OPIOID USE DISORDER

CASE-BASED APPROACH TO THE INPATIENT MANAGEMENT OF OPIOID USE DISORDER

Lisa W. Vercollone, MD, PharmD

Update in Hospital Medicine

October 23, 2023

DISCLOSURES

None

OBJECTIVES

- Review FDA-approved medications for opioid use disorder.
- Discuss performing a methadone initiation in the inpatient setting.
- Review how to manage acute pain in the setting of methadone and buprenorphine maintenance.
- Understand the mechanism of buprenorphine precipitated opioid withdrawal.
- Understand how heavy, chronic fentanyl use alters the pharmacokinetics of the drug.
- Practice the various strategies for buprenorphine initiation in the era of fentanyl.

MEDICATION FOR OPIOID USE DISORDER

What are the goals?

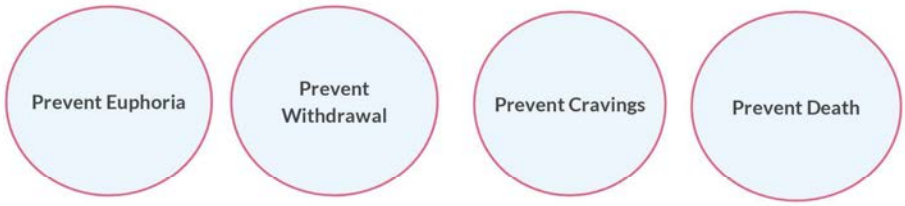
MEDICATION FOR OPIOID USE DISORDER

What are the goals?

↓

NOT detoxification

MEDICATION FOR OPIOID USE DISORDER



MEDICATION FOR OPIOID USE DISORDER

Prevent Euphoria

Prevent Withdrawal

Prevent Cravings

Prevent Death

Addiction -> Physiologic Dependence

MEDICATION FOR OPIOID USE DISORDER

Methadone

Naltrexone

Buprenorphine

NALTREXONE

- Full mu-antagonist
  - fully blocks the opioid mu-receptor
- Dosing: 50 mg po daily or 380 mg IM once monthly
- Eliminates tolerance - increased risk for overdose if non-adherent and relapses
- Risk of precipitated opioid withdrawal; must be opioid-free for 7-12 days
- No mortality benefit

MEDICATION FOR OPIOID USE DISORDER


JAMA Network | Open.

Original Investigation | Substance Use and Addiction

Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder

Sarah E. Wakeman, MD; Marc R. Larochelle, MD, MPH; Omid Ameli, MD, MPH; Christine E. Chaisson, MPH; Jeffrey Thomas McPheeters, BA; William H. Crown, PhD; Francisca Azocar, PhD; Darshak M. Sanghavi, MD

- 40,885 adults with opioid use disorder
- Only treatment with buprenorphine or methadone was associated with reduced risk of overdose


Annals of Internal Medicine

Search Journal

LATEST ISSUES IN THE CLINIC JOURNAL CLUB MULTIMEDIA SPECIALTY COLLECTIONS CME / MOC AUTHORS / SUBMIT

Original Research | 7 August 2018

Medication for Opioid Use Disorder After Nonfatal Opioid Overdose and Association With Mortality

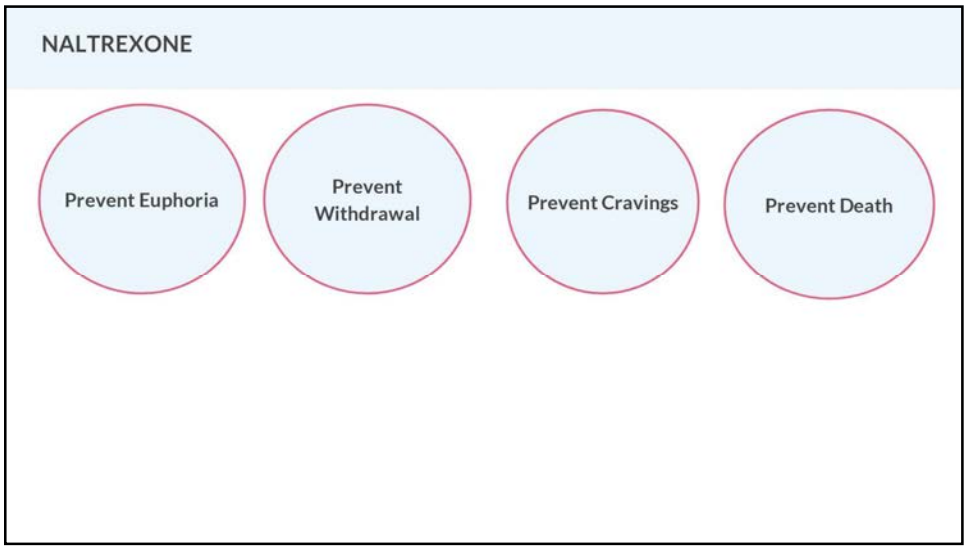
A Cohort Study

Marc R. Larochelle, MD, MPH; Dana Bernson, MPH; Thomas Land, PhD; ... View all authors +

Author, Article, and Disclosure Information

https://doi.org/10.7326/M17-3107

- 17,568 adults without cancer who survived an opioid overdose
- Only methadone and buprenorphine were associated with decreased all-cause mortality and opioid-related mortality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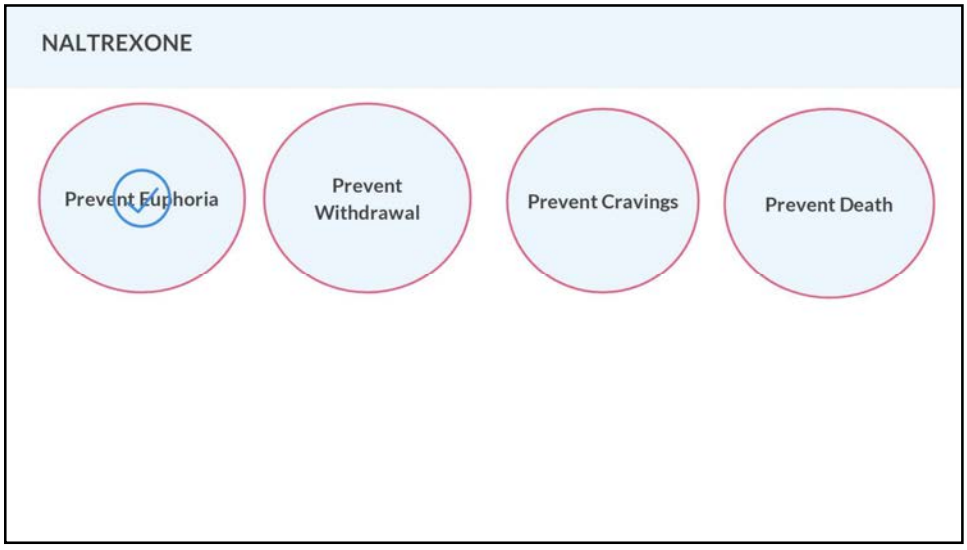
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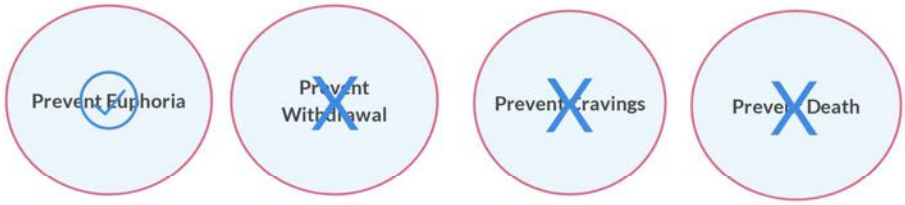

METHADONE

- Synthetic Full Mu-Agonist
- Metabolism: CYP450 3A4
- Drug interactions: MANY
- Dosing: wide variation
- High interpatient pharmacokinetic and pharmacodynamic variability
- Analgesia 6 - 8 hrs
- Daily commitment
- Remains highly federally-regulated
- Strict protocols have to be followed
- No risk of precipitated opioid withdrawal

BUPRENORPHINE

- Partial mu-agonist
  - mixed agonist and antagonist to mu-receptor
  - high affinity
  - low dissociation
- Metabolism: Hepatic
- Dosing: 8 - 32 mg/day
- Analgesia: 4-6 hrs
- available as a monoproduct and in combination with naloxone

- Prescriber must have X-waiver
- Maintenance supply/no daily clinic visits
- Reduces risk of overdose
- Ceiling effect on respiratory depression
- Risk of precipitated opioid withdrawal

BUPRENORPHINE

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  - mixed agonist and antagonist to mu-receptor
  - high affinity
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- ~~Prescriber must have X-waiver~~

12/2022: X-waiver no longer required

After June 27, 2023, doctors asking for new DEA licenses or renewing old ones must meet one of these requirements:

A total of eight hours of training on OUD

Board certification in addiction medicine

Graduation within five years from a program that included OUD curriculum lasting at least eight hours

WHAT IS PRECIPITATED WITHDRAWAL?

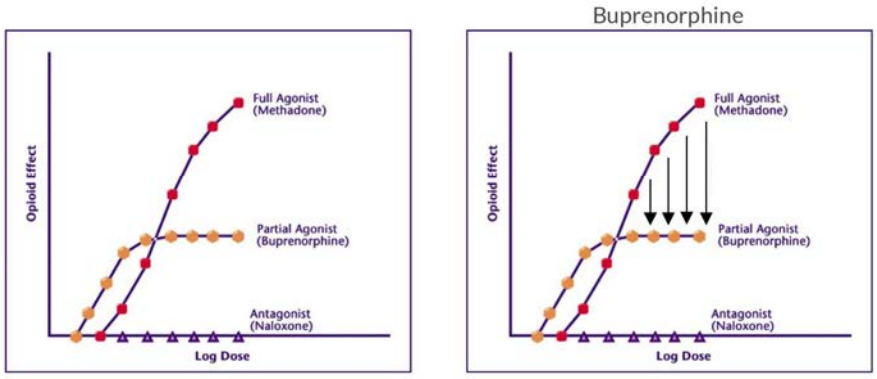
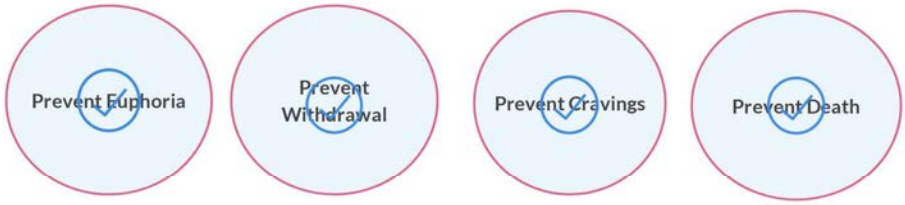


Image: https://www.naabt.org/education/technical_explanation_buprenorphine.cfm. Accessed 5/21/2021

METHADONE AND BUPRENORPHINE

- Prevent Euphoria
- Prevent Withdrawal
- Prevent Cravings
- Prevent Death

METHADONE AND BUPRENORPHINE



CASE - HG

23M with opioid use disorder who injects fentanyl daily admitted for fever and bacteremia diagnosed with endocarditis now requiring IV antibiotics.

He is motivated to be in recovery but quickly shuts down any discussion about starting buprenorphine after experiencing precipitated withdrawal a couple months ago.

He is requesting to start methadone.

CASE - HG

23M with opioid use disorder who injects fentanyl daily admitted for fever and bacteremia diagnosed with endocarditis now requiring IV antibiotics.

He is requesting to start methadone.

What is the best approach for starting methadone while patient is hospitalized?

A: Federal regulations prohibit the prescribing of methadone in the inpatient setting for treatment of opioid use disorder.
B: Start methadone 10 mg q4h prn once COWS > 8
C: Start methadone 30 mg po daily
D: B or C

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METHADONE

Methadone initiation

Do not exceed total dose of 40 mg/day.

Option 1:

Methadone 10 mg q4h prn opioid withdrawal (not to exceed 4 doses in 24 hours)

Option 2:

Methadone 30 mg po x 1 dose, then additional 10 mg in > 4 hrs prn opioid withdrawal

METHADONE

Methadone Dose Titration

Journal of Substance Use and Addiction Treatment
Volume 148, May 2023, 209004

Safety of rapid inpatient methadone initiation protocol: A retrospective cohort study ☆

Savitha Rachu [a], Sapan M. Patel [a b], Loyal T. Bou Harfouch [a b], Olivia Berger [c], Megan E. Buresh [a d]

- more aggressive dose titrations needed in the fentanyl era
- initial dose = 30 mg, then increase by 10 mg daily until 60 mg po qday
- 25 hospitalized patients
- no major adverse events

Methadone Continuation

Must confirm methadone clinic involvement, current dosing, and last dose.

If unable to confirm, do not exceed 40 mg/day

CASE - HG

2 years later...

25M with opioid use disorder complicated by endocarditis (on methadone and remains in remission) admitted for acute pancreatitis after a weekend of binge drinking alcohol.

CASE - HG

2 years later...

25M with opioid use disorder complicated by endocarditis (on methadone and remains in remission) admitted for acute pancreatitis after a weekend of binge drinking alcohol.

Step 1: his methadone clinic confirms the following: methadone 120 mg po daily - last dose yesterday

CASE - HG

25M with opioid use disorder complicated by endocarditis (on methadone 120 mg po daily and remains in remission) admitted for acute pancreatitis after a weekend of binge drinking alcohol.

How do you manage his acute pain?

A: order methadone 120 mg po daily and add hydromorphone IV prn.
B: order methadone 30 mg po q6h and add hydromorphone IV prn.
C: hold methadone, give equivalent dose of hydromorphone IV and additional doses prn.
D: continue home methadone and manage pain with non-opioid medications due to concern for causing a relapse.
E. A or B

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D: continue home methadone and manage pain with non-opioid medications due to concern for causing a relapse.
E. A or B

METHADONE AND ACUTE PAIN

Continue already established methadone dose

Consider dividing the dose and administering every 6 - 8 hr

Do not consider methadone to be adding any considerable pain relief

Address acute pain via a multimodal approach

Non-pharmacological options

Non-opioid adjuvant pain medications

Opioids: short-acting full agonists

Be concerned about relapse if pain is *untreated*!

Untreated pain is more likely to result in relapse

CASE - MR

56M with opioid use disorder on buprenorphine and diabetes mellitus admitted for left diabetic foot infection requiring midfoot amputation in 2 days.

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He has been stable on buprenorphine 8 mg SL bid for 3 years.

CASE - MR

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How do you manage his perioperative pain?

- A: hold buprenorphine since it is a partial agonist and will impede acute pain control
- B. increase buprenorphine to 8 mg SL q8h
- C: transition to dose equivalent of methadone
- D: divide home buprenorphine to 4 mg SL q6h to take advantage of 6 - 8 hr analgesia window
- E: B and D

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- E: B and D

BUPRENORPHINE AND ACUTE PAIN

Do not stop buprenorphine!

Transition back may be difficult as would likely require an induction

Risk of destabilization and relapse

Consider giving home buprenorphine as divided doses every 4 to 8 hrs.

Non-pharmacological options

Non-opioid adjuvant pain medications

Control pain with addition of a short-acting full agonist

Use high-affinity IV short-acting opioid-R agonists.

Hydromorphone or fentanyl

Expect to high dose requirement to control pain

FENTANYL

"Fentanyl is the single deadliest drug threat our nation has ever encountered"

- DEA Administrator Anne Milgram

Over 150 people die every day from overdoses related to synthetic opioids like fentanyl.

https://www.cdc.gov/drugoverdose/deaths/index.html. Accessed

FENTANYL

- 1959 - Synthesized by Paul Janssen
  - Created as means to create a drug with greater safety profile than morphine
  - 50 - 100 x more potent than morphine; 25 - 40 x more potent than heroin

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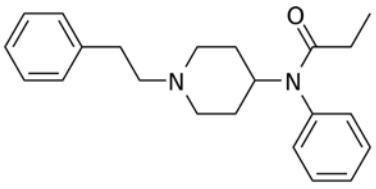
Fentanyl on the streets is not diverted pharmaceutical grade product.

FENTANYL ANALOGS

New Synthetic Opioids (NSO) - derived from fentanyl, "designer" fentanyl

- Scant pharmacological data
- 4 structural features which can be modified
  - piperidine ring
  - anilinophenyl ring
  - 2-phenylethyl substitute
  - carboxamide moiety
- Medically used: sufentanil and carfentanil
  - carfentanil 100 x more potent than fentanyl



Wilde et al., 2019

CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

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26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

- Injecting 3 "grams" of fentanyl daily.
- Last use was "a few hours ago."
- Seen by ortho who recommends CT wrist and admission for IV antibiotics.
- Admit to general medicine.

CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

- Arrives on the floor.
- **COWS = 4**
- Urine toxicology screen positive for amphetamine, cocaine, and fentanyl
- He has experienced self-inflicted buprenorphine precipitated opioid withdrawal in the past.
- He is requesting a buprenorphine initiation this admission.

CLINICAL OPIATE WITHDRAWAL SCALE (COWS)

Each item scored 0 - 4 or 5:

- heart rate
- sweating
- restlessness
- GI upset
- Tremor
- Yawning
- pupil size
- bone/joint aches
- runny nose/tearing
- anxiety/irritability
- gooseflesh

SEVERITY

5 - 12: Mild
13 - 24: Moderate
25 - 36: Moderately severe
> 36: Severe

CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

How do you want to proceed with the buprenorphine initiation?

BUPRENORPHINE INITIATION

- Option 1: Traditional Approach
- Option 2: Low Dose Approach
- Option 3: High Dose Approach

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Option 1: Traditional buprenorphine initiation

TRADITIONAL BUPRENORPHINE INITIATION

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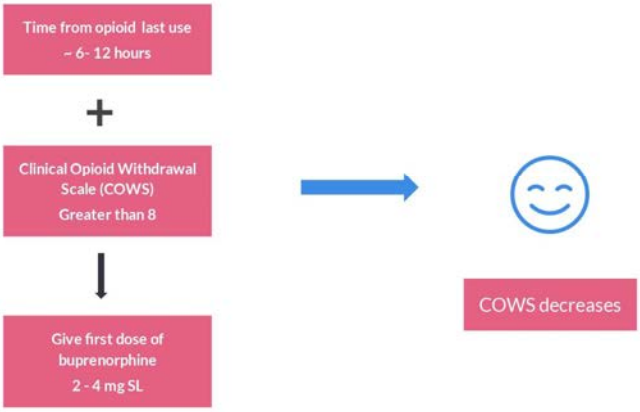

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Option 1: Traditional buprenorphine initiation

- But his COWS = 4
- Wait for withdrawal to worsen
- Goal COWS > 8

CASE - LC

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Option 1: Traditional buprenorphine initiation

- Return to see the patient the following morning (~ 14 hours later)
- COWS = 15
- Start buprenorphine initiation

CASE - LC

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Option 1: Traditional buprenorphine initiation

Give buprenorphine 2 mg SL x 1 dose

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Option 1: Traditional buprenorphine initiation

Received buprenorphine 2 mg SL x 1 dose

- 20 minutes later, bedside RN alerts you that the patient is not looking well.
- Diaphoretic, tremulous, extreme restlessness, vomiting, severe anxiety, tearful
- COWS = 27

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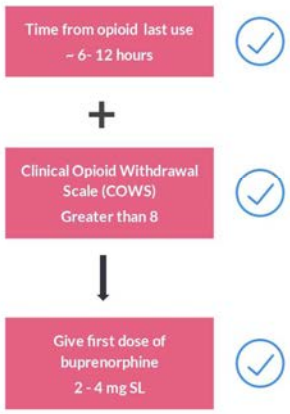
Severe Buprenorphine Precipitated Opioid Withdrawal

BUPRENORPHINE PRECIPITATED OPIOID WITHDRAWAL TREATMENT

- GIVE MORE Buprenorphine 8 mg - 16 mg SL, up to 32 mg total
- Alpha-2 agonists
  - Clonidine 0.1 mg po q6h prn opioid withdrawal (COWS > 5) and/or anxiety
- Antipsychotics
  - Haloperidol 2.5 – 5 mg IV/IM/PO q4h prn agitation
- Benzodiazepines
  - Lorazepam 1 – 2 mg IV/PO as needed for anxiety x 1 dose
- High potency opioids
  - Hydromorphone 4-8 mg IV q2h prn opioid withdrawal (COWS > 5)
- Ketamine 0.3 mg/kg IV slow push or IM x 1 dose for analgesia (max dose is 35 mg)

https://cabridge.org/resource/buprenorphine-bup-hospital-quick-start/ Accessed 8/7/2022

TRADITIONAL BUPRENORPHINE INITIATION



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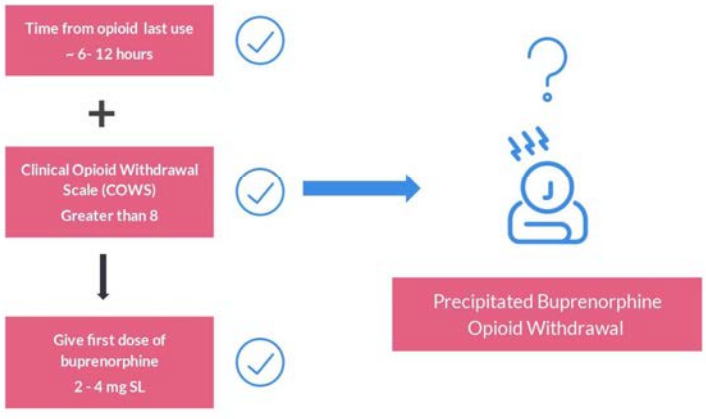


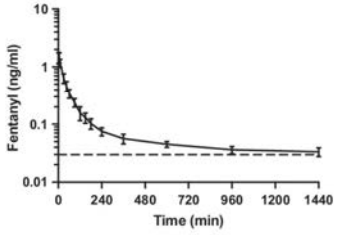
FENTANYL + PRECIPITATED WITHDRAWAL

- Despite lengthy withdrawal periods
- Despite moderate to high COWS
- Repeated IV and IN administration has never been tested
  - Daily use
  - High dose

Huhn et al. 2020
Comer et al., 2019

FENTANYL PHARMACOKINETICS

- Based on single dose or multiple doses within one day administration
- Half-life 1.5 - 6 hours
- Highly lipophilic
- Fast diffusion plasma -> CNS
- High affinity to mu-receptor



Smith et al. 2018

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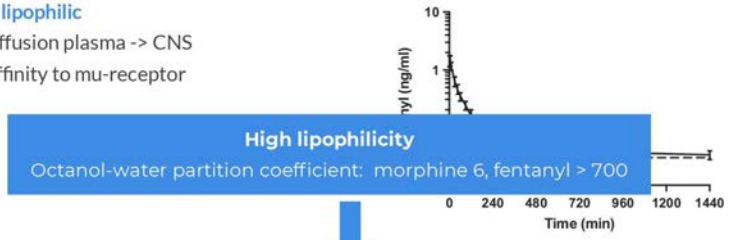


High lipophilicity
Octanol-water partition coefficient: morphine 6, fentanyl > 700

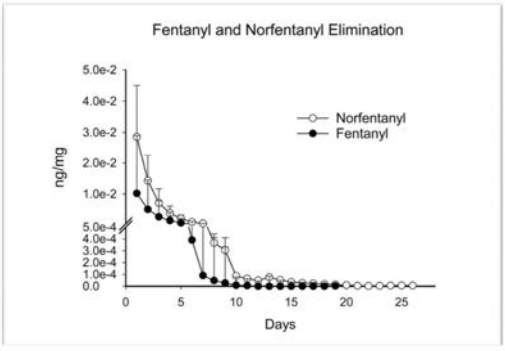
Sequestration in Adipose Tissue

Smith et al. 2018

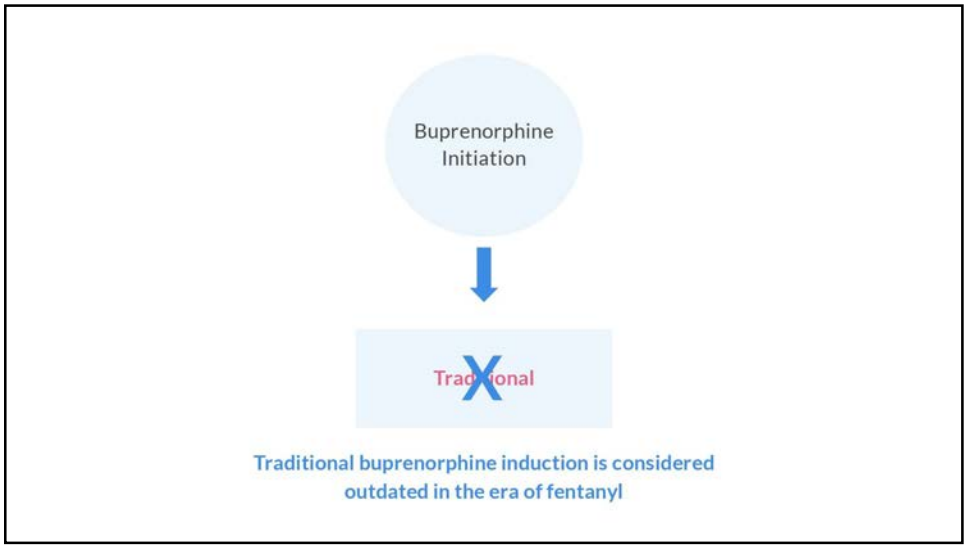
FENTANYL ELIMINATION

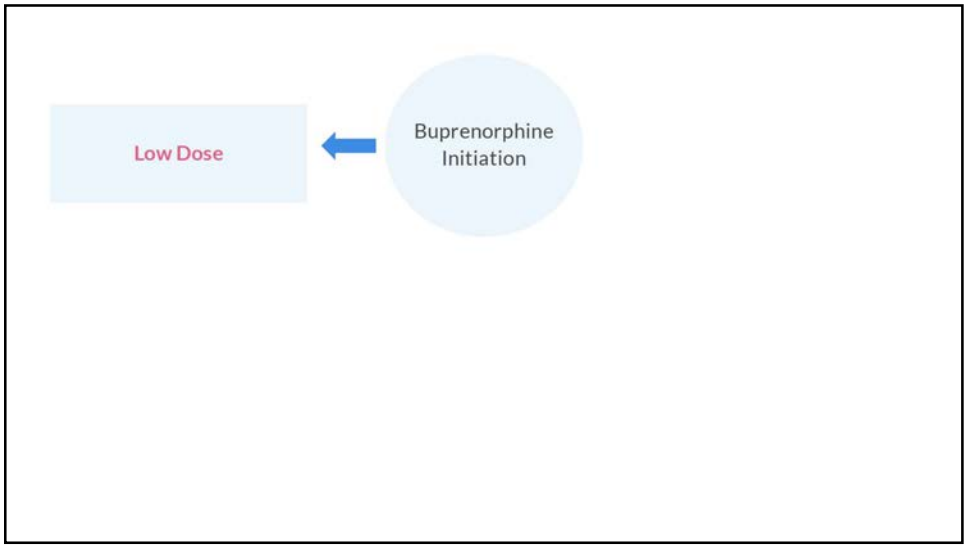
N = 12

- tested positive for fentanyl at intake
- urine samples taken every 2-3 days
- mean time for fentanyl and norfentanyl clearance
  - **fentanyl = 7.3 days**
  - norfentanyl: 13.3 days
  - one participant tested positive for fentanyl for 19 days and norfentanyl for 26 days



Huhn et al. 2020


Buprenorphine Initiation
Traditional
X
Traditional buprenorphine induction is considered outdated in the era of fentanyl


Low Dose
Buprenorphine Initiation

Low Dose

Buprenorphine Initiation

- Repeated microdoses of buprenorphine with sufficient dosing intervals should not precipitate withdrawal
- Buprenorphine will accumulate at the receptor because of the long receptor binding time
- Over time, an increasing amount of a full mu-agonist will be replaced by the buprenorphine at the opioid receptor
- Overlapping full mu-R agonist required

LOW DOSE INITIATION

"MICRO-DOSING" OR BERNESE METHOD

CASE SERIES

Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method

Robert Hämmig[1]
Antje Kemter[1]
Johannes Strasser[2]
Ulrich von Bardeleben[1]
Barbara Gugger[1]
Marc Walter[1]
Kenneth M Dürsteler[2]
Marc Vogel[1]

[1]Division of Addiction, University Psychiatric Services Bern, Bern, Switzerland; [2]Division of Substance Use and Addictive Disorders, University of Basel Psychiatric Hospital, Basel, Switzerland

This article was published in the following Dove Press journal:
Substance Abuse and Rehabilitation
20 July 2016
Number of times this article has been viewed

Background: Buprenorphine is a partial μ-opioid receptor agonist used for maintenance treatment of opioid dependence. Because of the partial agonism and high receptor affinity, it may precipitate withdrawal symptoms during induction in persons on full μ-opioid receptor agonists. Therefore, current guidelines and drug labels recommend leaving a sufficient time period since the last full agonist use, waiting for clear and objective withdrawal symptoms, and reducing pre-existing full agonist therapies before administering buprenorphine. However, even with these precautions, for many patients the induction of buprenorphine is a difficult experience, due to withdrawal symptoms. Furthermore, tapering of the full agonist bears the risk of relapse to illicit opioid use.

Cases: We present two cases of successful initiation of buprenorphine treatment with the Bernese method, ie, gradual induction overlapping with full agonist use. The first patient began buprenorphine with overlapping street heroin use after repeatedly experiencing relapse, withdrawal, and trauma reactivation symptoms during conventional induction. The second patient was maintained on high doses of diacetylmorphine (ie, pharmaceutical heroin) and methadone during induction. Both patients tolerated the induction procedure well and reported only mild withdrawal symptoms.

Discussion: Overlapping induction of buprenorphine maintenance treatment with full μ-opioid receptor agonist use is feasible and may be associated with better tolerability and acceptability in some patients compared to the conventional method of induction.

Keywords: subutex, suboxone, heroin, opiate, substitution

Table 1

Buprenorphine dosing and use of street heroin in case 1

Day	Buprenorphine (sl)	Street heroin (sniffed)
1	0.2 mg	2.5 g
2	0.2 mg	2 g
3	0.8+2 mg	0.5 g
4	2+2.5 mg	1.5 g
5	2.5+2.5 mg	0.5 g
6	2.5+4 mg	0
7	4+4 mg	0
8	4+4 mg	0
9	8+4 mg	0

Hammig et al. 2016

LOW DOSE INITIATION

"MICRO-DOSING" OR BERNESE METHOD

CASE SERIES

Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method

This article was published in the following Dove Press journal:
Substance Abuse and Rehabilitation
20 July 2016
Number of times this article has been viewed

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Background: Buprenorphine is a partial μ-opioid receptor agonist used for maintenance treatment of opioid dependence. Because of the partial agonism and high receptor affinity, it may precipitate withdrawal symptoms during induction in persons on full μ-opioid receptor agonists. Therefore, current guidelines and drug labels recommend leaving a sufficient time period since the last full agonist use, waiting for clear and objective withdrawal symptoms, and reducing pre-existing full agonist therapies before administering buprenorphine. However, even with these precautions, for many patients the induction of buprenorphine is a difficult experience, due to withdrawal symptoms. Furthermore, tapering of the full agonist bears the risk of relapse to illicit opioid use.

Cases: We present two cases of successful initiation of buprenorphine treatment with the Bernese method, ie, gradual induction overlapping with full agonist use. The first patient began buprenorphine with overlapping street heroin use after repeatedly experiencing relapse, withdrawal, and trauma reactivation symptoms during conventional induction. The second patient was maintained on high doses of diacetylmorphine (ie, pharmaceutical heroin) and methadone during induction. Both patients tolerated the induction procedure well and reported only mild withdrawal symptoms.

Discussion: Overlapping induction of buprenorphine maintenance treatment with full μ-opioid receptor agonist use is feasible and may be associated with better tolerability and acceptability in some patients compared to the conventional method of induction.

Keywords: substex, suboxone, heroin, opiate, substitution

Table 1

Buprenorphine dosing and use of street heroin in case 1

Day	Buprenorphine (sl)	Street heroin (sniffed)
1	0.2 mg	2.5 g
2	0.2 mg	2 g
3	0.8+2 mg	0.5 g
4	2+2.5 mg	1.5 g
5	2.5+2.5 mg	0.5 g
6	2.5+4 mg	0
7	4+4 mg	0
8	4+4 mg	0
9	8+4 mg	0

Hammig et al. 2016

LOW DOSE INITIATION

"MICRO-DOSING" OR BERNESE METHOD

CASE SERIES

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6	2.5+4 mg	0
7	4+4 mg	0
8	4+4 mg	0
9	8+4 mg	0

Hammig et al. 2016

LOW DOSE INITIATION

- Formulations utilized to provide low/micro-doses:
  - transdermal patch
  - buccal films
  - swallowing sublingual tablets
  - cutting sublingual films
  - intravenous

LOW DOSE INITIATION

REVIEWS

Low Dose Initiation of Buprenorphine: A Narrative Review and Practical Approach

Cohen, Shawn M. MD; Weimer, Melissa B. DO, MCR; Levander, Ximena A. MD; Peckham, Alyssa M. PharmD, BCPP; Tetrault, Jeanette M. MD; Morford, Kenneth L. MD

Author Information

Journal of Addiction Medicine 16(4):p 399-406, 7/8 2022. | DOI: 10.1097/ADM.0000000000000945

Metrics

- Stepwise approach to creating a site-specific guideline or protocol
  - Partnering with hospital pharmacy and nursing administration
  - Review which formulations of buprenorphine are available on the hospital's formulary
- Flowchart of various hospital-based low dose initiation protocols

CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

- Arrives on the floor.
- **COWS = 4**
- Urine toxicology screen positive for amphetamine, cocaine, and fentanyl
- He has experienced self-inflicted buprenorphine precipitated opioid withdrawal in the past.
- He is requesting a buprenorphine initiation this admission.

CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

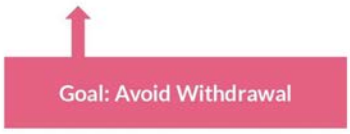
Option 2: Low dose buprenorphine initiation

CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

Option 2: Low dose buprenorphine initiation

- COWS = 4



CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

Option 2: Low dose buprenorphine initiation

- **Goal is to maintain COWS < 5**
- **Step 1: Start a full opioid agonist immediately!**
  - methadone 30 mg po x 1 now, repeat 10 mg in 4-6 hours if needed, then 40 mg po qam
- **Step 2: Start buprenorphine buccal/SL protocol**

CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

Day	Buprenorphine Dose	Full Agonist Dose
1	225 mcg buccal film once	methadone 30 mg
2	225 mcg buccal film BID	methadone 40 mg
3	450 mcg buccal film BID	methadone 40 mg
4	2 mg SL BID	methadone 40 mg
5	4 mg SL BID	methadone 40 mg
6	4 mg SL TID	methadone 40 mg
7	8 mg SL BID	stop

CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

Maintanence dose = 24 -32 mg daily (once or in divided doses)

Day	Buprenorphine Dose	Full Agonist Dose
1	225 mcg buccal film once	methadone 30 mg
2	225 mcg buccal film BID	methadone 40 mg
3	450 mcg buccal film BID	methadone 40 mg
4	2 mg SL BID	methadone 40 mg
5	4 mg SL BID	methadone 40 mg
6	4 mg SL TID	methadone 40 mg
7	8 mg SL BID	stop

LOW DOSE INITIATION

CASE REPORTS

Hospital-based Buprenorphine Micro-dose Initiation

Weimer, Melissa B. DO, MCR, FASAM; Guerra, Michael PharmD; Morrow, Gina PharmD; Adams, Kathleen PharmD

Author Information

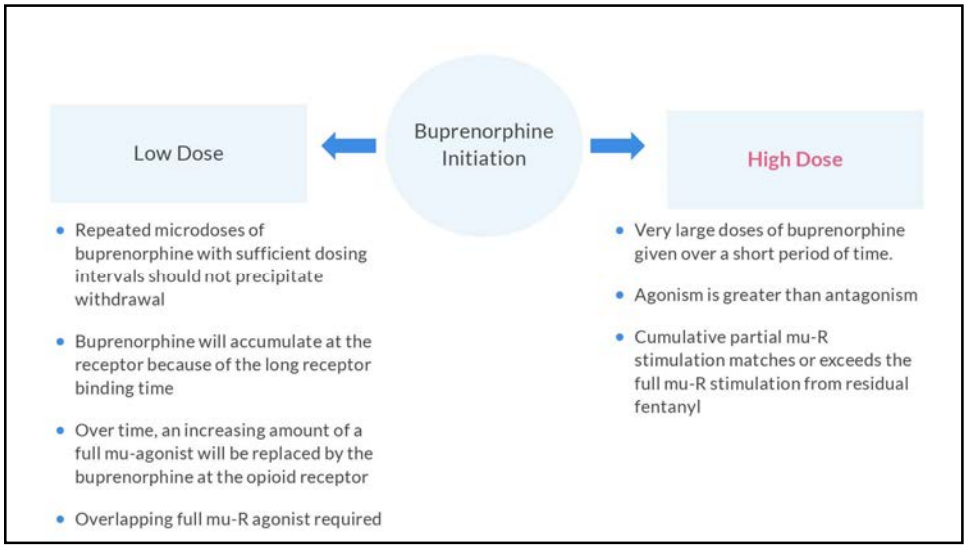
Journal of Addiction Medicine 15(3):p 255-257, May/June 2021.

TABLE 2 - Buccal Buprenorphine Induction Strategy

Day	Buccal Buprenorphine Film Dose	SL Buprenorphine/Naloxone Film Dose	Full Opioid Agonist Dose
1	225 mcg PO once (75 mcg film + 150 mcg film)		Full dose
2	225 mcg PO twice daily (75 mcg film + 150 mcg film)		Full dose
3	450 mcg PO twice daily		Full dose
4		2 mg SL BID	Full dose
5		4 mg SL BID	Full dose
6		4 mg SL TID	Full dose
7		4 mg SL TID – 8 mg SL BID	Stop

BID, twice daily; PO, per oral; SL, sublingual; TID, 3 times daily.

- Repeated microdoses of buprenorphine with sufficient dosing intervals should not precipitate withdrawal
- Buprenorphine will accumulate at the receptor because of the long receptor binding time
- Over time, an increasing amount of a full mu-agonist will be replaced by the buprenorphine at the opioid receptor
- Overlapping full mu-R agonist required



HIGH DOSE INITIATION

Original Investigation | Substance Use and Addiction

July 15, 2021

High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder

Andrew A. Herring, MD[1,2]; Aidan A. Vosooghi, MS[1,3]; Joshua Luftig, PA[1]; et al

> Author Affiliations | Article Information

JAMA Netw Open. 2021;4(7):e2117128. doi:10.1001/jamanetworkopen.2021.17128

- Aim to examine the safety and tolerability of high-dose (>12 mg) buprenorphine induction
- N = 579 encounters/391 unique patients
- 138 doses (23.8%) were > 28 mg; No cases of respiratory depression
- 5 (0.8%) cases of precipitated withdrawal

Research Letter | Substance Use and Addiction

March 30, 2023

Incidence of Precipitated Withdrawal During a Multisite Emergency Department-Initiated Buprenorphine Clinical Trial in the Era of Fentanyl

Gail D'Onofrio, MD, MS[1,2,3]; Kathryn F. Hawk, MD, MHS[1,3]; Jeannarie Perrone, MD[4]; et al

> Author Affiliations | Article Information

JAMA Netw Open. 2023;6(3):e236108. doi:10.1001/jamanetworkopen.2023.6108

- 28 emergency departments
- randomized to 8 mg - 16 mg SL buprenorphine or 7-day extended-release SQ buprenorphine
- N = 1200 patients
- 9 (0.8 %) cases of precipitated withdrawal

CASE - LC

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CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

Option 2: High dose buprenorphine initiation

- Wait for withdrawal to worsen
- Goal COWS $\geq$ 8

CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

Option 2: High dose buprenorphine initiation

- Return to see the patient the following morning (~ 14 hours later)
- COWS = 15
- Start high dose initiation

CASE - LC

26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

Option 2: High dose buprenorphine initiation

Time	Buprenorphine	COWS
9 AM	16 mg SL x 1	15
10 AM		10
10:30 AM	Repeat 16 mg SL x 1	

CASE - LC

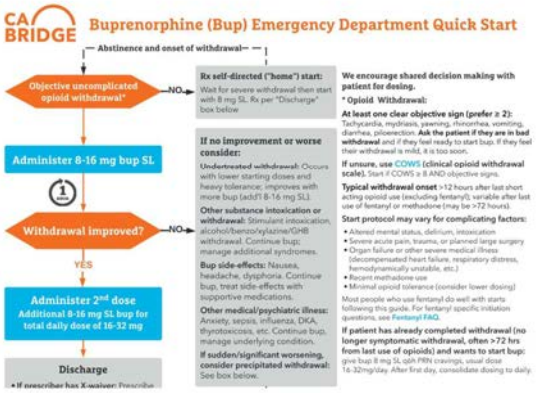
26M PMH with multiple substance use disorders: opioids (not on medication for OUD), alcohol, stimulants (cocaine and methamphetamine), and tobacco, depression and PTSD presents to ED with left wrist cellulitis.

Option 2: High dose buprenorphine initiation

Maintanence dose = 24 -32 mg daily (once or in divided doses)

Time		COWS
9 AM	16 mg SL x 1	15
10 AM		10
10:30 AM	Repeat 16 mg SL x 1	

CA BRIDGE BUPRENORPHINE QUICK START

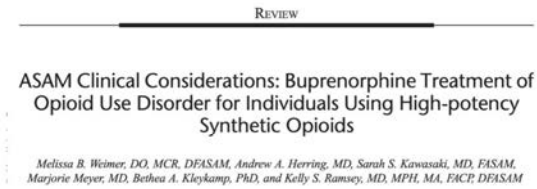


https://cabridge.org/resource/buprenorphine-bup-hospital-quick-start/ Accessed 8/7/2022

CA BRIDGE TREATMENT PROTOCOLS

https://bridgetotreatment.org/tools/resources/

AMERICAN SOCIETY OF ADDICTION MEDICINE STATEMENT ON BUPRENORPHINE (*J ADDICT MED 2023*)

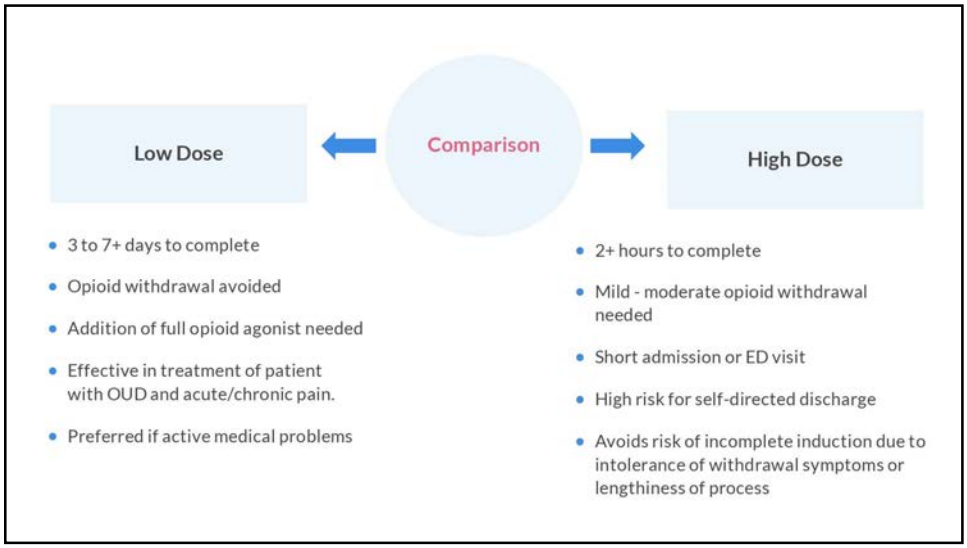


REVIEW

ASAM Clinical Considerations: Buprenorphine Treatment of Opioid Use Disorder for Individuals Using High-potency Synthetic Opioids

Melissa B. Weimer, DO, MCR, DFASAM, Andrew A. Herring, MD, Sarah S. Kawasaki, MD, FASAM, Marjorie Meyer, MD, Bethea A. Kleykamp, PhD, and Kelly S. Ramsey, MD, MPH, MA, FACP, DFASAM

- when to use low vs. high dose initiation strategies
- treating discomfort and precipitated withdrawal
- dosing strategies for stabilization and long-term treatment
- injectable vs sublingual
- how adulterants in the drug supply affect stabilization and long-term treatment
- treatment alternatives after failed initiation attempts



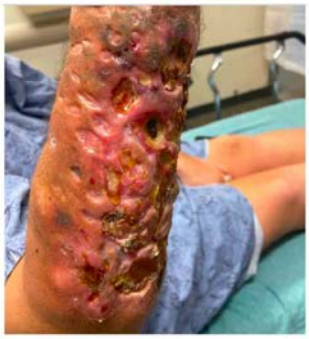
CASE - SP

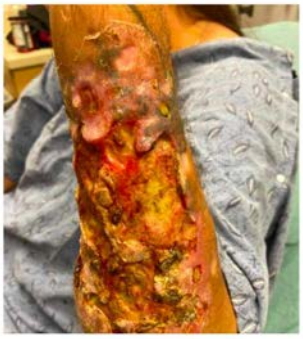
30W PMH opioid use disorder c/b recurrent SSTI and HCV s/p treatment who presents with bilateral upper extremity non-healing wounds.

- Had a 3 year period of abstinence
- Relapsed to daily intradermal fentanyl use one month ago

CASE - SP

30W PMH opioid use disorder c/b recurrent SSTI and HCV s/p treatment who presents with bilateral upper extremity non-healing wounds.





XYLAZINE "TRANQ"

- Non-opioid veterinary tranquilizer not approved for human use
  - MOA: alpha-2 adrenergic agonist/CNS depressant
- Largest impact -. Northeast
  - Highest prevalence data observed in Philadelphia (25.8% of deaths)
- Linked to increasing number of overdose deaths
- Often added to fentanyl to lengthen euphoric effects/lengthens duration
- Repeated exposure -> skin ulcers and abscesses REGARDLESS of route
  - direct vasoconstriction
- Confirmatory testing does not change management in the inpatient setting

https://nida.nih.gov/research-topics/xylazine. Accessed 1/20/23.

Friedman J et al. Xylazine spreads across the US. *Drug Alcohol Depend.* 2022;233:109380.

CASE - SP

30W PMH opioid use disorder c/b recurrent SSTI and HCV s/p treatment who presents with bilateral upper extremity non-healing wounds.

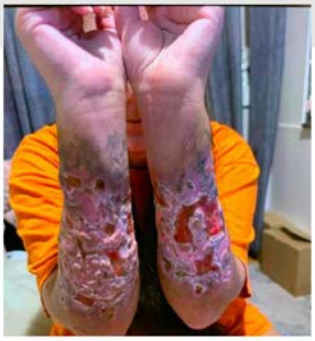
Treatment Course

- Seen by infectious diseases who recommended 5-day course of antibiotics
- Intensive outpatient wound care

CASE - SP

30W PMH opioid use disorder c/b recurrent SSTI and HCV s/p treatment who presents with bilateral upper extremity non-healing wounds.

2 weeks later...



SUMMARY

- Methadone can be prescribed in an inpatient setting for the management of opioid withdrawal syndrome and opioid use disorder.
- All attempts should be made to avoid stopping buprenorphine during the perioperative period or during episodes of acute pain.
- Low dose and high dose buprenorphine initiation strategies should be considered in patients with recent heavy fentanyl use.
- Hospitalists are well positioned to make a large impact on the opioid epidemic initiating treatment for opioid use disorder and arranging linkage to outpatient care prior to discharge.

Questions?