# Challenges and Solutions to Buprenorphine Induction in the Era of Fentanyl:

## Evidence and Policy Recommendations

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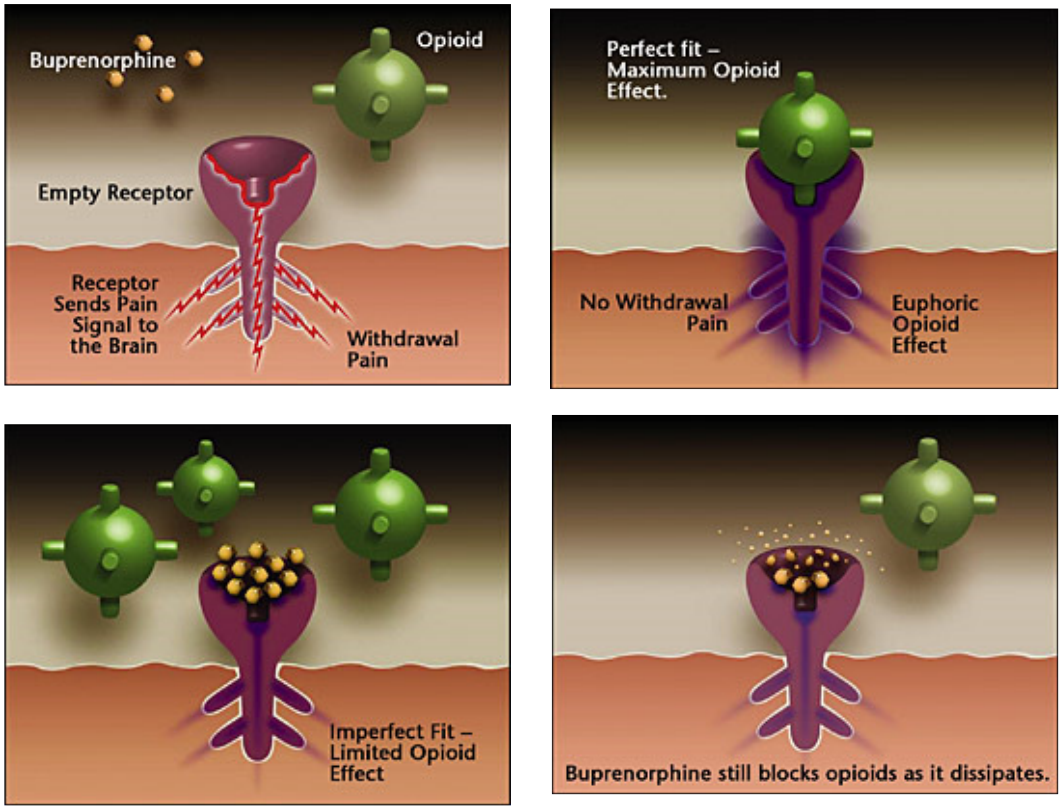
# Objectives

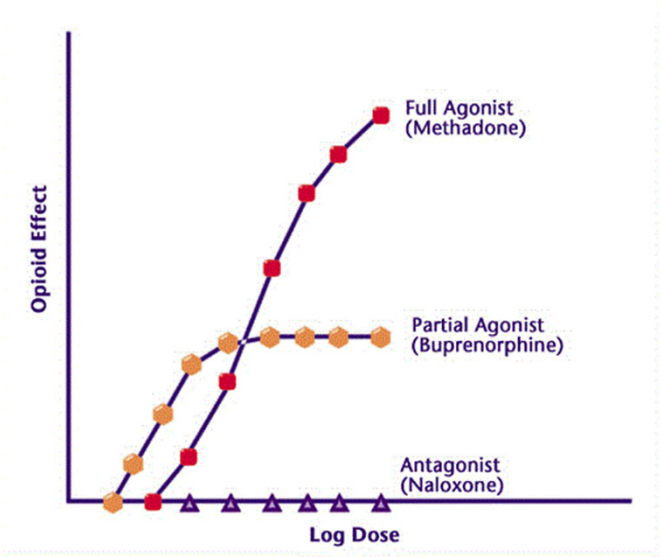
- The problem: Precipitated withdrawal and policy barriers to bupe induction
- Discuss evidence for newer induction methods
- Describe policy barriers to induction in the era of fentanyl
- Diversion: putting the elephant in the room in context
- Discuss near and long-term policy recommendations

# Review of Standard Induction



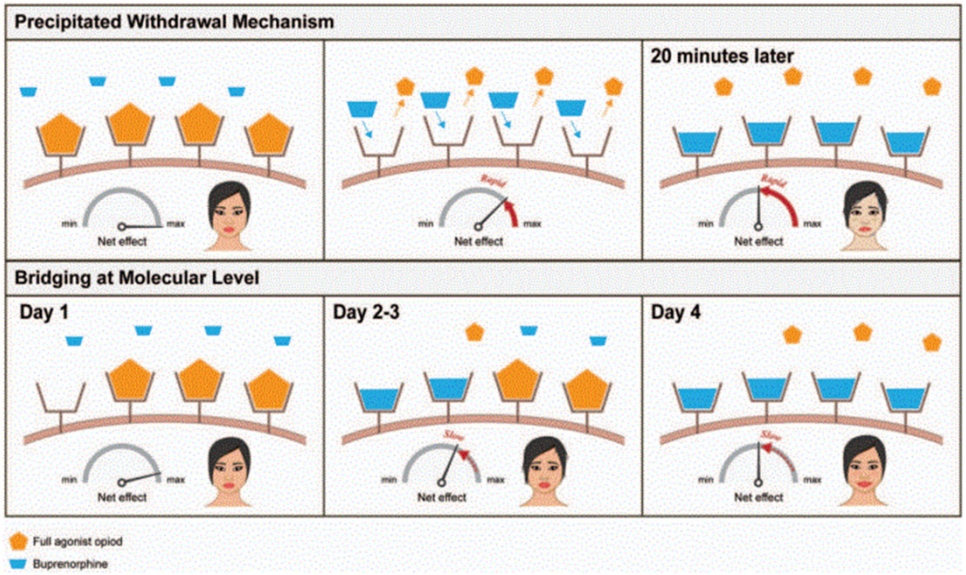
# First, what is precipitated withdrawal?

Buprenorphine: partial agonist (turns on receptor) and competitive antagonist (blocks receptor) + ceiling effect



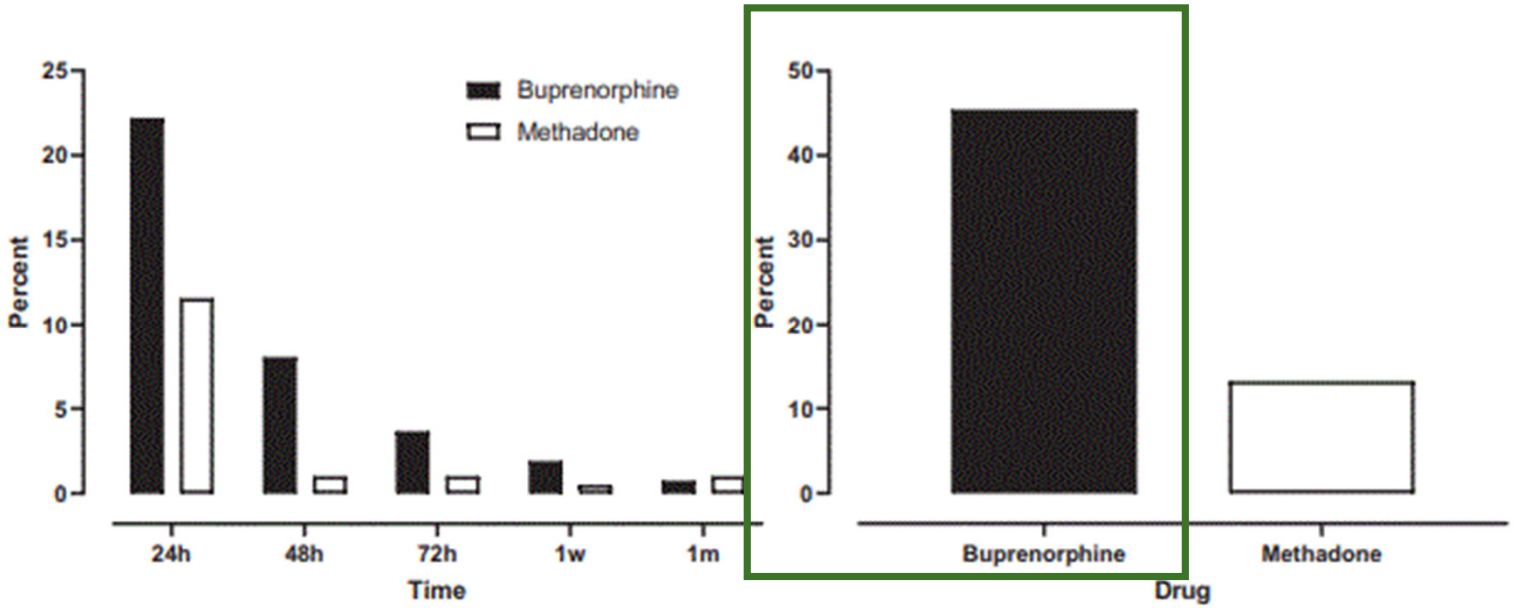

Source: naabt.org/education/technical_explanation_buprenorphine.cfm. Acc. 2/8/21.

Precipitated WD: When antagonist "kicks off" opioid agonist, provides less agonist effect




Source: Ghosh et al. Canadian Journal of Addiction. 10(4):41-50, 2019.

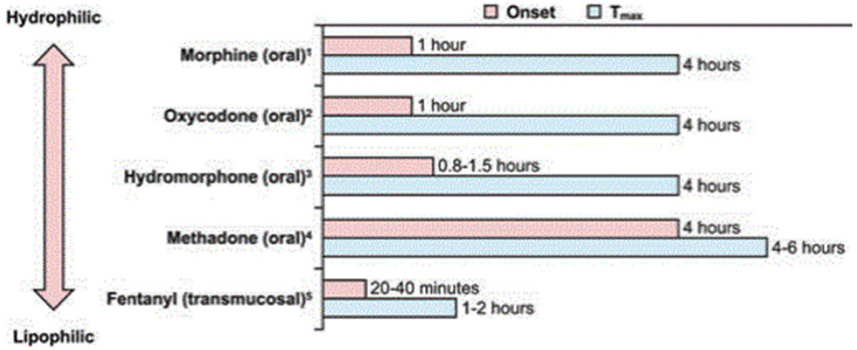
# Bupe-induced precipitated WD more common in people using fentanyl




Varshneya et al. J Addict Med. 2021 Nov 23.

# Why precipitated WD worse w/ fentanyl?

Fentanyl is very “lipophilic” (dissolves into fat) → fast action, stores in body fat[1] → sticks around...




Fentanyl has a higher binding affinity than other opioid agonists, except buprenorphine

**Table IV: Binding Affinity.**

| Opioids | Range of Ki Value | *withdrawal symptoms present when fentanyl added* | *no withdrawal symptoms present when fentanyl added* |
|---|---|---|---|
| Buprenorphine | 0.21 to 1.5 | *1.5* | *0.21* |
| Fentanyl | 0.7 to 1.9 | *0.7* | *1.9* |
| Methadone | 0.72 to 5.6 | | |
| Morphine | 1.02 to 4 | | |
| Naloxone | 1.0 to 3.0 (antagonist effects)* | | |
| Naltrexone | 0.4 to 0.6 (antagonist effects)* | | |

*Adapted from: Fudin J, Chu R, Ciani A, Raouf M. Opioid Agonists, Partial Agonists, Antagonists: Oh My! *Pharmacy Times*. January 6, 2018.

1) McCarberg B. Pain Med. 2007 Jan-Feb;8 Suppl 1:S8-13. 2) Huhn et al. Drug Alcohol Depend. 2020;214:108147.

# We need to do this differently.

## A Plea From People Who Use Drugs to Clinicians: New Ways to Initiate Buprenorphine are Urgently Needed in the Fentanyl Era

*Kimberly L. Sue, MD, PhD, Shawn Cohen, MD, Jess Tilley, and Avi Yocheved*

Other union members had not heard of low dose initiation but lamented that it may have given them a chance to access life-saving MOUD. Some people put forward anecdotes of friends or family who fatally overdosed shortly after unsuccessful and agonizing attempts to initiate with the traditional method in which precipitated withdrawal took place.

In our current fentanyl era, patients and people who use drugs are pleading with clinicians to be open to education on and willingness to attempt these novel initiation methods as we await larger trial results.[15] While it may seem contradictory to encourage clinicians to attempt this novel buprenorphine initiation method with a smaller evidence base than traditional methods, the Users Union leaders feel urgency akin to the human immunodeficiency virus/acquired immunodeficiency syndrome era, where affected patient-advocates from groups like AIDS Coalition To Unleash Power (ACT UP) pushed for access to any and all potentially life-saving treatments as they were being developed. In both contexts, directly

Sue et al. J Addict Med. 2022 Jan 11.

# Micro-induction: Bernese Method

- Usual care: STOP opioid agonist → begin to WD → start Bupe, escalate
- Bernese Method: CONT opioids → slowly ramp up bupe ~7-10 days
- Data: 100-200 case reports, 2 systematic reviews, largely very successful
- Challenges:
    1. Cont unsafe supply?
    2. Inability to prescribe pure opioid agonists for OUD
    3. PA limitations on max dose

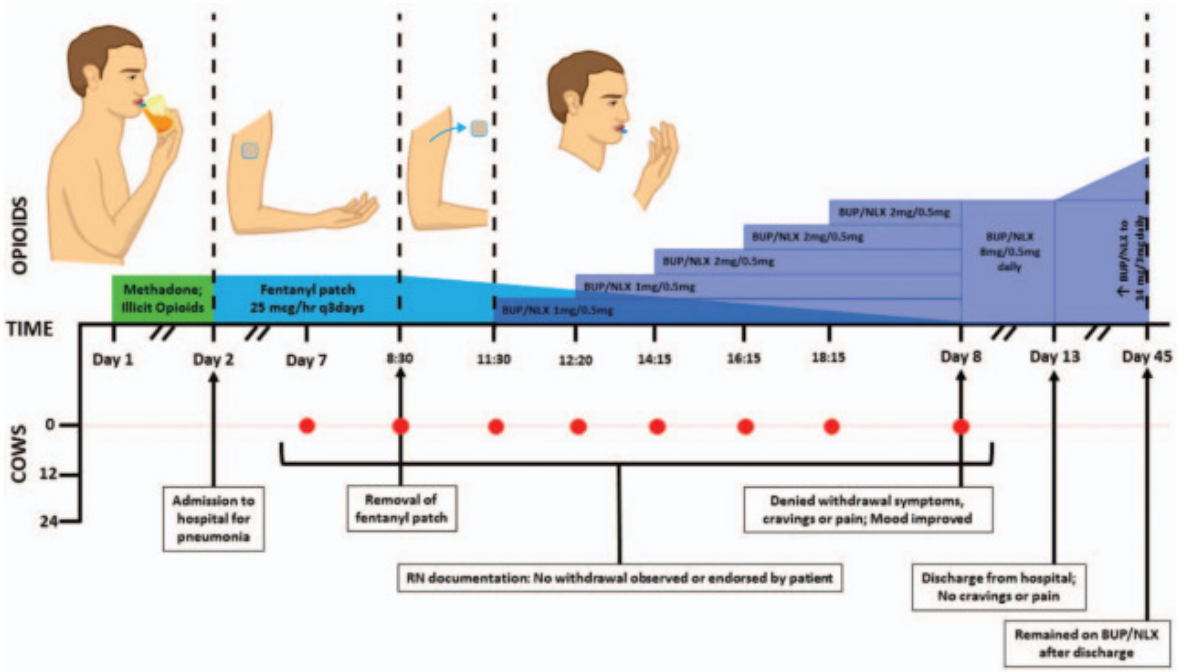
| Standard Plan | Morning Dose | Evening Dose | STOP Opioid Day |
|---|---|---|---|
| Day 1 | 0.5 mg | | |
| Day 2 | 0.5 mg | 0.5 mg | |
| Day 3 | 1 mg | 1 mg | |
| Day 4 | 2 mg | 2 mg | |
| Day 5 | 2 mg and 1 mg | 2 mg and 1 mg | |
| Day 6 | 4 mg | 4 mg | |
| Day 7 | 8 mg | 8 mg |  |
| Day 8 | Full Prescribed Daily Dose | | |

*Modified outpt version, BLP/Central City Concern, based on ref 2, 3 below

1) Ahmed et al. Am J Addict. 2021 Jul;30(4):305-315. 2) Button et al. J Addict Med. 2021 May 17:10. 3) Hämmig et al. Subst Abuse Rehabil. 2016 Jul 20;7:99-105. 4) Moe et al. Addict Behav. 2021 Mar;114:106740.

# Micro-induction w/ Transitional Opioid Agonist

- STOP opioids → START fentanyl patch → start low dose bupe (~Bernese / Micro-induction method) → STOP fentanyl patch ~ day 7-14
- We need to shift our thinking!!!




Azar et al. Am J Addict 2018;27:601-604.

# Micro-induction w/ Transitional Opioid Agonist

- STOP opioids → Morphine/SROM conversion → start low dose bupe (~Bernese / Micro-induction method) → STOP morphine/SROM day 7-14
- We need to shift our thinking!!

## Morphine / Slow Release Oral Morphine (SROM) Facilitated Induction

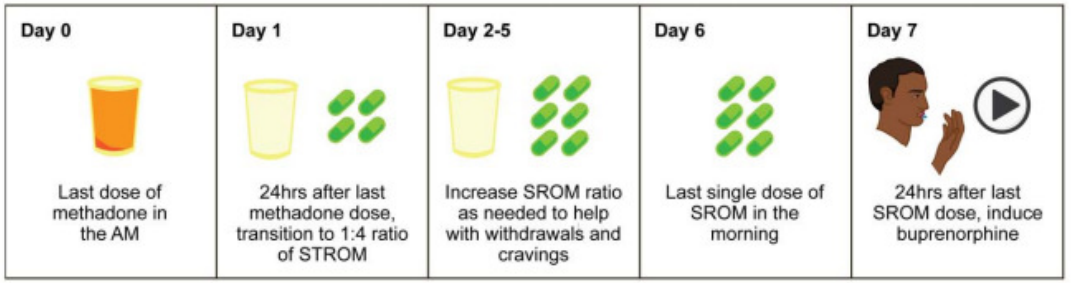



**Fig. 4.**
Calgary SROM conversion strategy. SROM = slow release oral morphine.

1) Azar et al. Am J Addict 2018;27:601-604. 2) Ghosh et al. Can J Addict. 1019; 10(9), 41-50. 3) Klimas et al. *BMJ Open* 2019;**9:**e025799.

# Rapid Micro-inductions vs. Rapid Low Dose Inductions

- Can be either with continued opioid use[1] or after cessation[2]
- Often followed by “macro-induction”
- Requires multiple 2mg tabs/films for accurate dosing
- Data: ~6 case series, clinical experience, very successful
- Challenges:
    1. Cont unsafe supply?
    2. Inability to prescribe pure opioid agonists for OUD
    3. PA limitations on max dose, # 2mg tabs/day

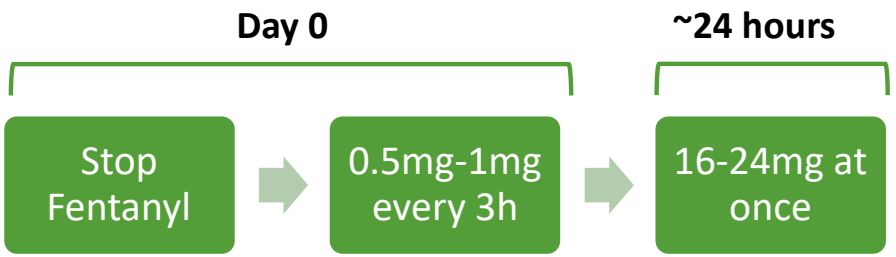
## Rapid Micro-Induction[1]

**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.

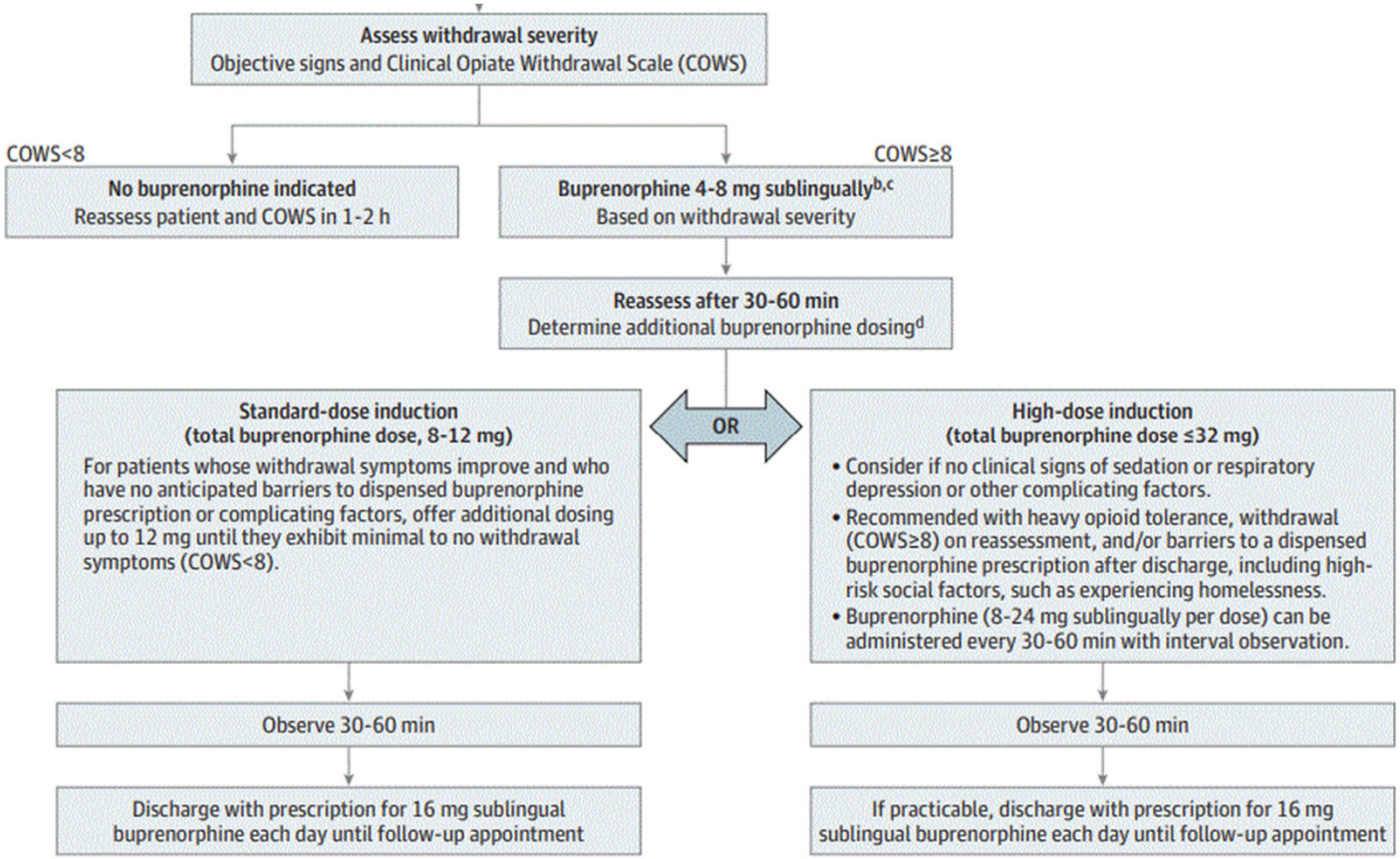
## Rapid Low Dose Induction[2]




1) Klaire et al. Am J Addict. 2019 Jul;28(4):262-265.2) De Aquino et al. J Addict Med. 2020 Sep/Oct;14(5):e271-e273. 2) Hartley et al. Prospective cohort pending publication. Fora Health, Portland, OR

# Macro-inductions: Documented Safety

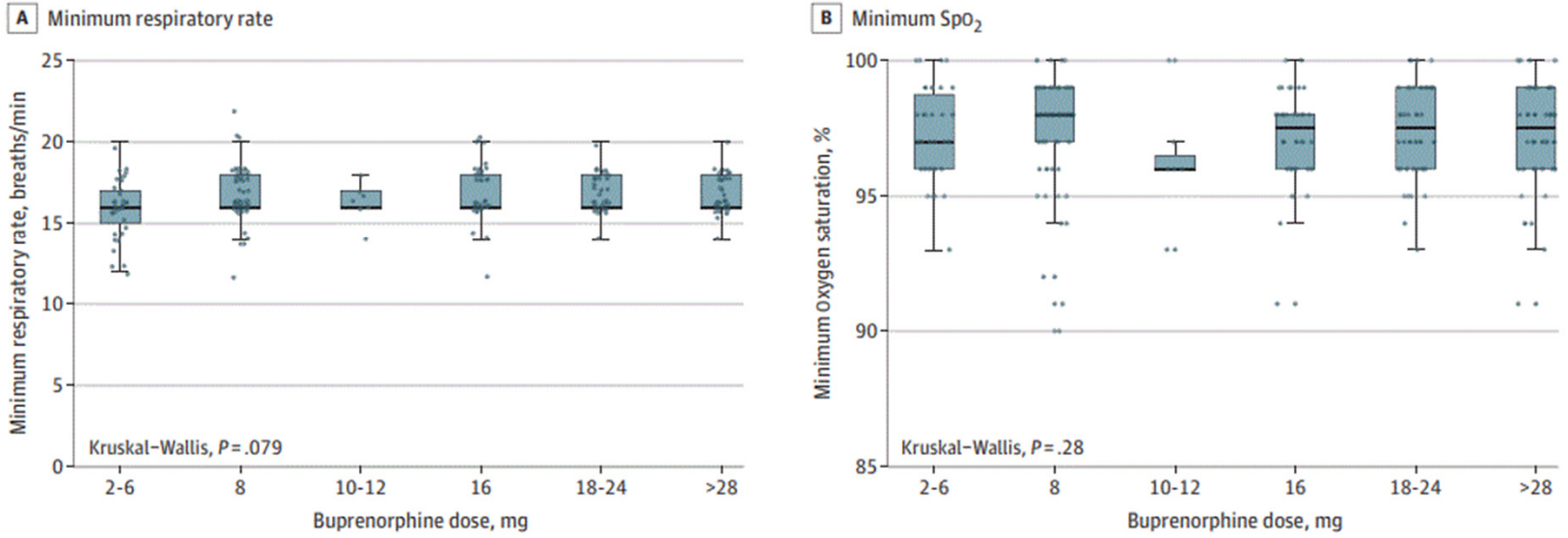
- Case series, 562 pts, ED setting
- High dose inductions: up to 24mg / 30 mins, max 32mg/day
- Monitored safety, efficacy
- 366 (63%) high dose inductions, ~ no adverse events




Herring et al. JAMA Netw Open. 2021 Jul 1;4(7):e211712o.

# Macro-inductions: No respiratory depression

**Figure 2. Minimum Respiratory Rate and Oxygen Saturation ($SpO_2$) Following Initial Dose by Buprenorphine Dose**




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

# Dispense with the Diversion Distraction!

- Usual care:
  begin to WD
- Bernese Me
  slowly ramp
- Data: 100-2
  successful
- Challenges:
  1. Cont ur
  2. Inability
  3. PA limit

| 2020 | |
|---|---|
| # | % |
| 5 | 10% |
| 6 | 4% |
| 2 | 1% |
| 8 | 37% |
| 39 | 88% |
| 0 | 25% |
| 8 | 11% |
| 0 | 6% |
| 2 | 27% |
| 7 | 11% |
| 6 | 4% |

1) Opioid-Related Fatal
https://www.healthver
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stance Use Disorder Among
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# Dispense with the Diversion Distraction!

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- Challenges:
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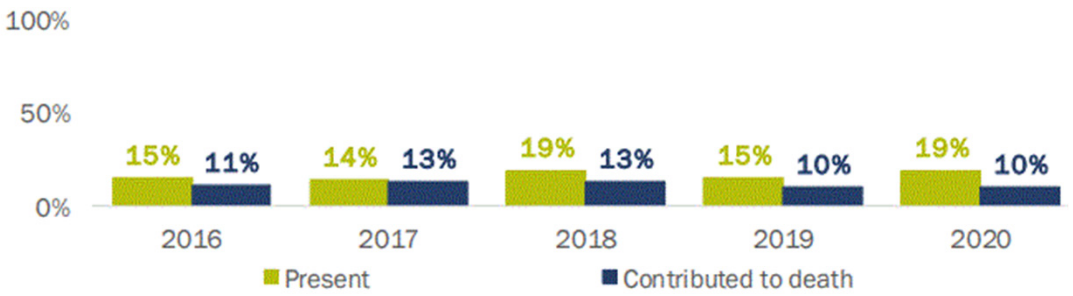
| Substance Involved | 2020 | |
|---|---|---|
| | # | % |
| Alcohol | 15 | 10% |
| Benzodiazepines | 6 | 4% |
| Buprenorphine | 2 | 1% |
| Cocaine | 58 | 37% |
| Fentanyl | 139 | 88% |
| Heroin | 40 | 25% |
| Methadone | 18 | 11% |
| Methamphetamine | 10 | 6% |
| RX opioid (no fentanyl) | 42 | 27% |
| RX stimulants | 17 | 11% |
| Tramadol | 6 | 4% |

1) Opioid-Related Fatalities Among Vermonters. Annual Data Brief. VDH, March, 2021. https://www.healthvermont.gov/sites/default/files/documents/pdf/ADAPOpioidFatalityDataBrief2020_Final.pdf. Accessed 2/16/2022. 2) VDH. Treatment for Substance Use Disorder Among People who Died of a Drug Overdose. https://www.healthvermont.gov/sites/default/files/documents/pdf/ADAP-treatment-for%20SUD-2016-2020.pdf Accessed 2/16/2022

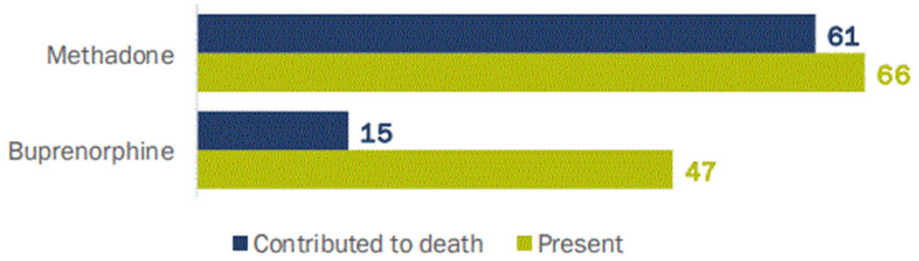
# Dispense with the Diversion Distraction!

- MOUD present in only 19% deaths 2020
- Bupe “contributed” to death in only 15/663 (2%) of deaths 2016-2020
- All despite widespread diversion

**Methadone and buprenorphine were not present in the toxicology results of most people who died of an overdose between 2016 and 2020.**




**Buprenorphine contributed to fewer deaths than methadone between 2016 and 2020.**




1) Opioid-Related Fatalities Among Vermonters. Annual Data Brief. VDH, March, 2021. https://www.healthvermont.gov/sites/default/files/documents/pdf/ADAPOpioidFatalityDataBrief2020_Final.pdf. Accessed 2/16/2022. 2) VDH. Treatment for Substance Use Disorder Among People who Died of a Drug Overdose. https://www.healthvermont.gov/sites/default/files/documents/pdf/ADAP-treatment-for%20SUD-2016-2020.pdf Accessed 2/16/2022

# Beyond Induction: PA and other barriers to maintenance

- Many patients require 24mg to reduce cravings, improve retention, but PA requirement can lead to gaps in pharmaco-continuity / withdrawal with dose changes, or prevention of optimal induction practice
- Limiting max #2mg doses/day can make tapering or smaller dose changes challenging
- Restrictions on dispensing partial buprenorphine strips complicates induction and dose titration, and adds cost to patients
- Limiting access to Subutex (based on real or perceived intolerance of bupe/nx), prevents many individuals form initiating treatment

# Summary

- Fentanyl has completely changed treatment, yet outdated prior authorizations based on old data (or no data) still rein
- Buprenorphine induction now more complicated, prior auth and dose frequency limitations put patients at risk of loss to follow up
- New induction technique data limited, but this is a crisis and largescale clinical trials take time: we must act now!
- High dose buprenorphine up to 32mg is safe
- Subutex (bupe monoproduct) may have a role in addressing perceived tolerability of treatment
- Diversion is common… very little will change this, but bupe is not the problem

# Policy Recommendations

- Remove all prior authorizations for FDA approved medications to treat OUD
  - Allow buprenorphine doses up to 24mg in all patients, up to 32 mg for at least short periods of time
  - Remove payer restrictions on number of smaller buprenorphine dose formulations (e.g. 2mg tabs/strips) to facilitate induction
  - Allow greater flexibility for partial buprenorphine strips and ask board of pharmacy to improve education and supervision of community pharmacies

# Policy Recommendations

- Recommend an assessment of methadone access in the state
  - Many methadone clinics have limited hours
  - Significant distances between clinics, large regions underserved
  - Mobile Methadone an option now, doesn't exist in the state
- Allow greater regulatory flexibility for treatment programs
  - Hub and Spoke has some successes, still can be rigid with areas underserved
  - No options to apply for new preferred providers, despite stagnant treatment rates

# Policy Recommendations

- Remove sunset on buprenorphine decriminalization
  - Bupe is not the issue – 1% deaths in 2020 with bupe in their system
- Maintain and increase Harm Reduction funding
- Focus new settlement funding on reparative work

# Long term we need real policy reform!

- Overdose Prevention Sites
  - We have missed our opportunity to pass OPS legislation this year, but I strongly urge you to move this legislation next year
- Decriminalization
  - Support H. 644 next session: We cannot start to heal until we begin to tell everyone who uses drugs that they are part of our community  and not criminals for simple use.

# Thank you


## Contact

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## Appreciations

- Jackie Bray, Erin O'Keefe, Safe Recovery
- Rich Rawson, UCLA