

Buprenorphine Dosing Strategies in the Age of Fentanyl

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Friday, April 1st, 2022
SUD MAT ECHO

Disclosures

- No financial disclosures to report
- The evidence for buprenorphine induction using micro- and macrodoses of buprenorphine are based on case reports, case series, as well as institutional experiences
- I may discuss non-FDA approved, exploratory uses for buprenorphine beyond the package insert
 - Resolution of Conflicts of Interest:
 - I will support my presentation and clinical recommendations with the “best available evidence” from the medical literature
 - I will refrain from making recommendations regarding products that are not FDA-approved
 - I submitted my presentation in advance to allow for adequate peer review

Learning Objectives

- Identify the basic pharmacology of fentanyl
- Describe the buprenorphine traditional induction strategy
- Explain the rationale for inducing buprenorphine using different induction strategies in the age of fentanyl
- Explore the microdosing and macrodosing approaches for inducing buprenorphine

Case

- XYZ is a 45-year-old male with a past medical history significant for **30-pack year smoking history** presenting for **recurring syncopal episodes and chest pain** starting several days prior to admission. Pt stated he had episodes of **heart palpitations since his early 20s occurring once a week that would self-resolve**. He built up his own **construction business during his 20s** and developed **chronic back pain**. He was then **started on oxycodone, then obtained it illicitly** (at a reported maximum dose of 600mg daily ~900 MME), then transitioned briefly to heroin in early 30s via insufflation and had used up **to 25 bags daily of heroin for a total of 3-4 months, with the intention of remaining functional**.
- He became **“well-read” for self-managing opioid dependence** as he did not want to deal with using opioids anymore but **refused MOUD because of the “stigma”** and instead read about transitioning to loperamide. For many years, has been taking **24 boxes of 16x2mg pills (>700mg) loperamide daily**. He also took **very high doses of vitamin, magnesium, D3, fish oil, and multivitamins, and zinc** to avoid electrophysiologic changes but stated that he mistakenly took multivitamin pills instead of Vitamin C and magnesium prior to the below event.
- In the hospital, was found to have cardiac arrest requiring CPR and shock and ultimate transvenous pacer placement and then removal due to intolerability and intensity of opioid withdrawal symptoms.

Case

- **Social History**

- Started taking oxycodone and hydrocodone for chronic lower back pain which was both initially prescribed and then obtained illicitly.
- Started using loperamide 10 years ago to help with opioid withdrawal
 - **>700mg loperamide daily via OTC to wean off opioids for the last 5 years**
 - **24 boxes of 16 x 2mg pills**
- Has attempted to get into inpatient rehab outpatient but difficulty due to insurance and ineligibility for admission

Case

- **Social History**
 - Lives with parents
 - Current employment: Manager in the food industry
 - Financial support: Job
 - Currently insured
- **SUD History**
 - +Tobacco, +opioids (no history of use of MOUD), +cocaine

Case

- Mental Status Evaluation
 - Appearance: Obese male, diaphoretic
 - Behavior/Attitude: Calm, cooperative
 - Speech: Normal rate and rhythm
 - Mood: “I don’t feel well” (COWS 7)
 - Affect: Depressed
 - Thought Process: Linear
 - Thought Content: No delusions
 - Level of Consciousness: AAO x4

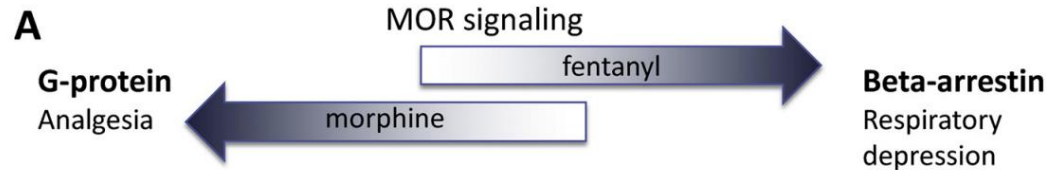
Case

- In summary, the patient was self-treating opioid withdrawal with high-dose loperamide (vs. MOUD) which also treated his pain, developed cardiac arrest, and develops withdrawal while not taking loperamide (loperamide-associated OUD?)
 - Loperamide – synthetic opioid that binds to mu-opioid receptors peripherally primarily in the GI tract with usual dose not to exceed 8-16mg.
 - Extensive first-pass metabolism
 - P-glycoprotein efflux pumps
 - Lipophilic
- What do you do?

Age of Fentanyl – Pharmacology

S.D. Comer, C.M. Cahill

Drug and Alcohol Dependence 214 (2020) 108147

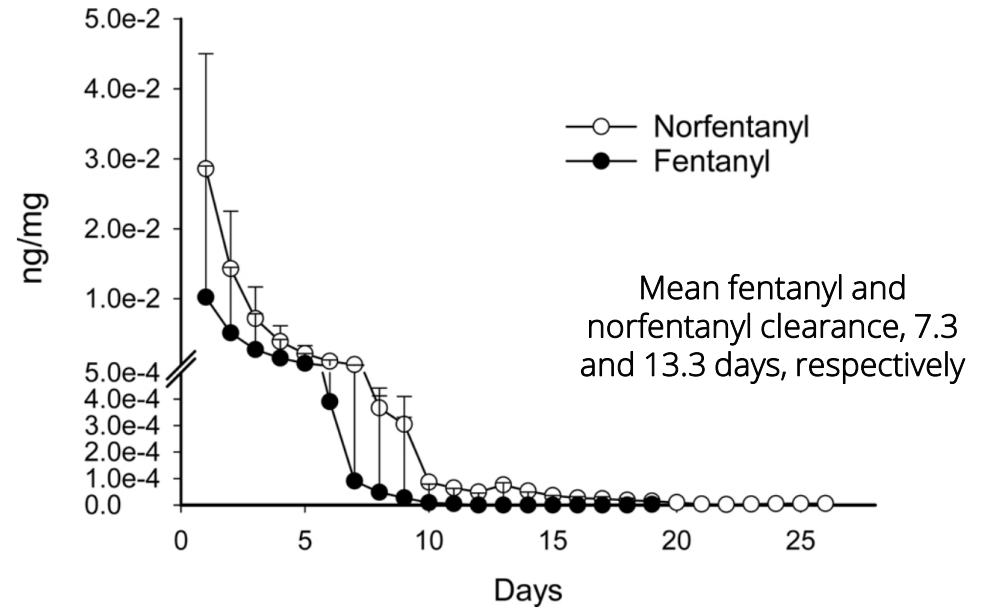


Morphine	Fentanyl
Less lipophilic	More lipophilic
Slow CNS entry	Rapid CNS entry

Fentanyl and analogs account for >70% of opioid overdose deaths

Illicit fentanyl is illegally synthesized, forming many different analogs

Fentanyl and Norfentanyl Elimination



Comer SD, et al. *Neurosci Biobehav Rev.* 2019 Nov;106:49-57.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Sep 1;214:108147.

What are the Implications of all this?

- Fentanyl, its analogs, and synthetic opioids have properties that are much different than opiates like heroin and morphine
- Fentanyl is now more often the primary opioid in the illicit opioid drug supply
- Our treatment for and ability to save lives is essentially a race to get everyone initiated on MOUD before future synthesized drugs are able to overcome current therapies

Morphine 30mg Oral ~ Fentanyl 0.1mg IV/SQ

Below is about 900 MME of fentanyl if given IV/SQ



Image from: <https://www.statnews.com/2016/09/29/why-fentanyl-is-deadlier-than-heroin/>

Why is Buprenorphine Getting the Attention?

- **Methadone** – limitations to the opioid treatment program setting
- **XR-Naltrexone**
 - High drop-out rates in trial setting during initiation
 - Retrospective study looking at mortality benefit of MOUD did not find improved mortality
 - Lower tolerance may increase risk in the age of fentanyl
 - Blocking effects may wane over a 3-week period vs. monthly
- **Buprenorphine** – the superior choice in the community-based setting?

Larochelle MR, et al. *Ann Intern Med.* 2018 Aug 7;169(3):137-45.
Lee JD, et al. *Lancet.* 2018 Jan 27;391(10118):309-18.

Many studies implemented before the age of fentanyl

Buprenorphine SL Traditional Induction

- Start with a dose of **2-4mg** of buprenorphine when patient exhibits moderate withdrawal (COWS 8-13)
 - Take 2-4mg every 2 hours as needed for a maximum dose of 16-24mg on day 1*
- On day 2, take the total daily dose of day 1 and may divide the dose. Patient can take up to a maximum dose of 24mg on day 2.*
 - Take 2-4mg every 2 hours as needed for a maximum of 24mg on day 2*
- Steady state may take 5-7 days

*As per guidance, day 1 and 2 maximum doses are 16mg and 24mg, respectively.

Requires the patient to continually assess withdrawal over several days

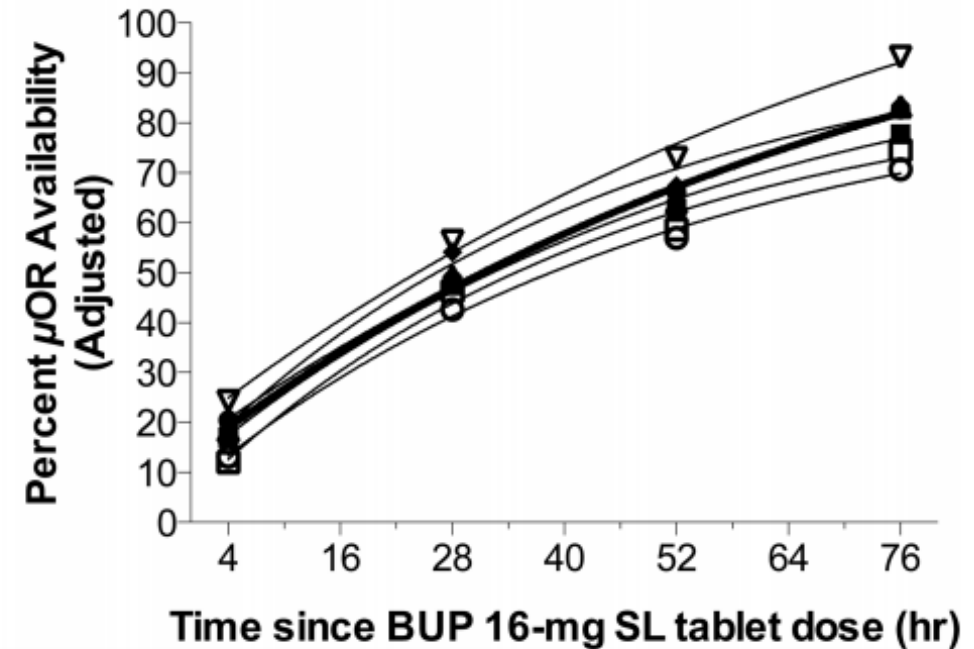
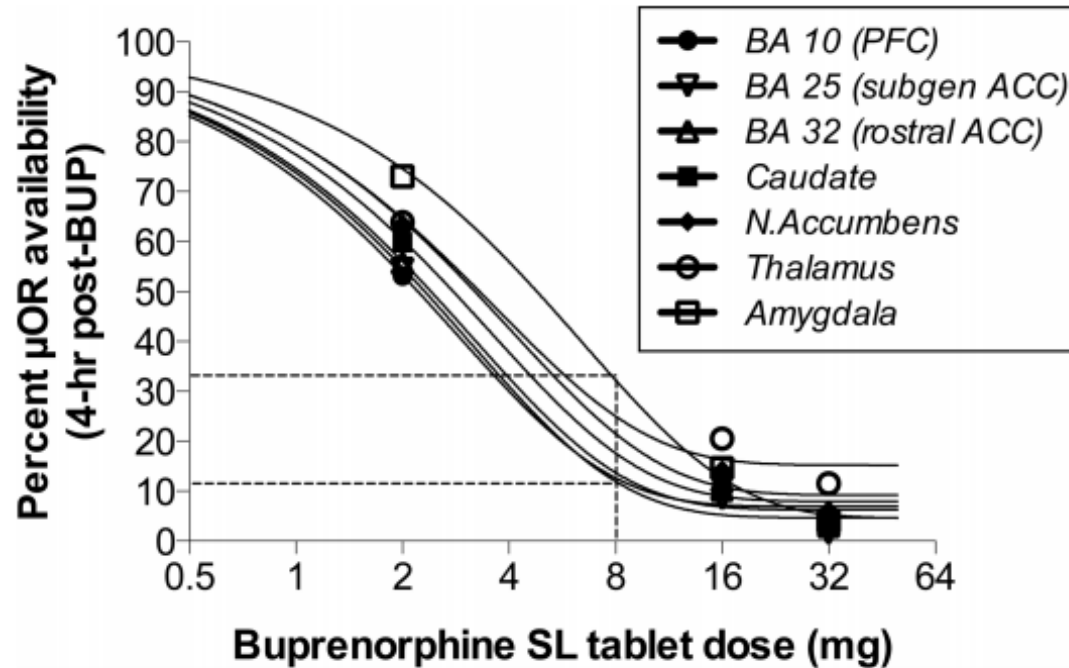
SAMHSA. Tip 63. Medications for opioid use disorder. 2018
Casadonte PP, et al. Buprenorphine Induction. Providers' clinical support system for medication assisted treatment, 2013.

Buprenorphine Maintenance Dosing

Most patients require <20% uOR availability to reduce the reinforcing effects of full opioids

Greenwald et al.

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Evidence suggests 16mg/day or more may be more effective than lower doses

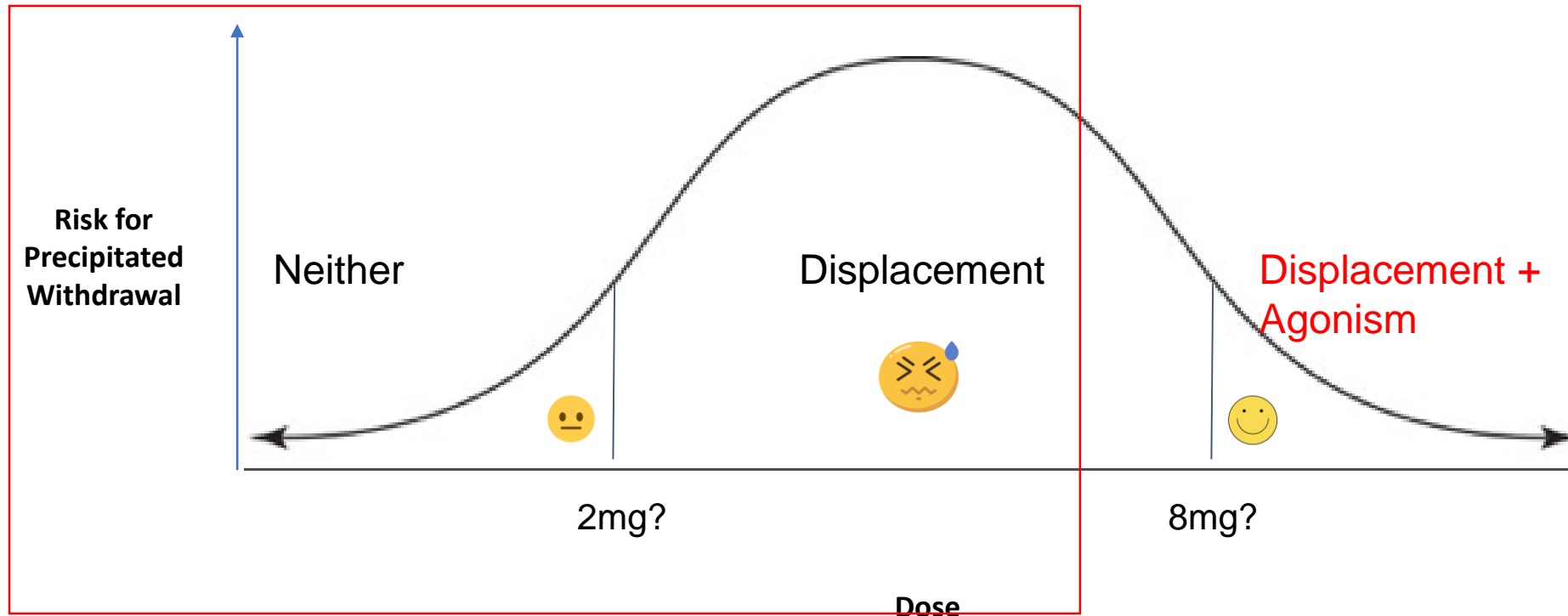
Greenwald MK, et al. *Drug Alcohol Depend.* 2014 Nov 1;144:1-11.
 Mattick RP, et al. *Cochrane Database Syst Rev.* 2014 Feb 6(2):CD002207.

So if buprenorphine is the “superior” choice outside of the opioid treatment program setting and given what we know of fentanyl and the increased risk of precipitated withdrawal, what methods are there to induct buprenorphine?

Microdosing

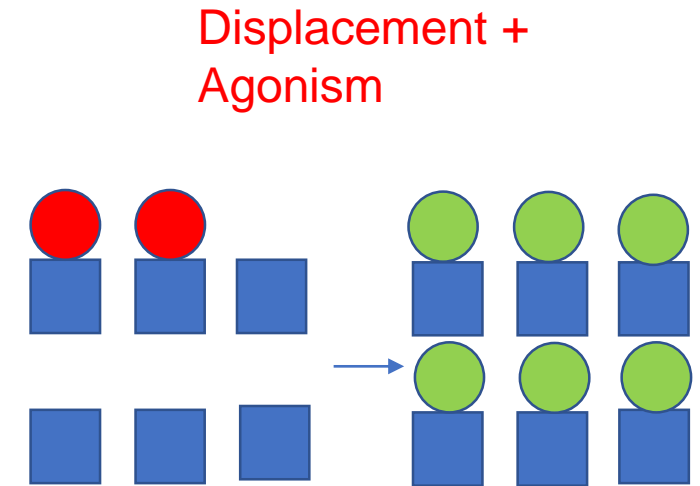
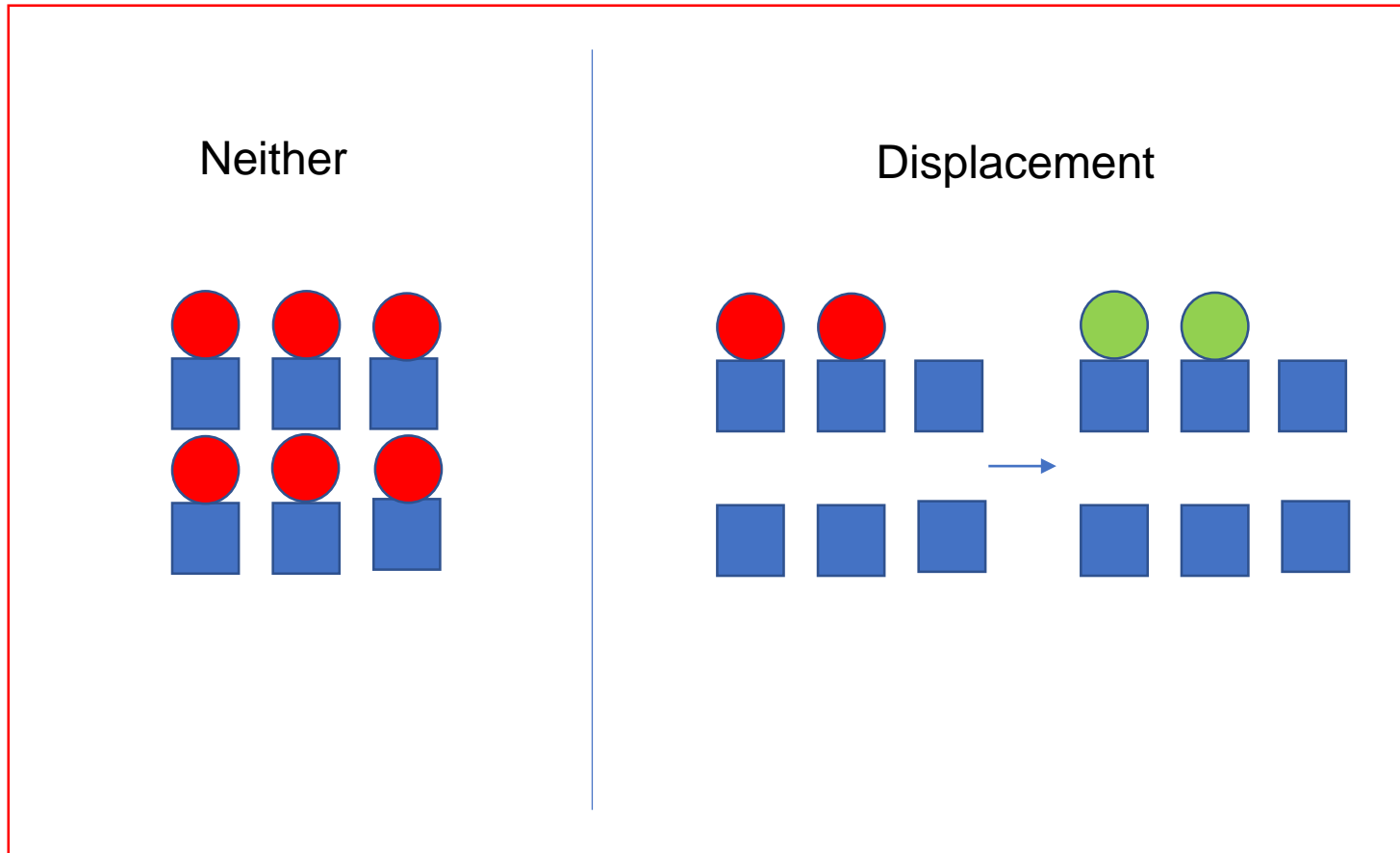
Microdosing Buprenorphine Induction - Think of a Bell-Shaped Curve...

Rationale: Avoids the need for patients to experience withdrawal before starting buprenorphine by using small successive doses



Herring AA, et al. *Am J Emerg Med.* 2019 Dec;37(12):2259-62.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Jul 2;214:108147.

Microdosing Buprenorphine Induction - Think of a Bell-Shaped Curve...



 = mu-opioid receptor

 = fentanyl

 = buprenorphine

Herring AA, et al. *Am J Emerg Med.* 2019 Dec;37(12):2259-62.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Jul 2;214:108147.

Buprenorphine Microdosing – Bernese Method

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.

^aFor our buprenorphine formulation, one-quarter of a 2-mg sublingual strip was used.

Table 3. Protocol Use in Patient 2

Protocol day	Buprenorphine total daily dose, mg	Methadone total daily dose, mg	Maximum pain score, 0–10
0	0	100	7
1	1.0	100	8
2	1.5	100	6
3	3	100	8
4	6	100	7
5	8	100	8
6	8	100	8
7	12	100	6
8	16	0	6
9	16	0	8
10	20	0	8
11	24	0	6

Buprenorphine Microdosing Using the Bernese Method – Acute Pain Management

Table 1: Microdosing Schedule for Case 1 (AB)

	Buprenorphine Dose (mg) [*]	HM
Day 1	0.5	2 mg IV q3h PRN = 6mg total
Day 2	0.5	2 mg IV q3h PRN = 8mg total
Day 3	1	2 mg IV q3h PRN = 12 mg total
Day 4	1.5	2 mg IV q3h PRN = 8mg total
Day 5	2	2 mg IV q3h PRN = 8mg total
Day 6	3	2 mg IV q3h PRN = 8mg total
Day 7	4	2-4 mg PO q3h PRN = 20mg total
Day 8	4	2-4 mg PO q3h PRN = 16 mg total
Day 9	4	2-4 mg PO q3h PRN = 12 mg total
Day 10	5	2-4 mg PO q3h PRN = 12 mg total
Day 12	6	2-4 mg PO q3h PRN = 8 mg total
Day 13	8	No HM
Day 14	10	No HM
Day 15	Discharged	

HM = hydromorphone, IV = intravenous; PO = per os.
^{*}Dispensed as buprenorphine-naloxone.

Table 2: Microdosing Schedule for CASE 2 (CD)

	Buprenorphine Dose [*]	HM
Day 1	0.5 mg	4 mg IV q3h
Day 2	0.5 mg	2 mg IV q2h then 4 mg
Day 3	1 mg	6 mg IV q3h
Day 4	1.5 mg	6 mg IV q3h
Day 5	2 mg	6 mg IV q3h
Day 6	3 mg	6 mg IV q3h
Day 7	4 + 2 + 2 mg	6 mg IV q3h
Day 8	4 mg BID + 2 mg	6 mg IV q3h
Day 9	4 mg TID	6 mg IV q3h
Day 10	4 mg TID	6 mg IV q3h
Day 12	8 mg BID	6 mg IV q3h
Day 14	12 mg BID	HM Contin 21 mg BID + PRN
Day 15	12 mg BID	Resumed 4 mg IV q3h
Day 16	24 mg daily	7 mg PO q3h routine
Day 17	Discharged	

HM = hydromorphone, IV = intravenous, PO = per os.
^{*}Dispensed as buprenorphine-naloxone.

Buprenorphine Microdosing Using the Bernese Method – Chronic Pain Management

Table 1. Daily Schedule of Buprenorphine Uptitration and Discontinuation of Full Agonist Opioid Therapy for Patient Receiving Controlled-Release Oxycodone, 80 mg 3 Times Daily

Day	Buprenorphine-Naloxone (Only Buprenorphine Dosage Listed)	Controlled-Release Oxycodone Dosage
1	0.5 mg twice daily*	80 mg 3 times daily
2	1 mg twice daily†	80 mg 3 times daily
3	1 mg 3 times daily†	80 mg 3 times daily
4	2 mg 3 times daily	80 mg twice daily
5	4 mg 3 times daily	None
≥6	Adjust dose to symptoms	None

* One-quarter 2-mg tablet.

† One-half 2-mg tablet.

Rapid “Microinduction” Using Microdosing

TABLE 1. Titration schedule for Case 1

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		1-4 mg IV q4h PRN	3 mg
Day 1	0.25g SL q4h	1 mg	1-4 mg IV q4h PRN	11 mg
Day 2	0.5 mg SL q4h	2.5 mg	1-4 mg IV q4h PRN	15 mg
Day 3	1 mg SL q4h	5 mg	1-4 mg IV q4h PRN	15 mg
Day 4	2 mg SL q4h	8 mg	1-4 mg IV q4h PRN	4 mg
Day 5	16 mg SL daily	16 mg	Discontinued	

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

Klaire et al. July 2019

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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.

“Microdosing” Without Continuing Full-Opioid Agonist

- Full opioid agonist is NOT continued
- Small doses of buprenorphine started with adjunctive therapy to prevent withdrawal
 - Primarily with alpha-2 agonist – clonidine
- May work but reason the patient may still be experiencing withdrawal is the patient is not likely meeting their opioid requirements
 - Buprenorphine more effective in treating all of the symptoms of opioid withdrawal and may need more to saturate more opioid receptors

Outpatient Microdosing Protocol

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

Advantages/Disadvantages of Microdosing

Advantages

- Eliminates the barrier of needing to experience opioid withdrawal prior to initiating buprenorphine
- Allows for overlap of full opioid agonist as buprenorphine is titrated especially in those requiring pain management
- Allows for easier conversion of methadone to buprenorphine
- May be utilized for those requiring longer lengths of stay
 - Endocarditis
 - Osteomyelitis
 - Cellulitis

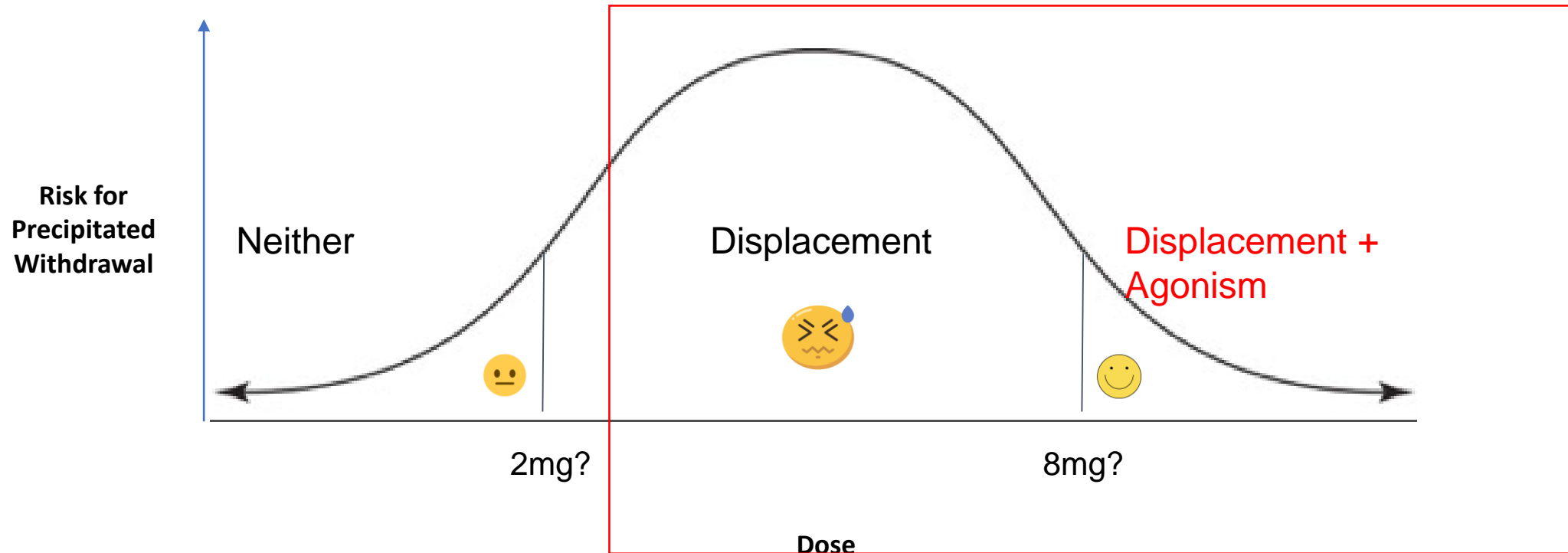
Disadvantages

- May take up to 14 days
 - Rapid microinduction?
- Most appropriate in the inpatient setting
- Requires highly motivated patient given the complexity
- Is like an “art” form – ensure that you meet patient’s opioid requirements
 - Complex in patients with comorbid OUD and pain
- Current available literature is via case series
 - Ongoing open-label, parallel-group, superiority RCT – Wong ISH et al

Macro dosing

Macro dosing Buprenorphine Induction - Think of a Bell-Shaped Curve...

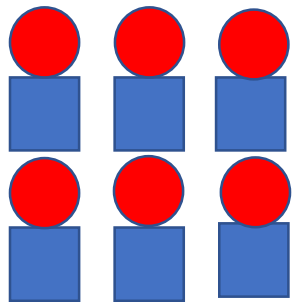
Rationale: Speeds up buprenorphine induction by reducing time in opioid withdrawal and reduces risk of precipitated withdrawal



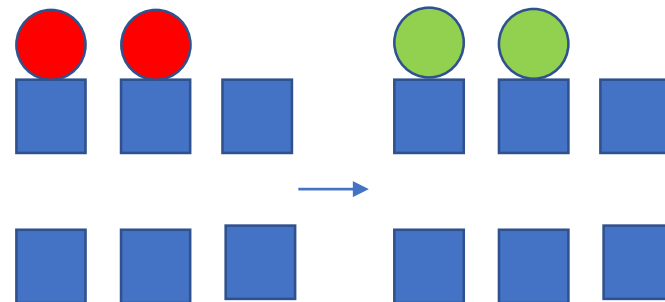
Herring AA, et al. *Am J Emerg Med.* 2019 Dec;37(12):2259-62.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Jul 2;214:108147.

Macro dosing Buprenorphine Induction - Think of a Bell-Shaped Curve...

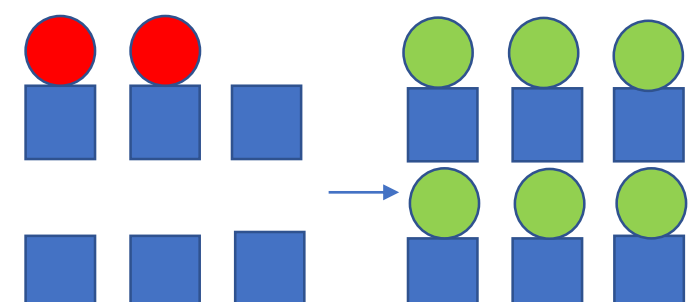
Neither




Displacement



Displacement +
Agonism



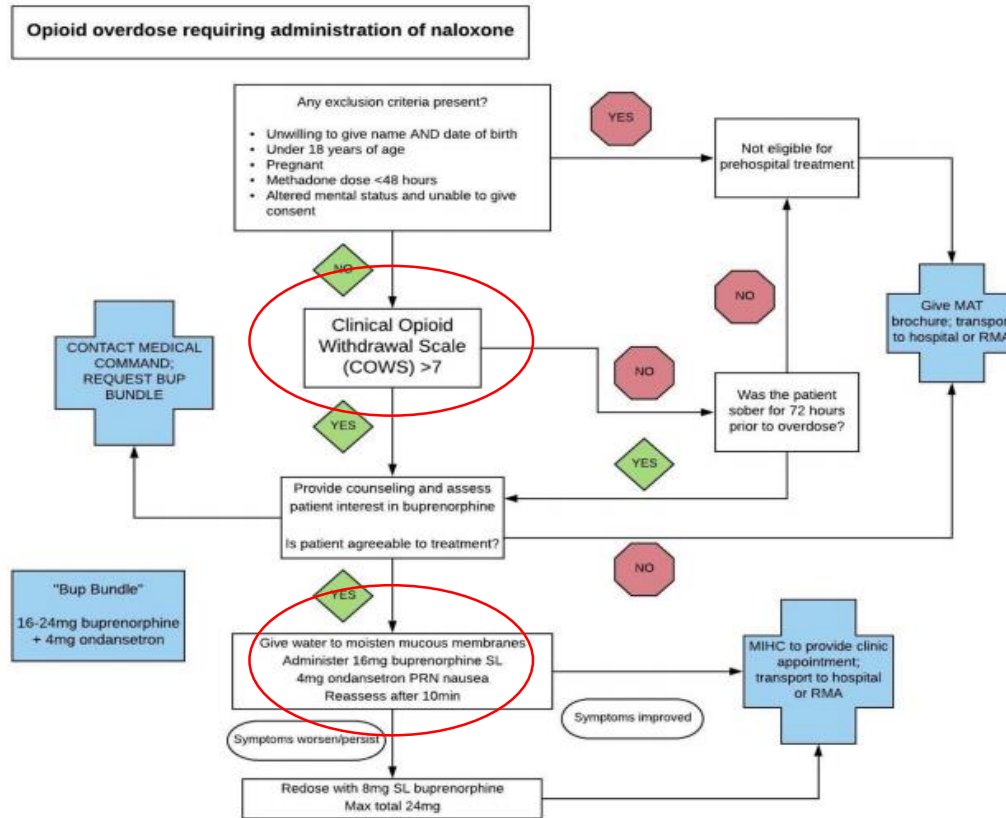
 = mu-opioid receptor

 = fentanyl

 = buprenorphine

Herring AA, et al. *Am J Emerg Med.* 2019 Dec;37(12):2259-62.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Jul 2;214:108147.

Macro dosing in the Pre-Hospital Setting



Eligibility Criteria:
COWS > 7 OR opioid-free for at least 72 hours prior to overdose

TABLE 1. Patient Characteristics and Treatment

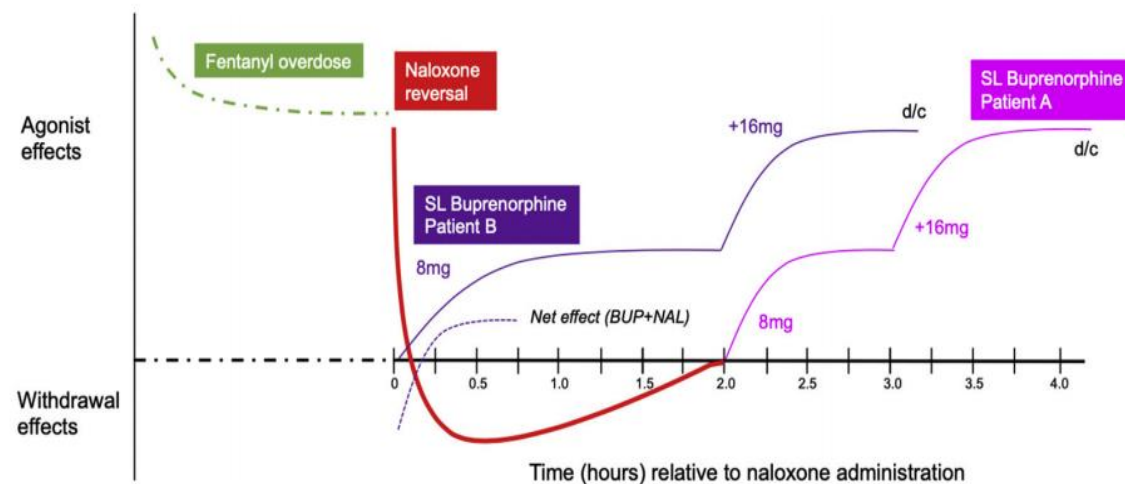
Patient	Naloxone given	Initial COWS	Buprenorphine given	Repeat COWS	1 st visit	30 day retention
A	2 mg IM	13	16 mg	3	Yes	Yes
B	2mg IM	15	16-32 mg	3	Yes	No
C	4 mg IN	12	16 mg	4	Yes	Yes

FIGURE 1. Bupe FIRST EMS Protocol.

Macro dosing in the ED Setting

- Concerns about:
 - Lipophilicity of fentanyl with chronic use
 - Protracted renal clearance

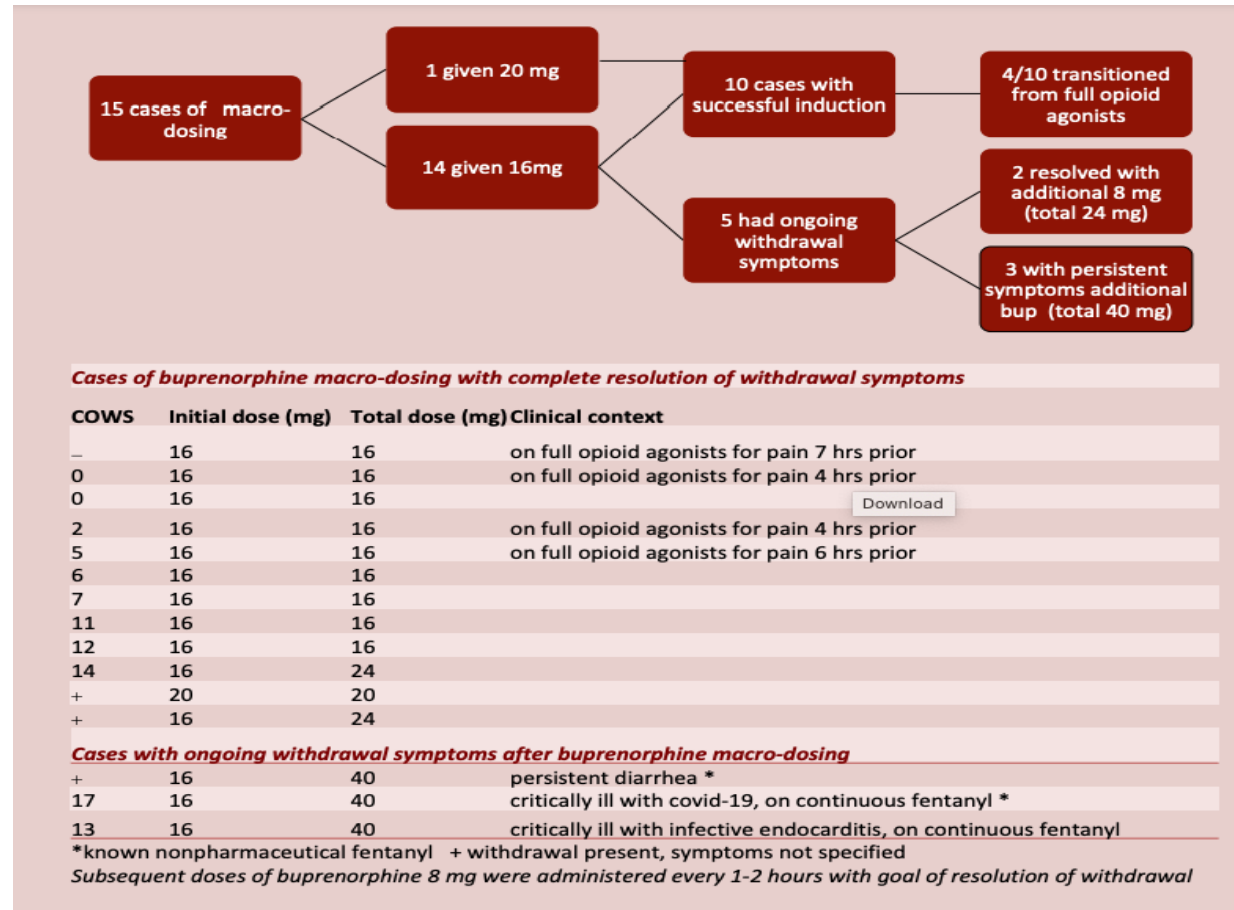
Goal: Keep fentanyl from re-binding by utilizing buprenorphine's long half-life and duration of action



Herring AA, et al. *Am J Emerg Med.* 2019 Dec;37(12):2259-62.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Jul 2;214:108147.

Fig. 3. Hypothesized opioid agonist/withdrawal outcome of ED-based naloxone reversal and buprenorphine administration for patients A and B following fentanyl overdose.

Macro dosing in the Inpatient Consult Service



Monteiro C, Golden R. ASAM Poster. Buprenorphine macro-dosing induction for OUD in the inpatient setting: a case series.

Sample Inpatient Dosing Protocol

- Buprenorphine 8mg SL x 1 on day #1 for COWS of at least 5 or significant withdrawal while awake
- After 1 hour from the initial dose,
 - Buprenorphine 8mg SL x 1 one hour after initial dose if mild improvement
 - Buprenorphine 8mg SL x 1 eight hours after initial dose if significant improvement
 - **Buprenorphine 16mg SL x 1 one hour after initial dose if withdrawal symptoms worsen**
- Maximum dose of 32mg/day?

Sample Inpatient Dosing Protocol (Continued)

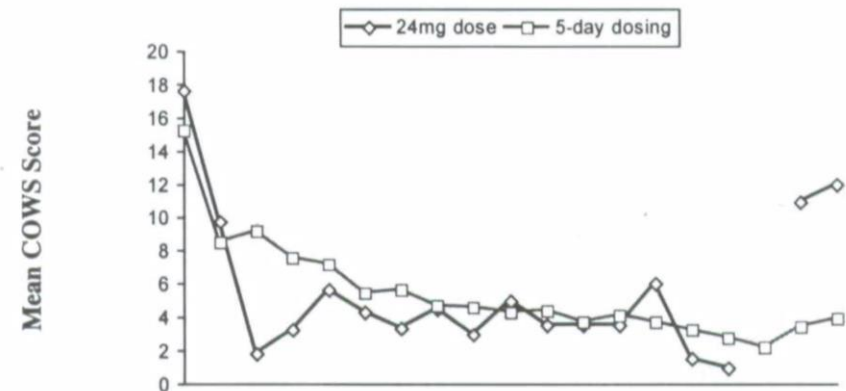
- Clonidine 0.1mg PO q8 hours PRN opioid withdrawal symptoms not controlled one hour after 2nd dose of buprenorphine. Hold for SBP<90, HR<60
- Acetaminophen 650mg PO every 4 hours PRN headache, musculoskeletal pain
- Ondansetron 4mg PO every 6 hours PRN nausea/vomiting
- Trazodone 100mg PO QHS PRN insomnia
- Lorazepam 1mg PO every 4 hours PRN severe anxiety/agitation (up to 10mg/day)
- Gabapentin 600mg PO TID PRN moderate anxiety/restlessness

Adjuncts to be used if the patient is still experiencing withdrawal after successive doses of buprenorphine

High-Dose Buprenorphine in the Literature

- Ang-Lee, et al.
 - Rationale: Single dose of 24mg for heroin detoxification due to patients leaving AMA
 - Utilize buprenorphine's long half-life and high affinity for the mu-receptor
 - Minimal use of adjunctive medication – none required diphenhydramine, loperamide, lorazepam
 - **No significant tachycardia, hypotension, or hypertension**

FIGURE 2
Mean Change in COWS, ARSW, and VAS Scores Over Time Between Subjects Given a Single Dose of 24 mg of Buprenorphine Versus Subjects Given a More Typical Five-Day Dosing



Ang-Lee K, et al. *J Psychoactive Drugs*. 2006 Dec;38(4):505-12.

High-Dose Buprenorphine in the Literature

- Ahmadi, et al.
 - Rationale: Determine the safety and efficacy of buprenorphine of using a single, high-dose of buprenorphine on craving during withdrawal over 5 days of abstinence from use of other opioids
 - 90 patients randomized to 3 groups and received either a single 32, 64, or 96mg of buprenorphine
 - Lower craving for the high-dose groups (no difference between 64 vs. 96mg)
 - **No severe respiratory, cardiovascular or GI adverse effects although hypotension observed in the 96mg group**

Table 4

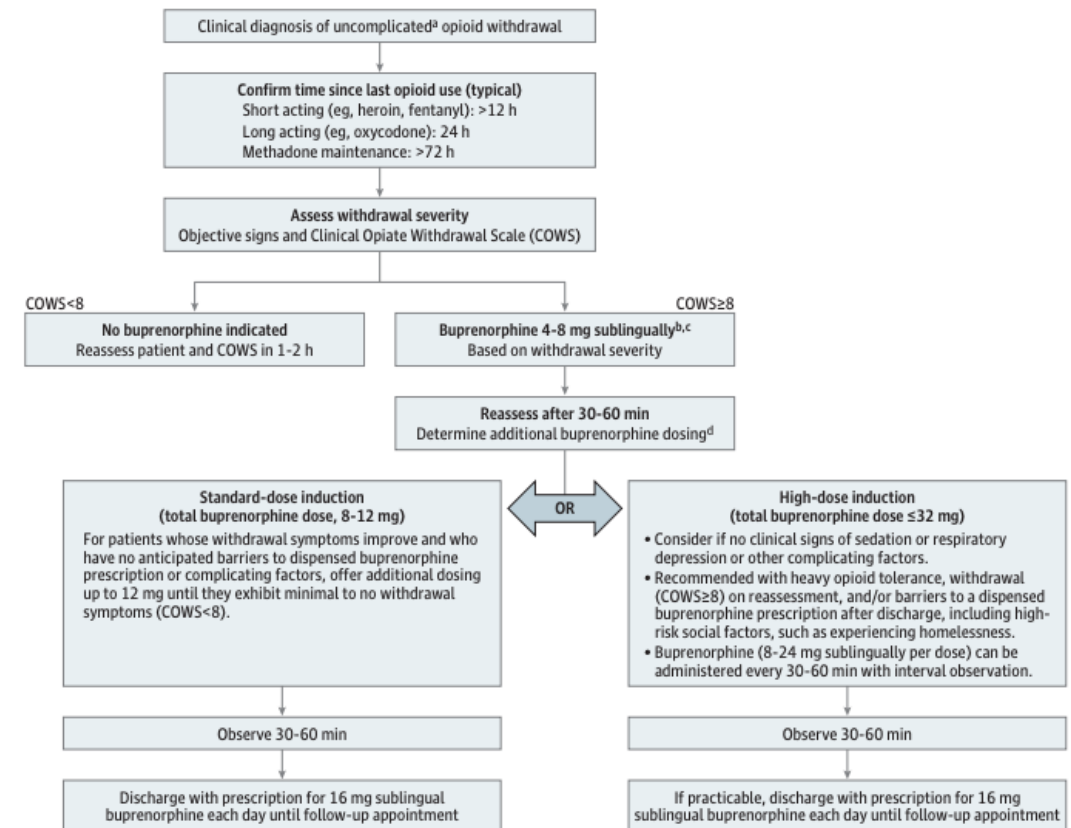
Post hoc *t* test *p* values of the three groups

Group	Baseline <i>p</i> value	Day 1 <i>p</i> value	Day 2 <i>p</i> value	Day 3 <i>p</i> value	Day 4 <i>p</i> value	Day 5 <i>p</i> value
32 vs 64	0.743	0.553	0.469	0.069	0.004	0.001
32 vs 96	0.716	0.579	0.017	0.003	0.002	0.000
64 vs 96	0.489	0.252	0.002	0.223	0.835	0.583

High-Dose Buprenorphine in the Literature

- Herring, et al. (2021)
 - **Question:** Is high-dose buprenorphine (>12 mg) induction safe and well tolerated in patients with untreated OUD presenting to the ED to help increase the safety between ED discharge and outpatient follow-up?
 - 570 cases → 391 unique cases
 - Doses up to 28mg provided (23.8%)
 - All patients appropriate with at least COWS of 8 received buprenorphine 4-8mg
 - **High-dose considered if no clinical signs of sedation or respiratory depression or other complicating factors** (>65 years, altered mental status, pregnant, methadone, intoxication with sedatives, long-term therapy for pain, or serious acute illness) after 30-60 minutes
 - No documented episodes of respiratory depression or excessive sedation
 - Vital signs, use of supplemental oxygen, presence of precipitated withdrawal, sedation, respiratory depression, adverse events, length of stay, and hospitalization
 - Precipitated withdrawal was rare (0.8%) but not associated with the dosing

Figure 1. High-Dose Buprenorphine Treatment Pathway



Herring, et al. *JAMA Netw Open*. 2021 Jul 1;4(7):e2117128.

Advantages/Disadvantages of Macrodosing

Advantages

- Faster induction that reduces the anxiety of induction
- Reduction in risk of precipitated withdrawal
- Greater receptor saturation of >90% allows for cumulative agonistic effect that reduces risk of precipitated withdrawal
- Low risk of severe adverse reactions
 - No significant hemodynamic effects
- Benefit in linking patients to care from ED to clinic
 - Reduce return of withdrawal symptoms
- No continuing of full-opioid agonist

Disadvantages

- Current literature only available in case series
 - Clinical trial currently recruiting patients evaluating loading 32mg of buprenorphine (2x16mg doses) and evaluated for successful induction
- Risks unclear with:
 - Pregnancy?
 - Concomitant alcohol/BZD use?
 - Switching from methadone with last dose <48 hours
 - Severe cardiovascular/respiratory disease?
 - Overall?

An Alternative Approach to Buprenorphine Home Induction?

- Start with a dose of **8mg** of buprenorphine when patient exhibits mild-moderate withdrawal (COWS 8-10)
 - If the patient feels worse (precipitated withdrawal), advise the patient to take 4-8mg (or more?) additional buprenorphine hourly until symptoms resolve (higher doses for greater symptoms of withdrawal)
 - Take 4mg every 2 hours as needed for a maximum dose of 24mg on day 1*
- ***In our experience**, some patients may have been advised to take more than 8mg especially if they feel worse, especially those with several failed inductions where patients may self-treat with the illicit drug*
- On day 2, take the total daily dose of day 1 and may divide the dose. Patient may take up to a maximum dose of 24mg on day 2.*
- Steady state may take faster than 5-7 days
- As per guidance, day 1 and 2 maximum doses are 16mg and 24mg, respectively.
 - **However, some patients may require more!**

What About Starting Patients Who are Beyond the Initial Acute Withdrawal Phase?

- Start at lowest possible available dose - 2mg and titrate to effect
- Observe for intoxication and side-effects
- Concern with physiologic dependence but REMEMBER...
 - Opioid Use Disorder as a chronic, relapsing disease in the setting of post-acute withdrawal syndrome
 - Multiple episodes of active, opioid use
 - Risk of overdose death especially in the era of fentanyl
- May also be an opportunity to start XR-Naltrexone

Case

- Initiation of buprenorphine
 - Given 32mg of SL buprenorphine – with little improvement of yawning, discomfort, diaphoresis
 - Given another 32mg SL buprenorphine – symptoms still not improved
 - Also, trialed on 0.6mg buprenorphine IV
 - Started on diazepam PRN for agitation - stopped
 - Initiated on 8mg of buprenorphine SL TID

Loperamide – synthetic opioid known to cause respiratory depression and cardiac arrhythmia. Case series of high-dose loperamide withdrawal treated with 16-32mg SL with good effect but need individualization of treatment

Conclusions

- Fentanyl and its analogs brings with them many challenges for treating those with OUD
- Alternative strategies need to be employed to ensure successful induction onto buprenorphine
- Microdosing and macrodosing are currently based only on **case series** of patients and **an understanding of the pharmacology of buprenorphine**
 - Strategies are still being evaluated
- Recommendations should be individualized based on patient factors
- Applying more harm reduction strategies are also needed to combat the overdoses caused by fentanyl and its analogs

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Thank you!
Questions & Discussion

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