Inpatient Buprenorphine Treatment for Opioid Use Disorder

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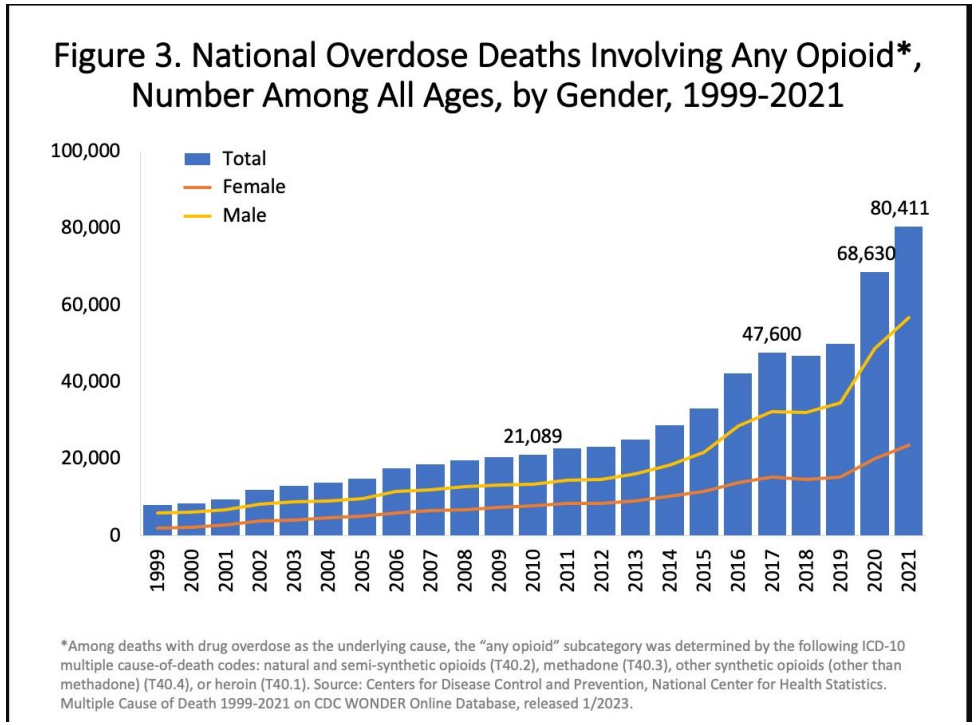
Learning Objectives

- Describe the pathophysiology of opioid use disorder (OUD)
- Review medications used in the treatment of OUD and withdrawal
- Discuss the pharmacology of buprenorphine
- Identify continuation and initiation strategies of buprenorphine in the inpatient setting

- I have no conflicts to disclose

Epidemiology-United States

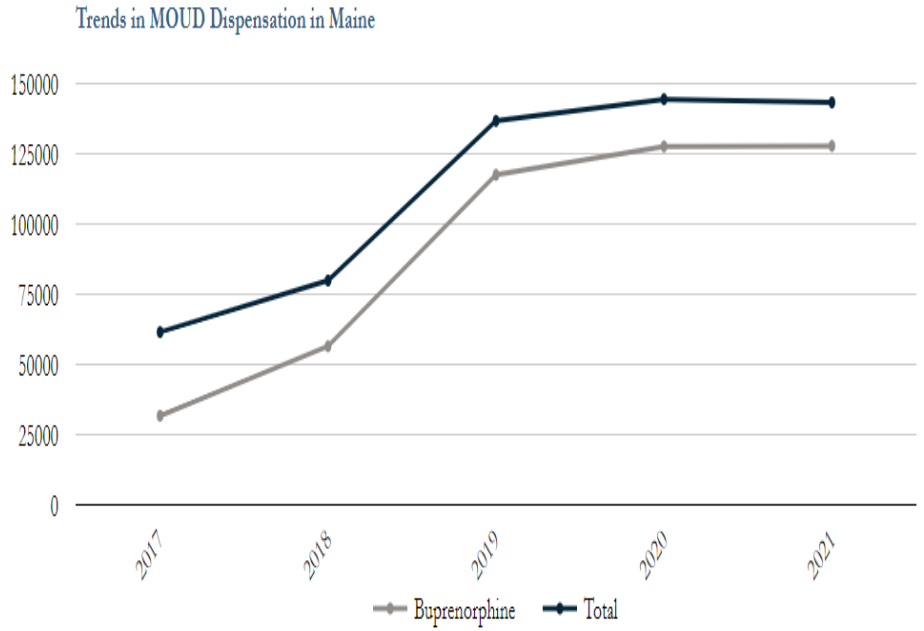
- 71,000 drug overdose deaths from synthetic (not methadone) opioids in 2021
- 6.1 million people ages 12+ in US had OUD in 2022
- Only 1.1 million received medications for OUD (MOUD)



https://www.cdc.gov/drugoverdose/deaths/opioid-overdose.html
SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2022
https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

Maine Statistics

- Maine is 8th for overdose death rates
- In Maine, from 2019-2020 OD deaths rose from 380 to 515
  - 80% involved fentanyl
- 16% decline in 2023
  - 723→607
- 15,704 Mainers received treatment for OUD in 2019 (2X from 2015)
- Almost 10% of Mainers did not receive treatment despite diagnosis



https://www.cdc.gov/nchs/pressroom/sosmap/drug_poisoning_mortality/drug_poisoning.htm
Drug overdose deaths in Maine declined by 16% in 2023 | Maine Public February 2, 2024
https://mainedrugdata.org/why-is-this-happening/
https://mainedrugdata.org/focus-area-treatment/

Diagnosis

DSM-V Criteria for Diagnosis of OUD
1. Opioids taken in larger amounts or duration than intended
2. Persistent desire for or inability to cut down use
3. Substantial time spent to obtain, use opioids or recover from effects
4.Craving to use opioid
5. Interfering with major obligations such as work, school or home
6. Continued use despite negative social consequences
7. Important activities given up because of opioid use
8. Recurrent use in situations where it is physically hazardous
9. Continued use despite knowledge of physical or psychological problem exacerbated by opioid use
10. Tolerance
11. Withdrawal

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed. American Psychiatric Association, 2013:540-6.

Patient Interview

- Elicit patient goals regarding opioid use and OUD treatment
- Explore treatment experience
- Understand patient plans and preferences
- Practical considerations
  - Local resource availability
  - Place to safely store medication?
  - Health insurance implications

Torres-Lockhart, et al. Addiction. 2022; 1-11 DOI: 10.1111/add.15818

SBIRT

- **S**creening, **B**rief **I**ntervention, and **R**eferral to **T**reatment
- Comprehensive, integrated public health approach to delivery of early intervention to those with or at risk of substance use disorders
- Screening
  - Quickly assess severity of substance use and ID appropriate level of treatment
- Brief Intervention
  - Focus on increasing insight regarding substance use and enhance motivation
- Referral to Treatment
  - Provides those identified as needing more extensive treatment with access to care

Screening, Brief Intervention, and Referral to Treatment (SBIRT) | SAMHSA

Stigma

Self Stigma	• Accepting and internalizing negative stereotypes about self
Public Stigma	• Negative attitudes that isolate those with addiction
Stigma Against Medication	• Belief that MOUD just trades one addiction for another
Structural Stigma	• Excluding those with addiction from opportunities and resources

Overcoming Stigma

- Addressing institutional policies and systems that fragment care
- Expanding hospital-based models of care
  - Low-threshold buprenorphine in ED, embedded addiction med specialists
- Comprehensive training during medical school/residency
- Contact based interventions

Cheetham, et al. 2022 Subs Abuse and Rehab 2022. 13: 1-12

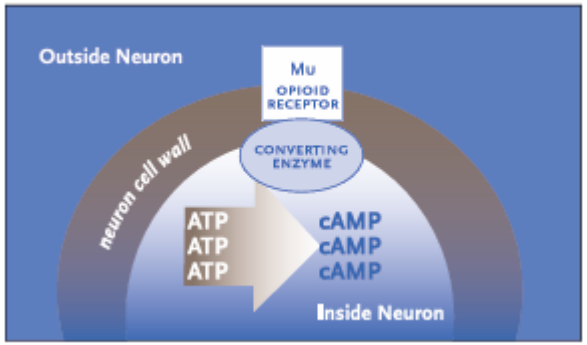
Stigma-Words Matter

Instead of….	Use….	Because…
Addict/User/Abuser	Person with OUD; person who uses drugs	Person first language shows person has a problem but isn't defined by it
Habit	Substance use disorder	Implies person is choosing to use substance
Abuse	Illicit-use; RX-misuse	Abuse found to have high association with negative judgements
Clean	Tox results: testing negative; other: remission or recovery	Use clinically accurate terminology as for other medical conditions
Dirty	Tox: testing positive	Use clinically accurate terminology; may decrease patient hope

Words Matter - Terms to Use and Avoid When Talking About Addiction | National Institute on Drug Abuse (NIDA) (nih.gov)

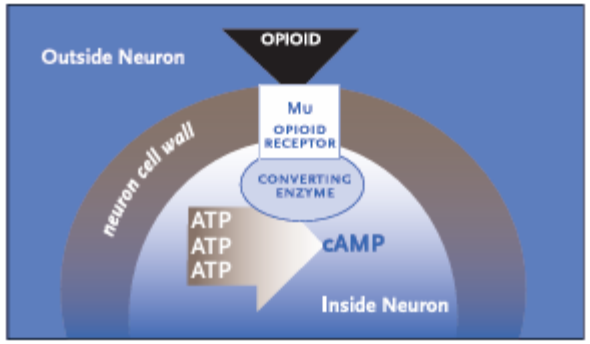
Pathophysiology-Opioid Withdrawal

A. Baseline: Normal production of NA



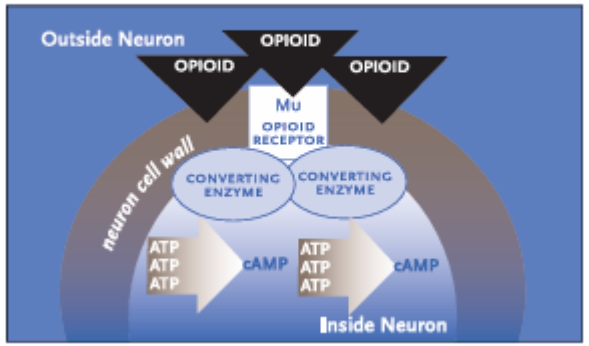
Body producing normal level of norephinephrine (NE)

B. Acute opioid inhibition of converting enzyme: Abnormally low production of NA



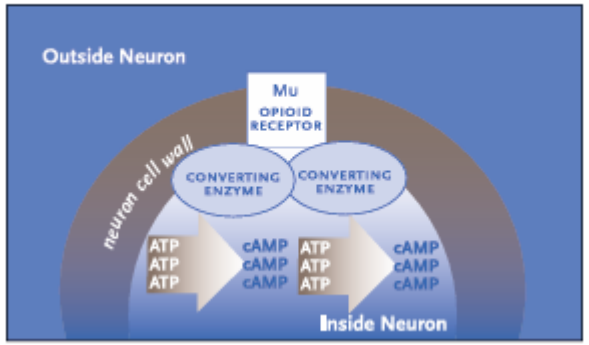
Opioid inhibits enzyme to make cAMP→↓NE results in ↓respiration, alertness, muscle tone and ↑ sedation

C. Chronic opioid inhibition leads to increased converting enzyme activity: Normal NA level



Repeated opioid exposure, neuron adapts and makes more cAMP, resulting in tolerance

D. Discontinuing opioid leads to increased cyclic AMP due to loss of inhibition: NA excessively high



Opioid stopped→lose inhibition results in excess NE→jitters, anxiety, cramps

Kosten, T, George T. Sci & Practice Perspectives July 2002

Opioid withdrawal

- Symptoms: nausea, vomiting, diarrhea, insomnia, anxiety, pain, sweating, chills, hypertension

Short acting (heroin, oxycodone IR)

- Onset: 8-12 hours
- Peak: 1-3 days
- Duration: up to 7-10 days

Long acting (methadone, ER oxy/morphine, fentanyl)

- Onset: 36 hours
- Peak: 72 + hours
- Duration: 14+ days

Opioid Withdrawal Symptoms, Timeline & Detox Treatment (americanaddictioncenters.org)

Monitoring (COWS)

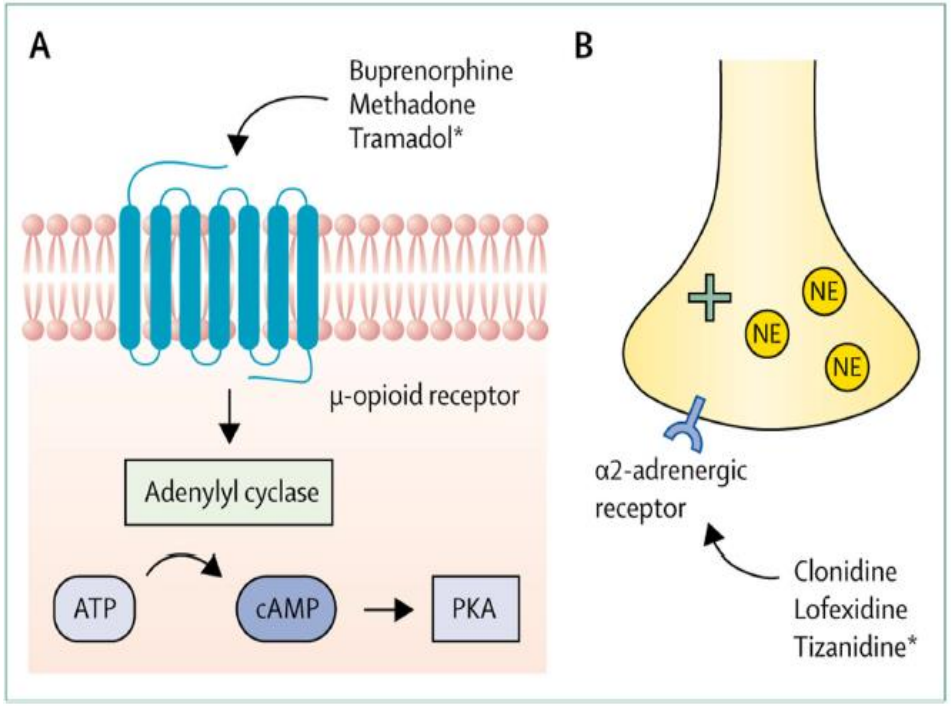
- Clinical Opiate Withdrawal Scale
- Not validated in inpatient setting
- Scoring
  - Mild=5-12
  - Moderate=13-14
  - Severe = 25-36

Resting pulse rate: 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI upset:** 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 Vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor:** 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness: 0 able to sit still 1 reports difficulty sitting still but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning:** 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 3 yawning several times/minute
Pupil size: 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or irritability:** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in assessment is difficult
Bone or joint aches: 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin:** 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection
Runny nose or tearing: 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items

Wesson DR et al. J Psychoactive Drugs 2003;35:253-9.

Treatment of Withdrawal-Opioids

- Buprenorphine > clonidine or lofexidine for withdrawal
  - Lower withdrawal score, longer retention in treatment, and increased likelihood of withdrawal treatment completion
- Buprenorphine = methadone for treatment of withdrawal



Srivastava, et al. Lancet. 2020 June 20; 395(10241): 1938-1948. doi: 10.1016/So140-6736(30)30852-7.

Non-opioid adjunctive medications

Symptom(s) targeted	*Medication*	*Class*	*Preferred route*	*Dose*	*Comments*
Autonomic hyperactivity	Clonidine	α-2 agonist	Oral	0.1–0.3 mg up to 4 times daily	-Monitor blood pressure and heart rate after initial dose and before up-titration -Lofexidine is FDA-approved for opioid withdrawal management; clonidine is not -Lofexidine is very costly
	Lofexidine[a]	α-2 agonist	Oral	0.54 mg up to 4 times daily	
Diarrhea	Loperamide	Peripheral μ opioid agonist	Oral	4 mg followed by 2 mg as needed for loose stools	-Maximum daily dose is 16 mg -Ensure adequate oral hydration
Insomnia	Trazodone	Sedating anti-depressant	Oral	25–100 mg nightly	
	Doxepin	Sedating anti-depressant	Oral	10–50 mg nightly	
Muscle aches, joint pain, headache	Ibuprofen	Non-steroidal anti-inflammatory	Oral	400–600 mg up to every 6 h	Avoid use in severe kidney disease and decompensated cirrhosis
	Acetaminophen	Aniline analgesic	Oral	650–1000 mg up to every 6 h	Use with caution in liver disease
Anxiety, restlessness	Diphenhydramine	Antihistamine	Oral	25–50 mg up to every 4 h	Can help with nausea Can be used in pregnancy
	Hydroxyzine	Antihistamine	Oral	25–100 mg up to every 6 h	Can help with lacrimation and rhinorrhea

[a]Availability varies by country.

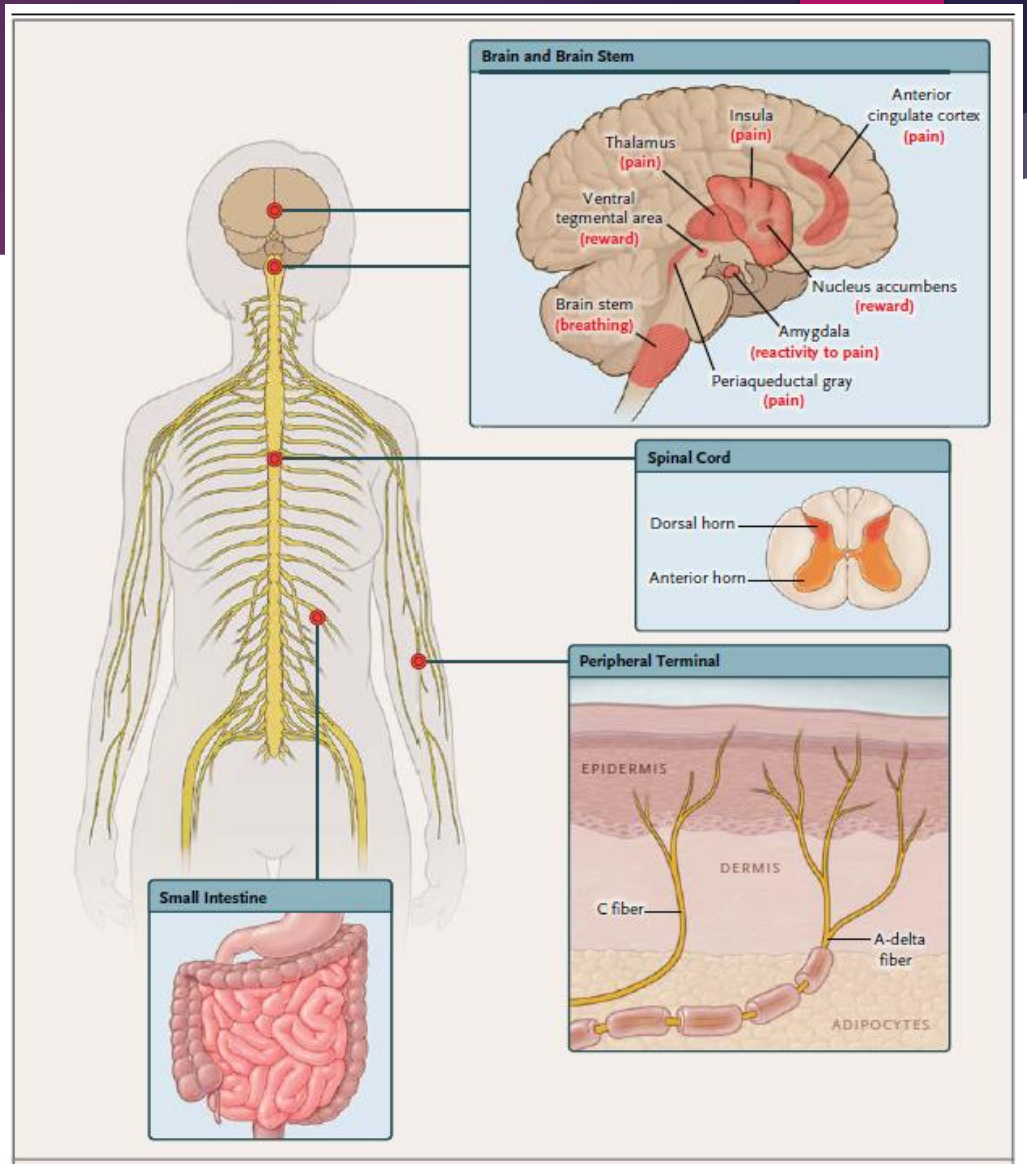
Torres-Lockhart, et al. Addiction. 2022; 1-11 DOI: 10.1111/add.15818

Pathophysiology of OUD

Reward network
- ↑ dopamine, serotonin, GABA

Executive control
- Prefrontal cortex deficits cause impairments in executive function

Emotional circuitry
- Avoid withdrawal, cravings, escape negative state, ↑ norepinephrine



Volkow, ND et al. NEJM 2015; 374: 1253-63 DOI: 10.1056/NEJMra1507771
Volkow, ND et al. Mol Psychiatry 2021; 26: 218-233 doi:10.1038/s41380-020-0661-4.

Treatment of OUD

- Medications for opioid use disorder (MOUD) favored over medication assisted treatment (MAT)-cornerstone of treatment
- 3 FDA approved medications
  - Methadone-full agonist
  - Naltrexone-antagonist (IM only)
  - Buprenorphine-partial agonist
- Bup/Methadone superior

Table 2. Adjusted Hazard Ratios for Overdose and Serious Opioid-Related Acute Care Use by Initial Treatment Group Compared With No Treatment[a]

	Adjusted Hazard Ratio (95% CI)	
Variable	3 Months	12 Months
Overdose		
No treatment	1 [Reference]	1 [Reference]
Inpatient detoxification or residential services	0.82 (0.57-1.19)	1 (0.79-1.25)
BH IOP	0.81 (0.50-1.32)	0.75 (0.56-1.02)
MOUD treatment with buprenorphine or methadone	0.24 (0.14-0.41)	0.41 (0.31-0.55)
MOUD treatment with naltrexone	0.59 (0.29-1.20)	0.73 (0.48-1.11)
BH other	0.92 (0.67-1.27)	0.69 (0.56-0.85)
ED or inpatient stay		
No treatment	1 [Reference]	1 [Reference]
Inpatient detoxification or residential services	1.05 (0.76-1.45)	1.20 (0.96-1.50)
BH IOP	0.84 (0.54-1.30)	0.90 (0.67-1.20)
MOUD treatment with buprenorphine or methadone	0.68 (0.47-0.99)	0.74 (0.58-0.95)
MOUD treatment with naltrexone	1.15 (0.69-1.92)	1.07 (0.75-1.54)
BH other	0.59 (0.44-0.80)	0.60 (0.48-0.74)

Wakeman S, et al. JAMA Network Open. 2020; 3(2):e1920622. doi: 10.1001/jamanetworkopen.2019.20622

MOUD-buprenorphine

- Death rates for OUD are highest in first month following discharge
  - **Buprenorphine NNT to prevent one death is <3!!!**
- Associated with a **37% reduction in all cause mortality** in the year following a non-fatal overdose
- 39% increased likelihood to remain in treatment 2 months post visit if buprenorphine initiation in ED

D'Onofrio G, et al. J Gen Intern Med 2017 32(6): 660-666 doi: 10.1007/s11606-017-3993-2
Kohan, et al. Reg Anesth Pain Med 2021; 46: 840-859. doi: 10.1136/rapm-2021-103007

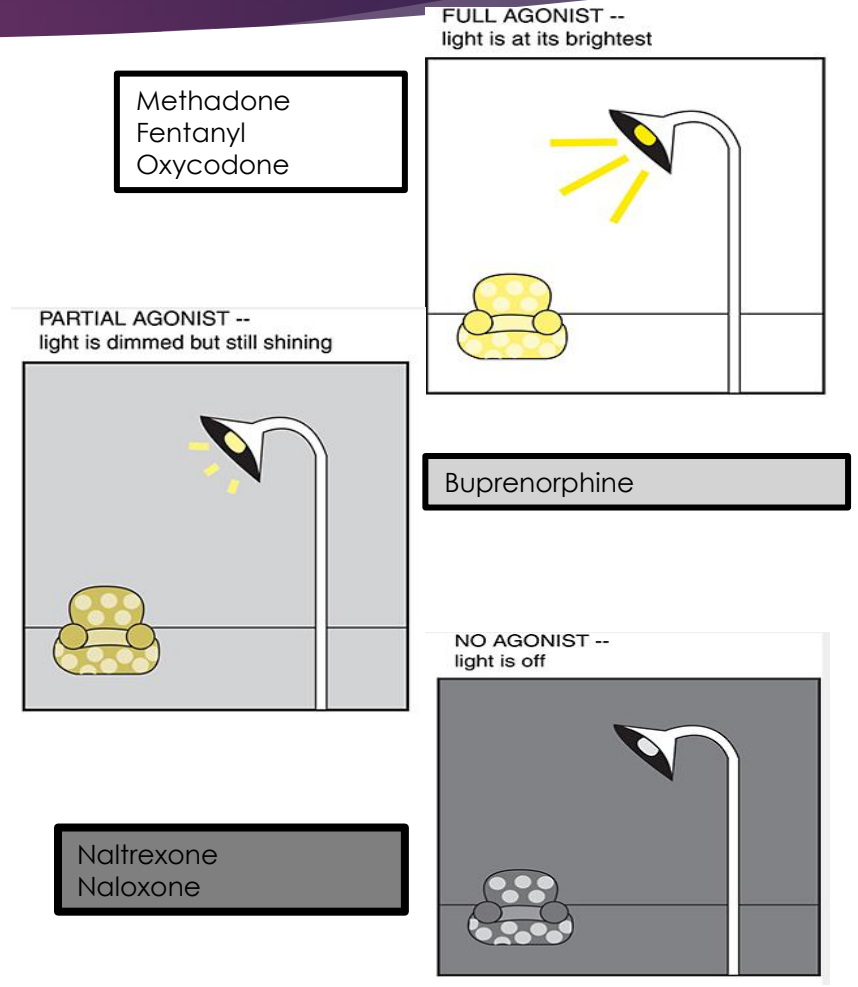
Barriers to Treatment

- Fewer than 10% of physicians completed previously required training
- Negative induction experience
- Stigma
- Inadequate education in schools and residencies
- Restrictive regulations (recently lifted)
- Insufficient coordination amongst specialists
- Prior authorizations or lack of insurance coverage

Miller, et al. Drugs in R&D 2023; 23: 339-362
Kohan, et al. Reg Anesth Pain Med 2021; 46: 840-859. doi: 10.1136/rapm-2021-103007

Buprenorphine pharmacology

- Partial mu opioid receptor (MOR) agonist, kappa/delta antagonist
- High binding affinity
- No ceiling effect for analgesia
- Ceiling effect on euphoria and respiratory depression
- Slow dissociation from MOR compared to fentanyl (166 min vs 7 min)



Gudin J, Fudin J. Pain Ther 2020; 9: 41-54. doi:10.1007/s40122-019-00143-6
Stahl, S. (2013). Stahl's Essential Psychopharmacology (4th ed.). Cambridge University Press.

Pharmacokinetics

Absorption	Distribution	Metabolism	Elimination
• 15-100% depending on formulation	• Highly lipophilic • Highly protein bound	• CYP3A4 to active metabolite	• Urine and feces • Half life varies by formulation (24 hours-60 days)

Gudin J, Fudin J. Pain Ther 2020; 9: 41-54. doi:10.1007/s40122-019-00143-6

Formulations

Buprenorphine mono products

- Sublingual tablets
  - *Subutex*
- Subcutaneous ER injection
  - *Sublocade* (monthly), *Brixadi* (monthly or weekly)

Buprenorphine/naloxone combo products

- Sublingual film, sublingual tablet
  - *Suboxone, Zubsolv*

Added as injection deterrent

Target Doses in setting of HPSO

- 2014 Cochrane review showed only high-dose buprenorphine (**≥ 16 mg**) suppressed illicit opioid use
- In the era of high-potency synthetic opioids (ie fentanyl and analogues), **≥ 32** mg has been required in some
- Patients on 16 mg had 20% increased likelihood to discontinue treatment vs **24 mg**
- 2024 study showed **>16** mg had 64% lower mortality than 8 mg in first 30 days of treatment

Mattick RP, et al. Cochrane Database of Systematic Reviews 2014 DOI: 10.1002/14651858.CD002207.pub4.
Weimer MB, et al. J Addict Med 2023 DOI: 10.1097/ADM.0000000000001202
Chambers LC, et al. JAMA Network Open 2023; 6(9): e2334540. doi: 10.1001/jamanetworkopen.2023.34540.
Lei, F, et al. J Addict Med 2024; 100: 00-00

Mono VS Combo Product

Naloxone is absorbed and can be detected in urine

Most patients who use non-prescribed route are treating withdrawal not to gain euphoria

Mono injected > combo product (tablets of both > film)

May be increased risk of overdose after cessation of combo therapy due to changes in opioid receptor exposure to naloxone

Blanket prohibition of prescribing mono may have unintended harmful consequences (shared decision making)

Increasing access to medication may mitigate diversion of either product

ER subcutaneous injection: Brixadi®

Brixadi®

- **New start**
  - SL Test dose for precipitated withdrawal
  - 16 mg (weekly)→3 days later 8 mg→24 hours later 8 mg more if needed

- **Patients currently receiving SL**

SL dose	ER weekly	ER Monthly
≤ 6 mg	8 mg	N/A
8-10 mg	16 mg	64 mg
12-16 mg	24 mg	96 mg
18-24 mg	32 mg	128 mg

ER Subcutaneous Injection: Sublocade®

Sublocade®

- SL buprenorphine x 7 days first
- 300 mg SQ monthly for first 2 months
- 100 mg or 300 mg monthly thereafter (≥26 days apart)
- Dosing delays up to 2 weeks should not impact treatment response
- Don't need SL overlap but in reality people do ~4 days

Pharmacokinetic parameters	Transmucosal Buprenorphine				SUBLOCADE	
	8 mg	12 mg	16 mg	24 mg	100 mg	300 mg
$C_{avg,ss}$ (ng/mL)	1.37 (40)	1.79 (40)	2.16 (40)	2.84 (40)	2.87 (32)	6.32 (32)
$C_{max,ss}$ (ng/mL)	4.27 (45)	5.60 (45)	6.77 (45)	8.86 (45)	5.10 (33)	11.81 (35)
$C_{trough,ss}$ (ng/mL)	0.66 (63)	0.87 (63)	1.04 (61)	1.37 (62)	2.46 (40)	5.47 (39)

Brixadi® VS Sublocade®

- Brixadi®
  - No refrigeration
  - More administration sites
  - Weekly option
  - No teratogenic ingredient in weekly version
- Sublocade®
  - Higher troughs with 300 mg
  - May be removed within 14 days if needed

Both have **REMS** programs for safe administration

- Serious adverse reactions including death may occur if injection is given intravenously

Pharmacokinetics of ER Injection

Brixadi® – Trough Concentrations	
7-day Formulation	
16mg	0.8 ng/mL
24mg	1.4 ng/mL
32mg	2.6 ng/mL
28-day Formulation	
64mg	1.3 ng/mL
96mg	2.0 ng/mL
128mg	2.1 ng/mL

Sublocade® – Trough Concentrations	
100 mg	2.46 ng/mL
300 mg	5.47 ng/mL

Sublocade. Package Insert. Indivior Inc; 2022
Brixadi. Package Insert. Braeburn Inc; 2023.

Buprenorphine ER Injection Evidence

- Potential advantages
  - Decreased need for visits, greater autonomy for travel, increased adherence/retention , less diversion/accidental exposure

Author	Design	Intervention	Outcomes
Lee, 2021	Open-label, randomized comparative effectiveness; n=52	XR monthly injection vs SL	Retention: 69.2 v 34.6% Opioid neg UDS: 55.3 v 38.4%
Cotton, 2022	Retrospective, VA population; n=26	300 mg XR injection vs 6 months prior on SL	At 6 months non-statistically significant decrease in hospitalizations, homelessness, and 90% negative urine
Marsden, 2023	Open label, multicenter, RCT; n=314	SOC (SL bup or methadone) vs bup XR injection	At 24 weeks injection had 20 more abstinent days (p 0.004); cost effective in severe OUD

Lee J, et al. JAMA Network Open 2021; 4(9): e2123032 doi:10.1001/jamanetworkopen.2021.23032
Cotton A, et al. The American Journal of Drug and Alcohol Abuse 2022; 48(3): 334-337. doi.10.1080/00952990.2021.1992773
Marsden J, et al. The Lancet 2023; 66: 102311 doi. 10.1016/j.eclinm.2023.102311

Continuation Upon Admission

- ASAM and perioperative guidelines recommend continuing buprenorphine when hospitalized
- If dose is ≥16 mg/day, may reduce dose but do not discontinue
- Split buprenorphine dose 3 X/daily for better pain control
- Why continue?
  - Patients who discontinue buprenorphine maintenance treatment had >50% chance of OUD recurrence or death
  - Risk of inadvertent overdose if medication is stopped
  - Patients are often fearful of discontinuing
  - Restarting can be difficult if on full agonist opioids

Goel A et al. Br J Anaesth 2019;123:e333-342.
American Society of Addiction Medicine (ASAM). J Addict Med 2020;14:1-91.
Kohan, et al. Reg Anesth Pain Med 2021; 46: 840-859. doi. 10.1136/rapm-2021-103007

Receptor Availability and Analgesia

Dose (mg)	Receptor availability
1	71-85 %
2	53-72 %
4	36-55 %
8	20-35 %
12	13-24 %
16	9-20 %
24	4-15 %
32	2-12 %

Common doses

- No studies investigating degree of analgesia with various level of buprenorphine receptor occupancy
- Study showed buprenorphine 16 mg did **NOT** fully block 12.5 and 25 mg heroin or 24 mg IV hydromorphone

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

Buprenorphine Initiation

Traditional

- Not high risk of precipitated withdrawal
- Feel comfortable with a 3-5 day initiation

Low

- First line for patients on full agonist opioid
- Patients with history of precipitated withdrawal
- Anticipated stay of >3-7 days

High

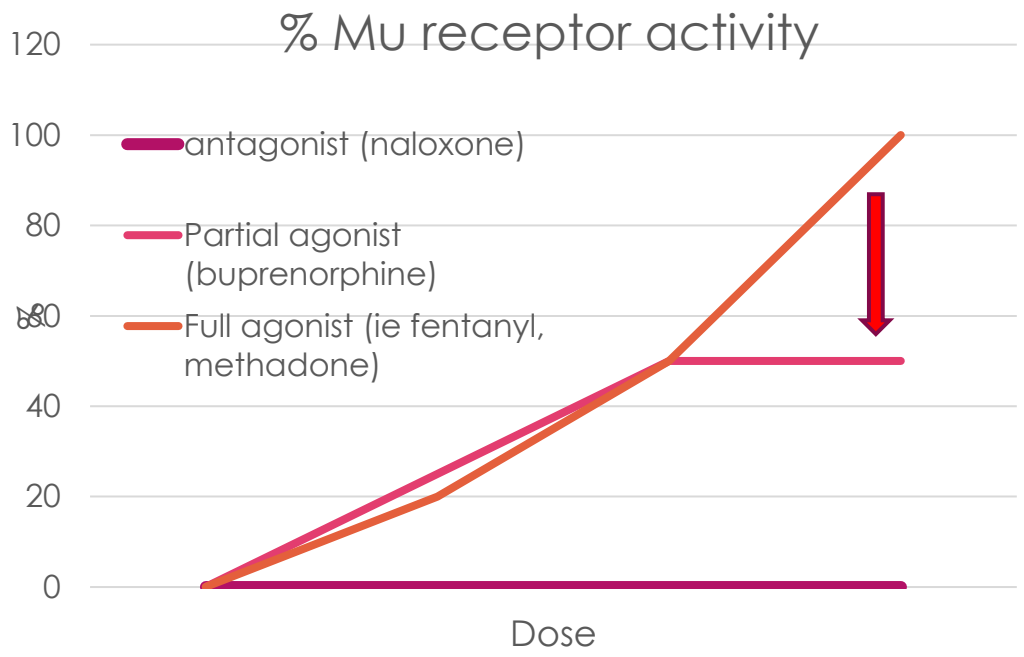
- COWS≥8
- Not admitted or brief admission anticipated
- Desire rapid titration
- Not high risk of precipitated withdrawal

Not as well studied in pregnancy, pt on sedatives, unstable medical illness and anticipated to undergo surgery in near future

Precipitated Withdrawal

- Binding affinities: lower number=higher affinity

Drug	K_i (nM)	Drug	K_i (nM)
Hydrocodone	41.58	Butorphanol	0.7622
Oxycodone	25.87	Levorphanol	0.4194
Diphenoxylate	12.37	Oxymorphone	0.4055
Alfentanil	7.391	Hydromorphone	0.3654
Methadone	3.378	Buprenorphine	0.2157
Nalbuphine	2.118	Sufentanil	0.1380
Fentanyl	1.346		
Morphine	1.168		



- Buprenorphine is a partial mu opioid agonist
- Sudden drop from full agonist to partial agonist can cause sudden withdrawal

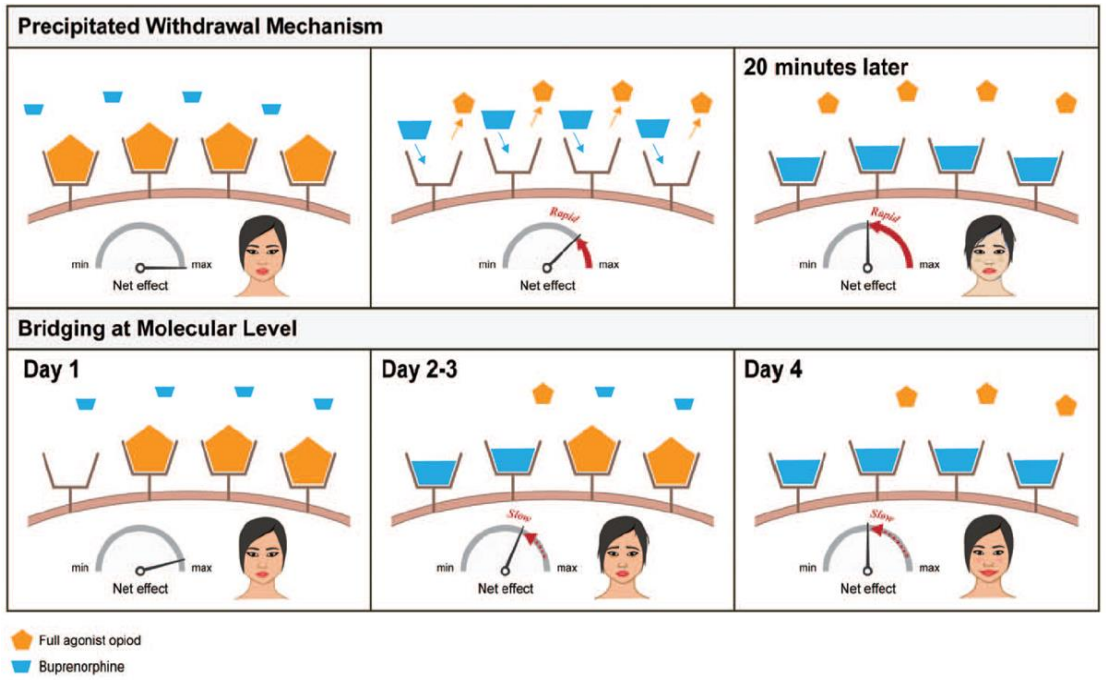
Volpe, et al. Regulatory Toxicology and Pharmacology 59 (2011) 385-390

Incidence of Precipitated Withdrawal

- ED study with 1200 participants (methadone (-), fentanyl (+))
- Randomized to 8 mg SL buprenorphine or ER buprenorphine weekly injection
- Last drug use 8 to >24 hours prior
- 9/1200 **(0.76%)** experienced precipitated withdrawal
  - 5 from SL group and 4 from ER injection group
  - All patients had fentanyl in drug screen (7/9 multiple drugs)
- 7 day follow up was 86%

D'Onofrio, et al. JAMA Network Open 2023. 6(3): 3236108. doi:10.1001/jamanetworkopen.2023.6108

Precipitated withdrawal-Prevention



- How to avoid it
  - Require withdrawal before start buprenorphine
  - Low dose initiation

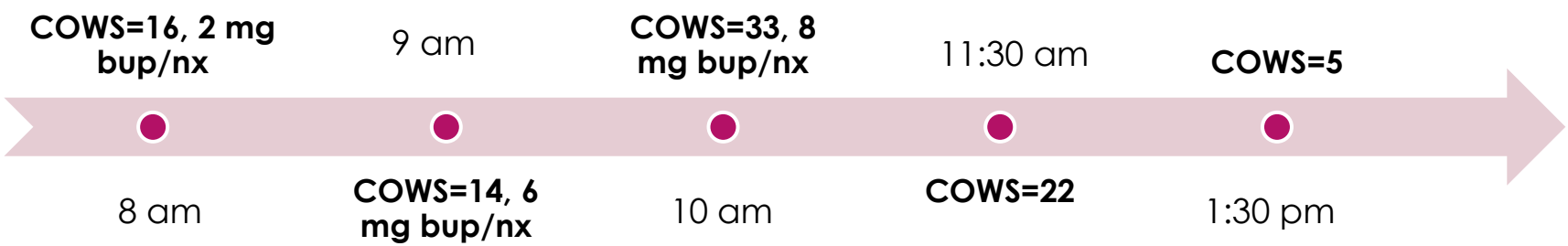
Ghosh S et al. The Canadian Journal of Addiction 2019 *DOI:* 10.1097/CXA.0000000000000072
Oakley, et al. Drug and Alcohol Review 2021; 40: 567-571. doi: 10.1111/dar.13228

Precipitated Withdrawal-Treatment

- Give full opioid agonists (i.e. hydromorphone)as needed
- Temporarily stop/slow down initiation
- Supportive medication
  - Loperamide, clonidine, ondansetron, methocarbamol, hydroxyzine
- "Flood" receptors with more buprenorphine

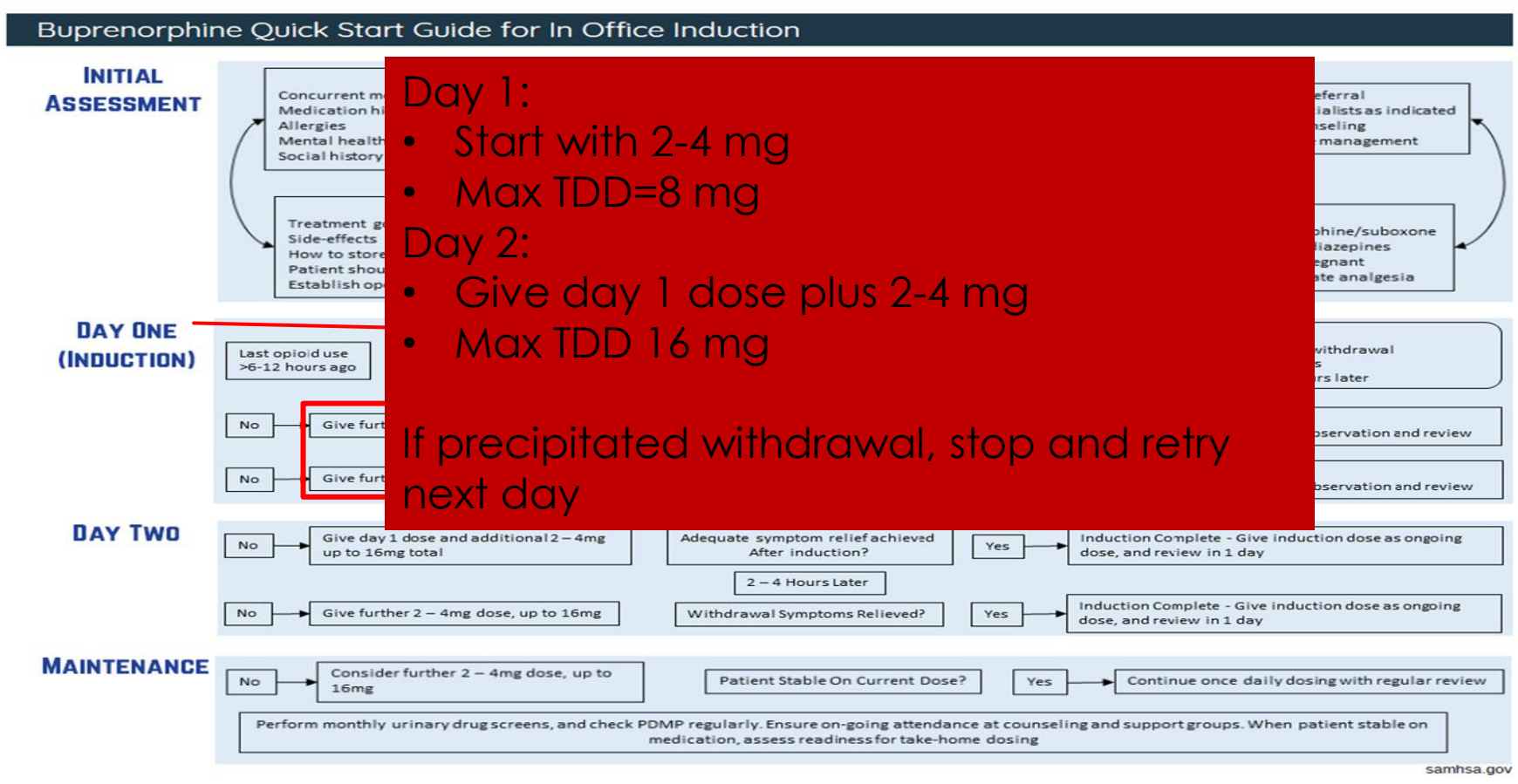
Buprenorphine for Precipitated Withdrawal

- ED macro dose study: 5/579 (0.8%) had precipitated withdrawal after 8 mg, relieved with total 28 mg
- Case report 53 year old male taking heroin and methadone



Oakley B, et al Drug and Alcohol Review 2021, 40: 567-571 DOI: 10.1111/dar.13228
Herring AA, et al JAMA Network Open 2021; 4(7): e2117128 doi:10.1001/jamanetworkopen.2021.17128

Traditional (Standard) Initiation



Day 1:

- Start with 2-4 mg
- Max TDD=8 mg

Day 2:

- Give day 1 dose plus 2-4 mg
- Max TDD 16 mg

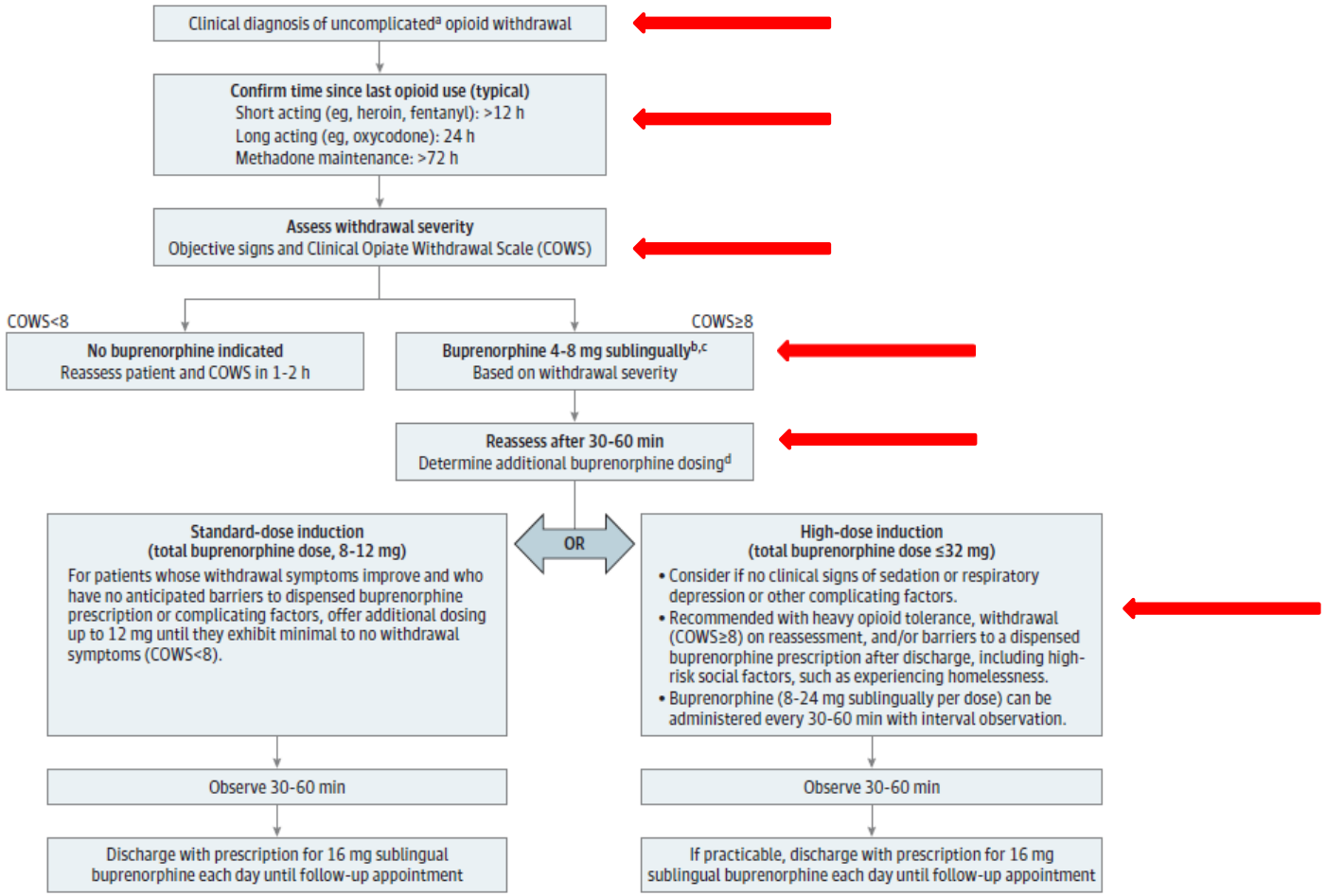
If precipitated withdrawal, stop and retry next day

High (Macro) dose initiation

Specialty consultation:

- Receipt of long-term opioid therapy for pain
- Intoxication with alcohol, benzodiazepines, or other sedatives
- Post-overdose reversal with naloxone
- Chronic pulmonary disease
- Serious acute illness and/or organ failure

Figure 1. High-Dose Buprenorphine Treatment Pathway



Herring A, et al. JAMA Network Open 2021; 4(7): e2117128 doi:10.1001/jamanetworkopen.2021.17128

High-Dose Buprenorphine Among Patients Using Fentanyl & Other Opioids

CA Bridge: implementation facilitation program for OUD in CA EDs	
Study population (2020)	16 EDs, 492 patients
Fentanyl use	44 (9.5%)
Stimulant/sedative use	40%
First buprenorphine dose	8-16 mg (80%)
Precipitated withdrawal	Overall 8(1.6%), fentanyl 2(4.5%)
Discharge Rx	>16 mg/day (25%)
Follow up @7-14 days; 30 days	46%; 37.6% (no diff with fentanyl)

Snyder H, et al. JAMA Network Open 2023; 6(3): e231572. doi: 10.1001/jamanetworkopen.2023.1572

High Dose Mono to ER injection

- Five patients testing positive for HPSO
- None on MOUD prior
- COWS ≥6
- 2-3 days of SL buprenorphine before ER injection (300 mg Sublocade®)
- Day 1 SL doses: 10-24 mg (4/5 had 24 mg)
- 2/5 got injection on day 2; 3/5 on day 3
- 4/5 patients had COWs of 0 on day of injection
- 3/5 had no opioid use at follow up (range 3-8+ weeks)

Mariani J, et al. Am J Addict. 2020; 29(4): 345-348. doi: 10.1111/ajad.13018.

High-Dose Buprenorphine/naloxone

Patient Case 1

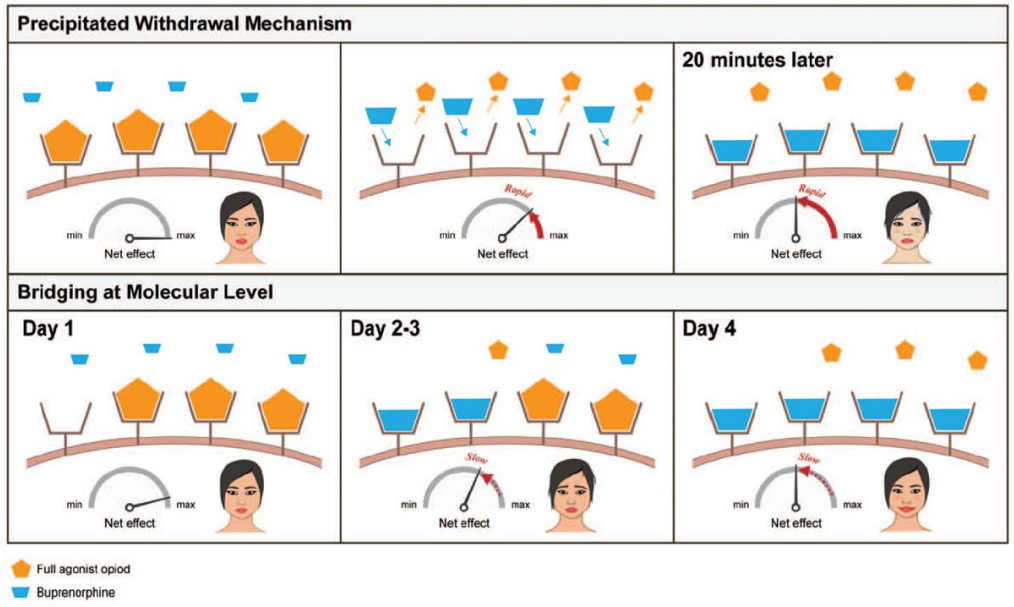
- 26 year old female injects fentanyl daily
- ED Day 1initial COWS score 16
  - 28 mg bup/naloxone in 8 hours, cows=5
  - Did have precipitated withdrawal after first 4 mg dose
- ED Day 2 received 32 mg SL followed by ER injection 4 hours later
- Followed up 4 week later for 2nd injection

Patient Case 2

- 46 year old male injects fentanyl daily x 5 years
- In ED 18 hours after last fentanyl use cows=25
  - 16 mg first dose
  - 32 mg bup/naloxone in 3 doses over 2 hours
  - Cows=14, 5 and 0
- ED Day 2 received 32 mg SL followed by ER injection 300 mg
- Followed up in 28 days reports no fentanyl use

Kahan M, et al. J Addict Med 2023; 00: 00-00

Low dose initiation



- Slowly displace full agonist opioid
- Useful for patients on full agonist opioids for OUD (ie methadone) or pain (hydromorphone, oxycodone, etc)
- No randomized trials published
- Many, many case reports and series

Ghosh S et al. The Canadian Journal of Addiction 2019 *DOI:* 10.1097/CXA.0000000000000072

Barriers to Successful Transition

- Factors associated with less likelihood of success in a review of 62 hospitalized patients
  - Older age
  - Transitioning due to discharge placement needs
    - Rehab won't take patients on methadone for OUD
  - Presence of withdrawal symptoms during transition
    - 39% of patients had some minor withdrawal
- Overall 82% successfully transitioned in this study

Bhatraju EP, et al. J Addict Med 2022; 16: 461-465 DOI: 10.1097/ADM.0000000000000947

Bernese Method

- 2 person case series
- Based on 3 part hypothesis
  1. Very small buprenorphine doses shouldn't precipitate withdrawal
  2. Buprenorphine will accumulate at receptor over time due to long binding time
  3. Over time, increasing amount of full agonist will be replaced by buprenorphine
- Demonstrated feasibility and tolerability

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

Abbreviation: sl, sublingual.

Hammig R, et al, Susbstance Abuse and Rehabilitation 2015: 7 99-105

Low Dose Initiation-Terasaki "7 Day Method"

- 3 person case report of hospitalized patients
- On methadone 40-100 mg/day
- All had successful transition
- Minimal symptoms of opioid withdrawal

Table 1. Buprenorphine Microdosing Protocol Used by Our Team

Day	Buprenorphine dosage	Methadone dose
1	0.5 mg[a] SL once/day	Full dose
2	0.5 mg[a] SL twice/day	Full dose
3	1 mg SL twice/day	Full dose
4	2 mg SL twice/day	Full dose
5	4 mg SL twice/day	Full dose
6	8 mg SL once/day	Full dose
7	8 mg SL in A.M. and 4 mg SL in P.M.	Full dose
8	12 mg SL/day	Stop

SL = sublingually.
[a]For our buprenorphine formulation, one-quarter of a 2-mg sublingual strip was used.

Terasaki D, et al Pharmacotherapy 2019 doi: 10.1002/phar.2313

Low dose Initiation-3 day sublingual

TABLE 2. Titration schedule for Case 2

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 1	0.5 mg SL q3h	2.5 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	26 mg
Day 2	1 mg SL q3h	8 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 3	12 mg SL daily	12 mg	Discontinued	

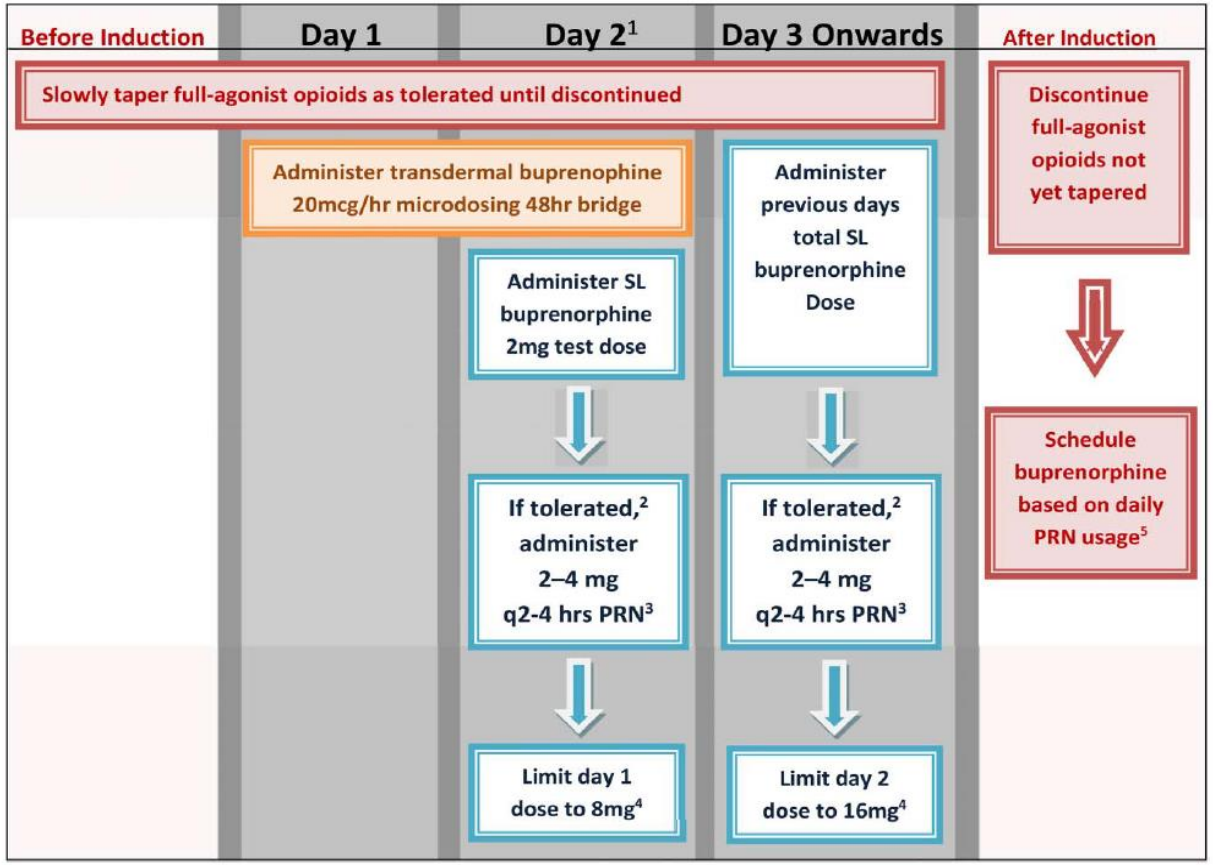
*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

- 2 case series-rapid "micro" induction
- Resulted in NO precipitate withdrawal symptoms

Klaire S, et al. Am J Addict 2019; DOI: 10.1111/ajad.12869

Low Dose Initiation-Transdermal (Off Label)

- 15 hospitalized patients
- Avg highest COWS score 3.9
- All patients who previously underwent traditional stated this was much more comfortable
- All patients reported pain controlled
- MME up to 300 mg at start



Raheemullah A, et al. American Journal of Therapeutics 2021: 28(4)

Low Dose Initiation-Other Off Label Methods

- **IV buprenorphine**
  - 3 separate case reports
  - Example 1 on 50 mg methadone
  - IV buprenorphine started at 0.1 mg up to 1.6 mg/day
  - Methadone kept same dose and discontinued on day 5 when SL buprenorphine added
  - Day 6 SL buprenorphine 10 mg
  - Experienced some withdrawal but successful transition with 4 week follow up

- **Buccal buprenorphine**
  - Case report of patient on morphine PCA (MME range 7650-1282 mg)

Day	Buprenorphine	Morphine
1	225 mcg	Full dose
2	225 mcg	Full dose
3	450 mcg	Full dose
4	2 mg SL BID	Full dose
5	4 mg SL BID	Full dose
6	4 mg SL TID	Full dose
7	16 mg SL	Stop

SL-sublingual, BID-twice daily, TID-three times daily

Spreen LA, et al Pharmacotherapy 2022; 42: 411-427 DOI: 10.1002/phar.2676
Weimer MB, et al. J Addict Med 2021; 15: 225-257 DOI: 10.1097/ADM.0000000000000745

Low Dose Sublingual to ER Injection: Brixadi®

- Outpatient case series of low dose SL buprenorphine to monthly ER injection (Brixadi®)

Day	1	2	3	4	5	6	7	8	9	10	11
Dose (mg)	0.4	0.4	0.8	1.2	1.6	1.6	2	4	6	8-12	16

Case	Demo	Full agonist	Day/dose ER
1	36 YOM	Methadone 70mg	14/96 mg
2	45 YOM	Heroin 0.5-1 G	19/96 mg
3	51 YOF	Heroin 0.5-1 G	8/96 mg
4	42 YOM	Heroin 1G + methadone 80 mg	13/128 mg
5	46 YOM	Heroin 1 G + methadone 40 mg	13/128 mg

Wee Teck JT, et al. Front. Pharmacol. d: 10.3389/fphar.2021.631784

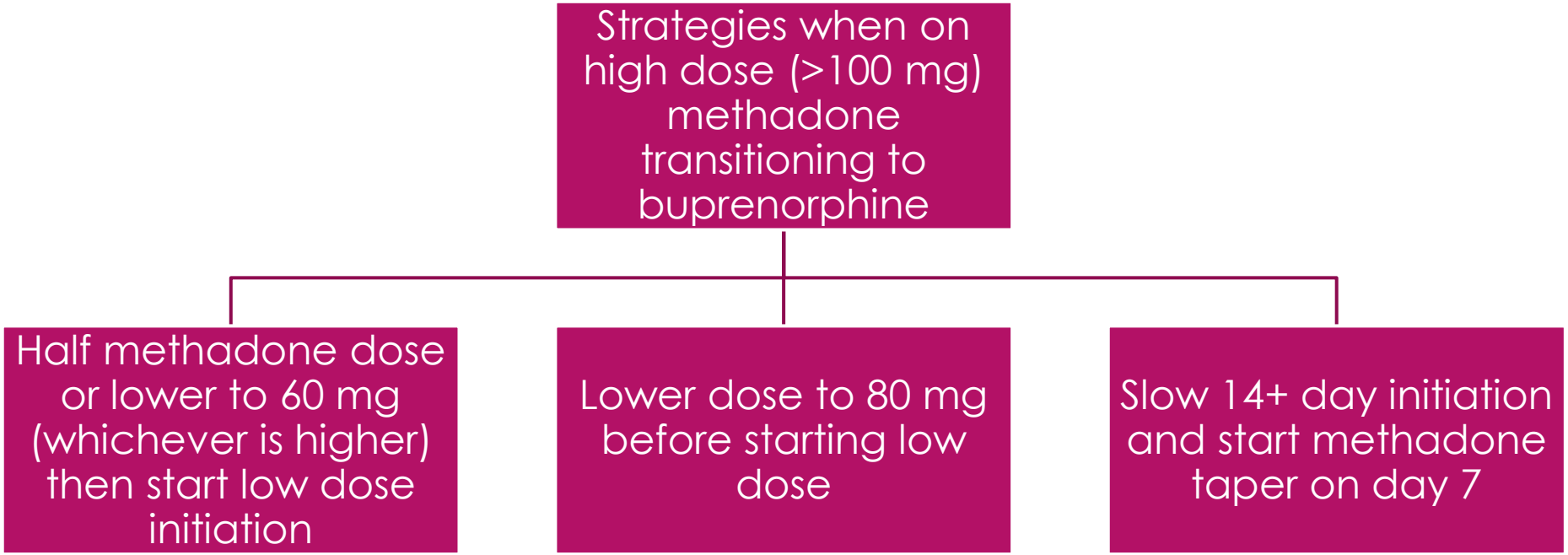
Low Dose Buccal to ER Injection: Sublocade®

- Inpatient case series of buccal buprenorphine 225 mcg doubled each day to target dose of 12 mg SL buprenorphine by day 6
- Full agonist continued and stopped on 7
- Sublocade® given on ~day 7; no COWS>5

Case	Demo	Full agonist	Infection	Surgery
1	35 YOF	Methadone 45 mg	Endocarditis	Valve
2	31 YOF	Morphine 30 mg+ hydrom 6 mg q3	Endocarditis	Valve
3	39 YOM	Methadone 60 mg + oxy 15 q4 prn	MSSA osteo	n/a
4	35 YOM	Methadone 115 mg	UE abscess	n/a
5	67 YOM	Methadone 30 mg + oxy 15 q4 prn	MRSA septic arthritis	Irrigation/debridement
6	44 YOM	Methadone 60 mg	COVID-19	n/a
7	29 YOM	IV hydro + oxy prn	Endocarditis	valve

Seval N, et al. J Addict Med 2023 DOI: 10.1097/ADM.0000000000001136

High Dose Methadone→Buprenorphine



Sulakvelidze N, et al. American Journal of Therapeutics 2023
Button D, et al. J Addict Med 2021 doi: 10.1097/ADM.0000000000000864
Wee Teck J, et al. Frontiers in Pharmacology 2021 doi: 10.3389/fphar.2021.631784

1000 Lives Campaign for Maine

- Problem Statement
  - Drug overdose deaths continue to rise in Maine. Maine needs it's healthcare organizations to partner with the State to take a leadership role in this effort to combat this crisis.
- Proposal
  - Systematic, clinician-led collaborative campaign to reduce # of opioid-related deaths in Maine by 1000 in the next 5 years
- Partners
  - Bundles: hospitals, EDs, primary pare Practices, family members, other organizations

1000 Lives Campaign-Hospital Bundle

1. Identify patients who should be initiated on MOUD
2. Offering initiation of buprenorphine
3. Maintaining patients admitted on buprenorphine or methadone during hospitalization
4. Providing bridging for patient sat time of discharge
5. Providing naloxone kits at discharge

Take Away Points

- Buprenorphine and methadone remain the cornerstone of life-saving treatment for OUD
- Buprenorphine should be continued or initiated in the hospital setting
- There are many different buprenorphine formulations and treatment approaches to best fit patient-specific scenarios
- Doses >16 mg of buprenorphine may be needed in the setting of HPSO
- We all need to do our part to contribute to saving 1000 lives in Maine in the next 5 years