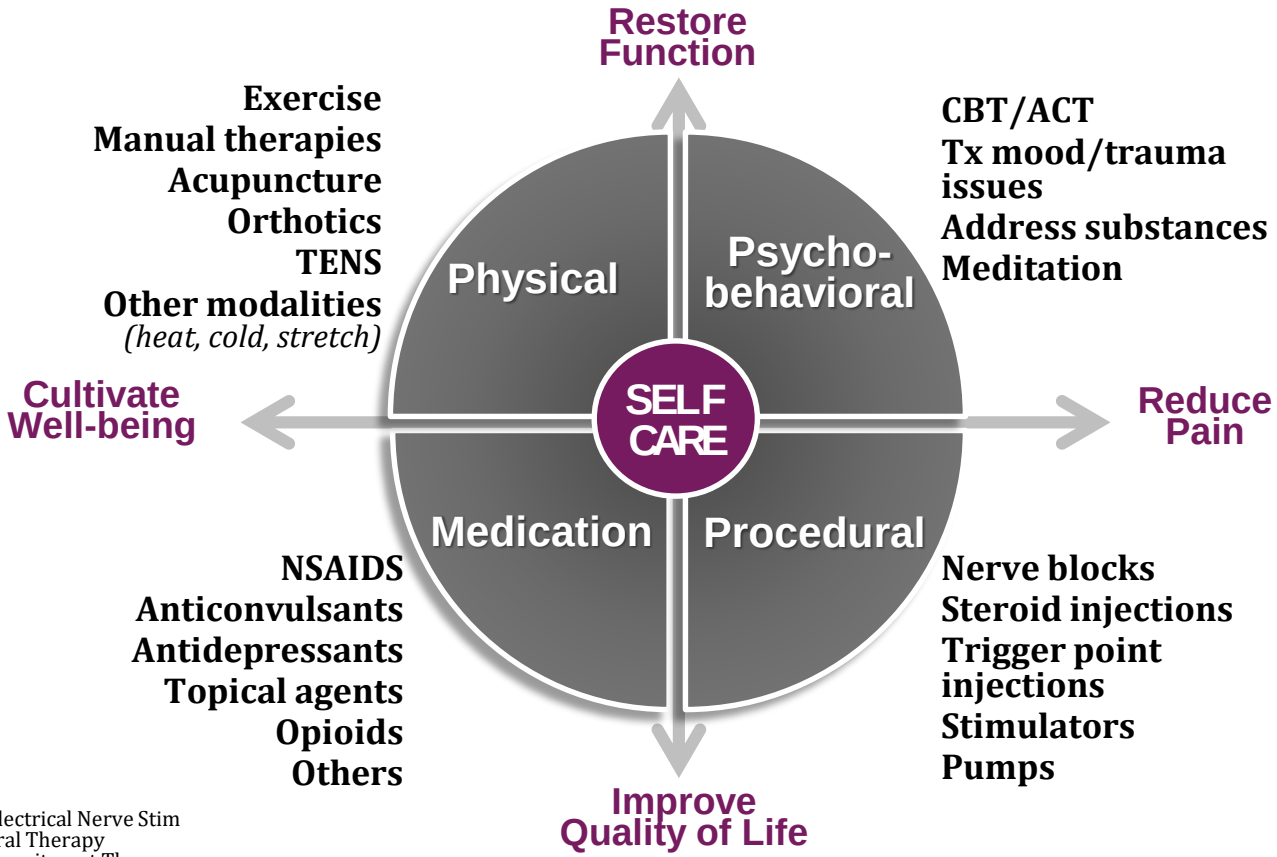
How can I get someone to take care of this patient's pain?

What pharmacological treatments might be available for this patient?

When would opioids be indicated in a patient with prior SUD?

If I did prescribe buprenorphine, are there specific formulations for pain?

Multidimensional Care



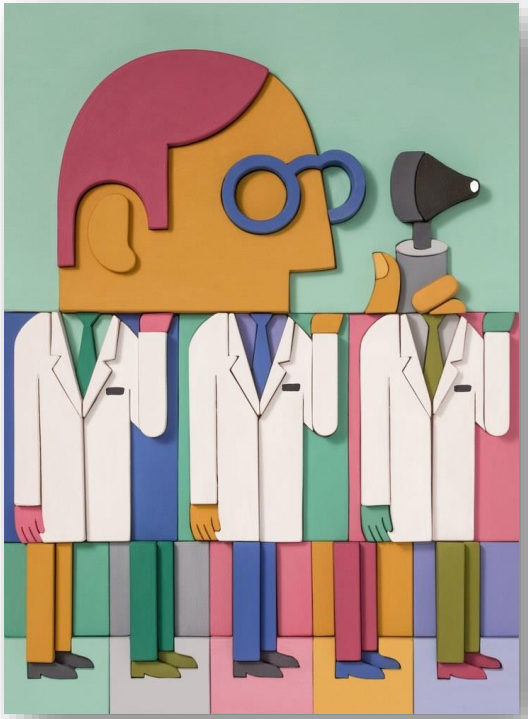
TENS Transcutaneous Electrical Nerve Stim
CBT Cognitive Behavioral Therapy
ACT Acceptance and Commitment Therapy

Case WP- Goals of Care

Realistic Expectations

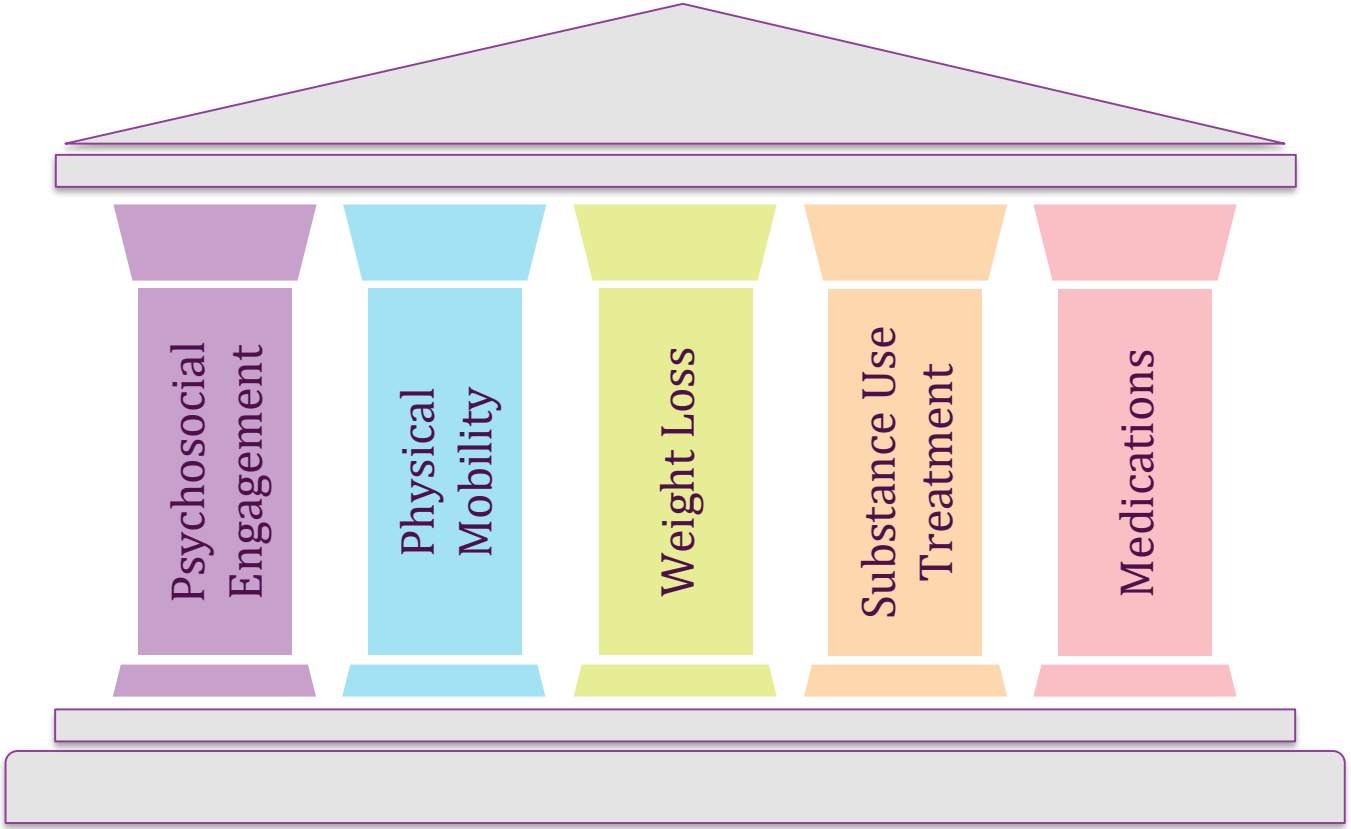
Incremental Care

Multimodal Treatment

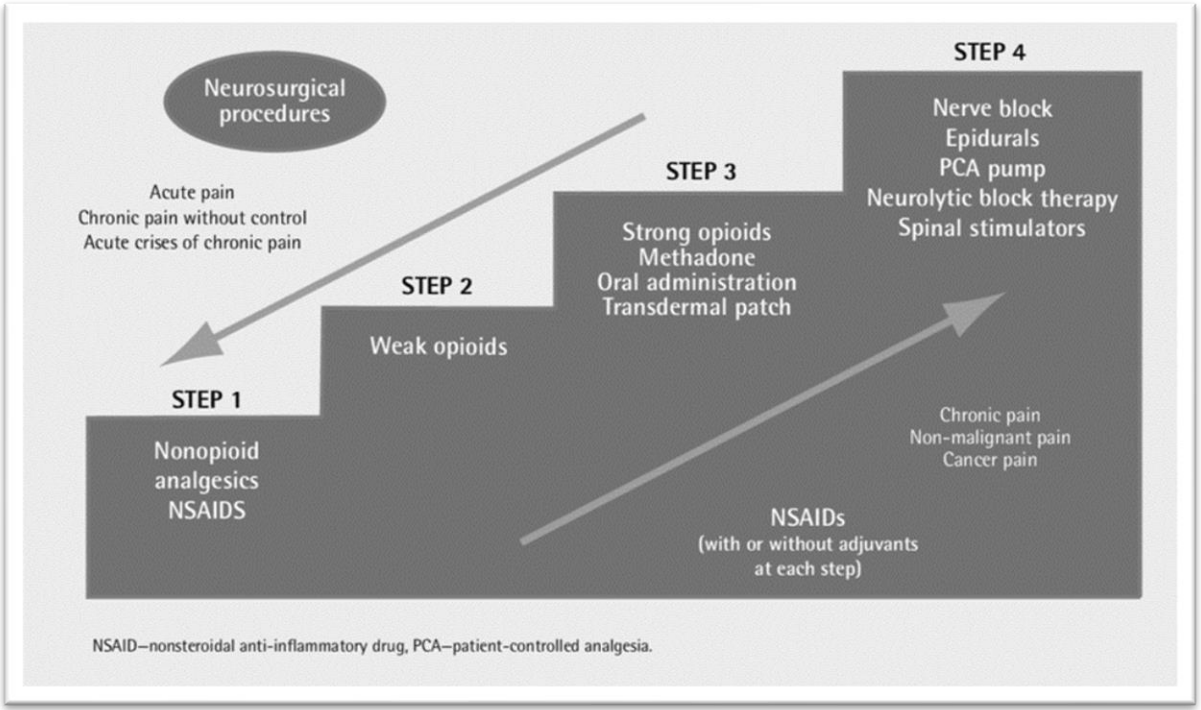


Gawande 2017 *New Yorker* “The Heroism of Incremental Care”

Five Pillars of Treatment



WHO Stepwise Pain Relief Ladder

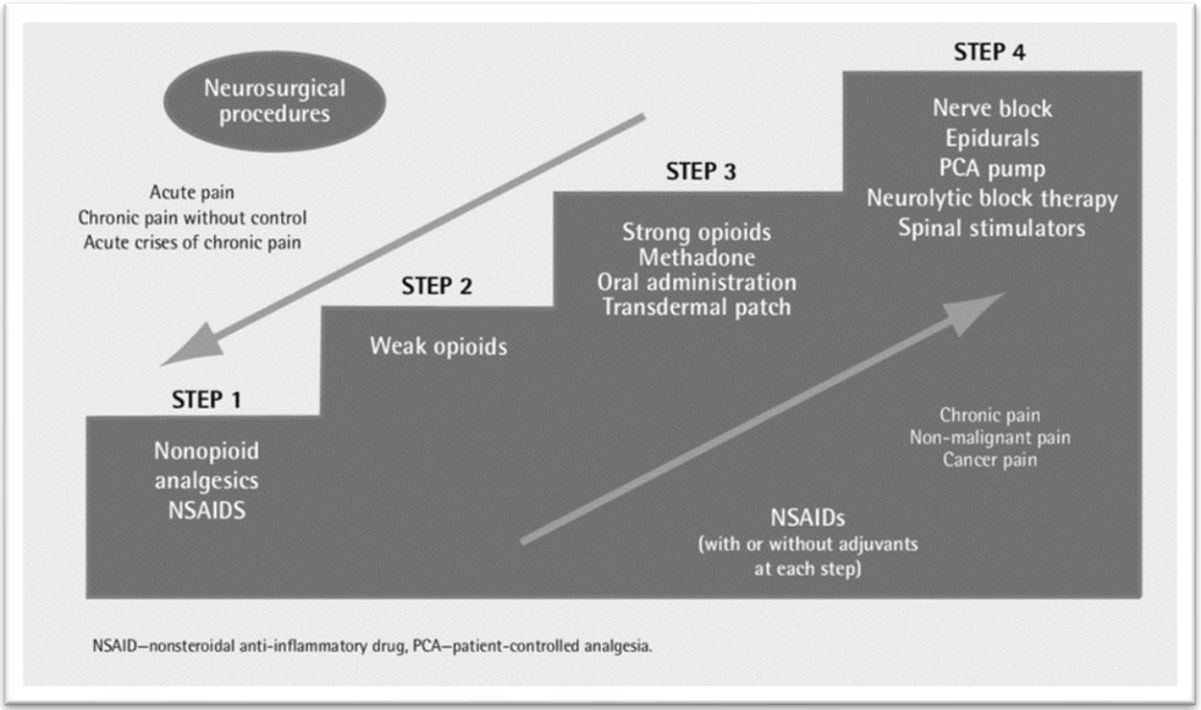


Step 1: Nonopioids

<u>Topicals</u>
Lidocaine Patch
NSAID Patch
Capsaicin Cream

<u>Oral</u>
Acetaminophen
NSAIDs

WHO Stepwise Pain Relief Ladder



Step 3: Adjuvants

Muscle relaxants

Anti seizure medication- neuropathic pain

TCAs: fibromyalgia

SSRIs – chronic pain

SNRIs

Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial

Nonopioid Arm

- Step 1:
  APAP, NSAID
- Step 2:
  - Topical, TCA
- Step 3:
  - Pregabalin, Duloxetine, Tramadol

Opioid Arm

- Step 1:
  - Morphine IR, Hydrocodone/ APAP, Oxycodone IR
- Step 2:
  - Morphine SA, Oxycodone SA
- Step 3:
  - Transdermal fentanyl

Krebs 2018 JAMA

SPACE Trial, Cont'd

- 240 Veterans (mean age 58, 13% female)
  - 6 months chronic hip or back pain
  - Collaborative care model
- No difference in main outcomes:
  - Brief Pain Inventory
- Functional response 60% both groups
- More side effects opioids

Opioids	Outcome	Non-Opioids
3.4	Pain Related Function BPI Interference Scale (1-10), Difference: 0.1 (-0.5 to 0.7), p=0.58	3.3
4	Pain Intensity BPI Severity Scale (1-10) Difference: 0.5 (0.0 to 1.0), p=0.03	3.5
1.8	Medication Related Adverse Effects Med Symptom Checklist (1-19) Difference: 0.9 (0.3 to 1.5), p=0.03	0.9

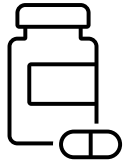
Case 3: Will Power

Treatment Options

- Acupuncture
- CBT
- Physical Therapy
- AA/NA meetings

“But Doc, I need some medicine”

Case 3: Risks For Pain Medications

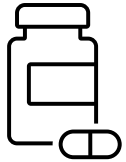


NSAIDS

GERD

Full Opioid Agonists

OUD, in remission
Tobacco Use Disorder



Acetaminophen

Cirrhosis

BUP for Pain: Formulations

Indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Butrans®

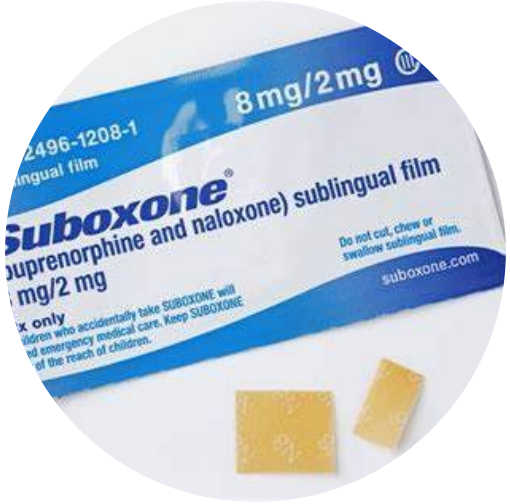
5 mcg/hour, 7.5 mcg/hour, 10 mcg/hour, 15 mcg/hour, 20 mcg/hour

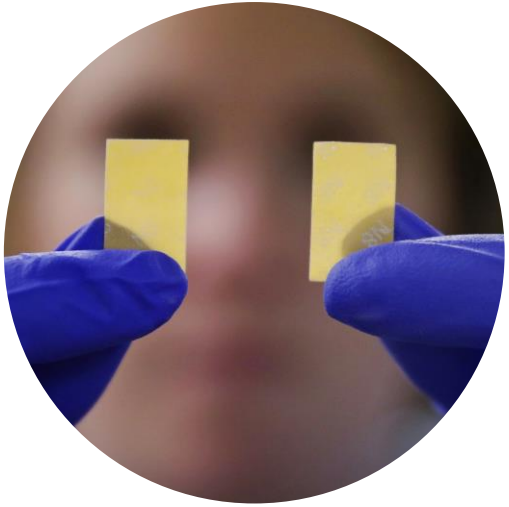
Belbuca®

75 mcg, 150 mcg, 300 mcg,
450 mcg, 600 mcg, 750 mcg, 900 mcg

Suboxone (off-label for pain)

- For co-occurring OUD and Pain
- Split dosing because analgesic effect short-acting





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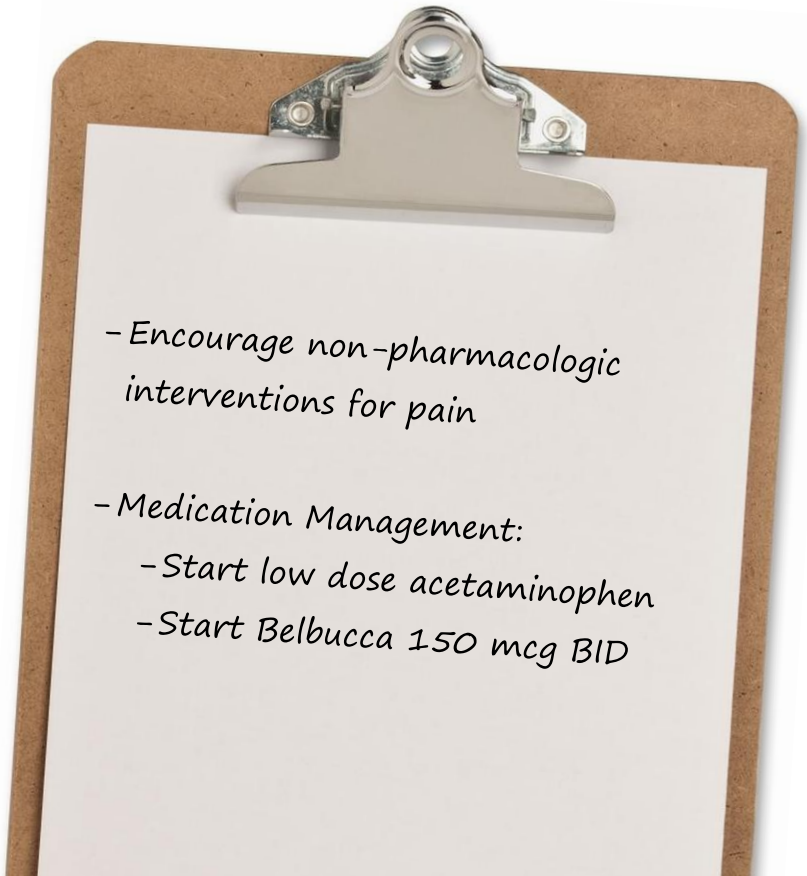
- Atenolol
- Metformin
- Inhalers
- Gabapentin
- Duloxetine
- Aspirin
- APAP
- Omeprazole



Key Points for Chronic Pain

Multimodal Treatment for Pain

Combining different approaches for pain can provide more effective relief and reduce reliance on opioids

Incremental Care with Trusted Clinician

Build a strong patient-provider relationship and ensure thorough, personalized treatment over time

Buprenorphine in Split Dosing

Analgesia can be optimized with split dosing – either of approved formulations for pain or combination formulations (off-label)

03

Additional Resources for Buprenorphine

Finding Support

Buprenorphine management can be **complex**, regardless of the indication for use. If you feel uncomfortable consider utilizing the following resources:

- Request an Addiction Medicine, Chronic Pain, or Acute Pain Management consult
- Reach out the patient's usual buprenorphine prescriber
- Refer the patient to an addiction specialist or an experienced addiction medicine physician
- Pursue additional trainings and education related to buprenorphine prescribing and management

Additional Resources

American Academy of Family Physicians	✓ Clinical Practice Guideline: Opioid Prescribing for Chronic Pain ✓ Management of Chronic Pain and Opioid Misuse: A Position Paper from the AAFP
American Association of Psychiatric Pharmacists	✓ Pharmacist Toolkit: Buprenorphine Initiation and Dosing Strategies ✓ Pharmacist Toolkit: Harm Reduction Strategies for People Who Inject Drugs ✓ SUD Long-Acting Injectables Training: Buprenorphine and Naltrexone
American Society of Addiction Medicine	✓ Clinical Considerations: BUP Treatment of OUD for Individuals Using High- Potency Synthetic Opioids ✓ National Practice Guideline for the Treatment of Opioid Use Disorder
Substance Abuse and Mental Health Services Administration	✓ Practical Tools for Prescribing and Promoting Buprenorphine in Primary Care Settings ✓ TIP 63: Medications for Opioid Use Disorder ✓ TIP 54: Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders
Veteran's Health Administration (VA/DoD)	✓ Clinical Practice Guideline: Management of Substance Use Disorders ✓ Clinical Practice Guideline: Opioid Therapy for Chronic Pain ✓ Clinical Practice Guideline: Perioperative Management of Buprenorphine

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Thanks!

Do you have any questions?

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