Oregon Fentanyl Crisis:
What We Have Learned & the Most Current Treatment Approaches

Jennifer Hartley PhD MD

Chief Medical Officer, Fora Health

Acknowledgements

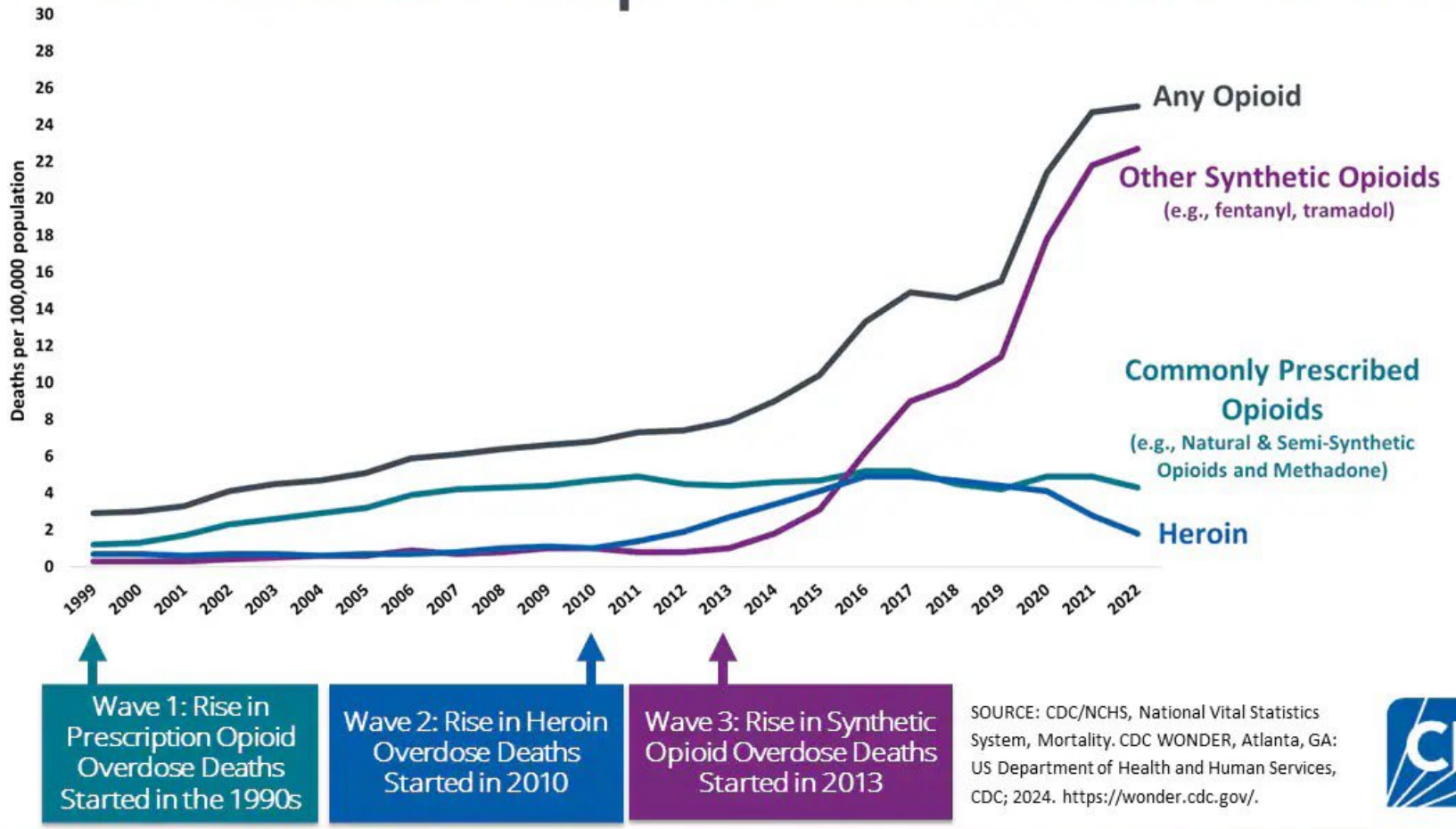
Bottom line (spoiler alert!)

- Fentanyl poses unique challenges for the treatment of opioid use disorder
- Collaboration was and will continue to be critical to addressing this crisis
- Pay close attention, with love, to each patient and their experience.

To get to the bottom line

- When fentanyl showed up
- Why it is different for patients and providers
- Innovations and Collaboration
- Next steps

Three Waves of Opioid Overdose Deaths

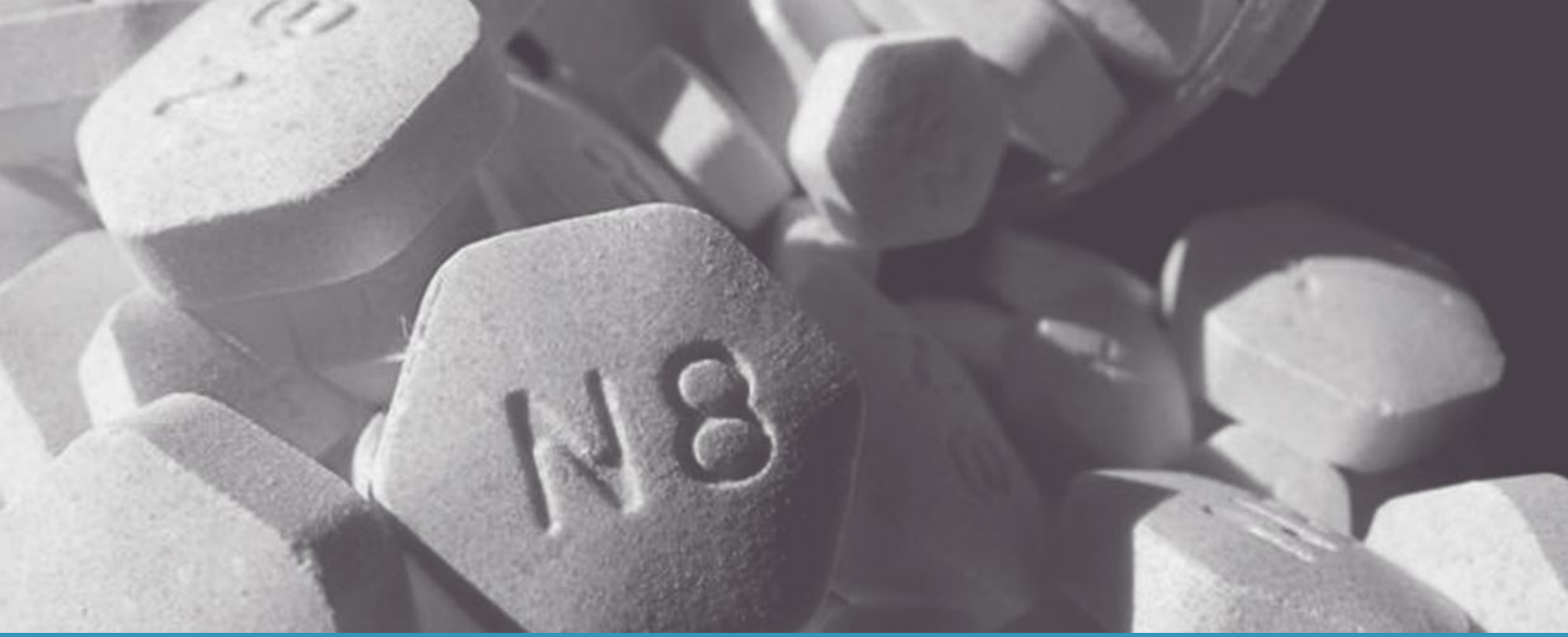


SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2024. https://wonder.cdc.gov/.

CDC

2019 - 2020 OHSU Addiction Medicine Fellowship

- Emphasis on addressing the opioid crisis
- Predominantly patients using IV/IM
- Focus on the use of buprenorphine to address withdrawal and craving for opioids



Buprenorphine

Why is it so great?

- It decreases opioid cravings, withdrawal, and use.
- It can be prescribed by providers in any setting just like any other medication.

Why is it so great?

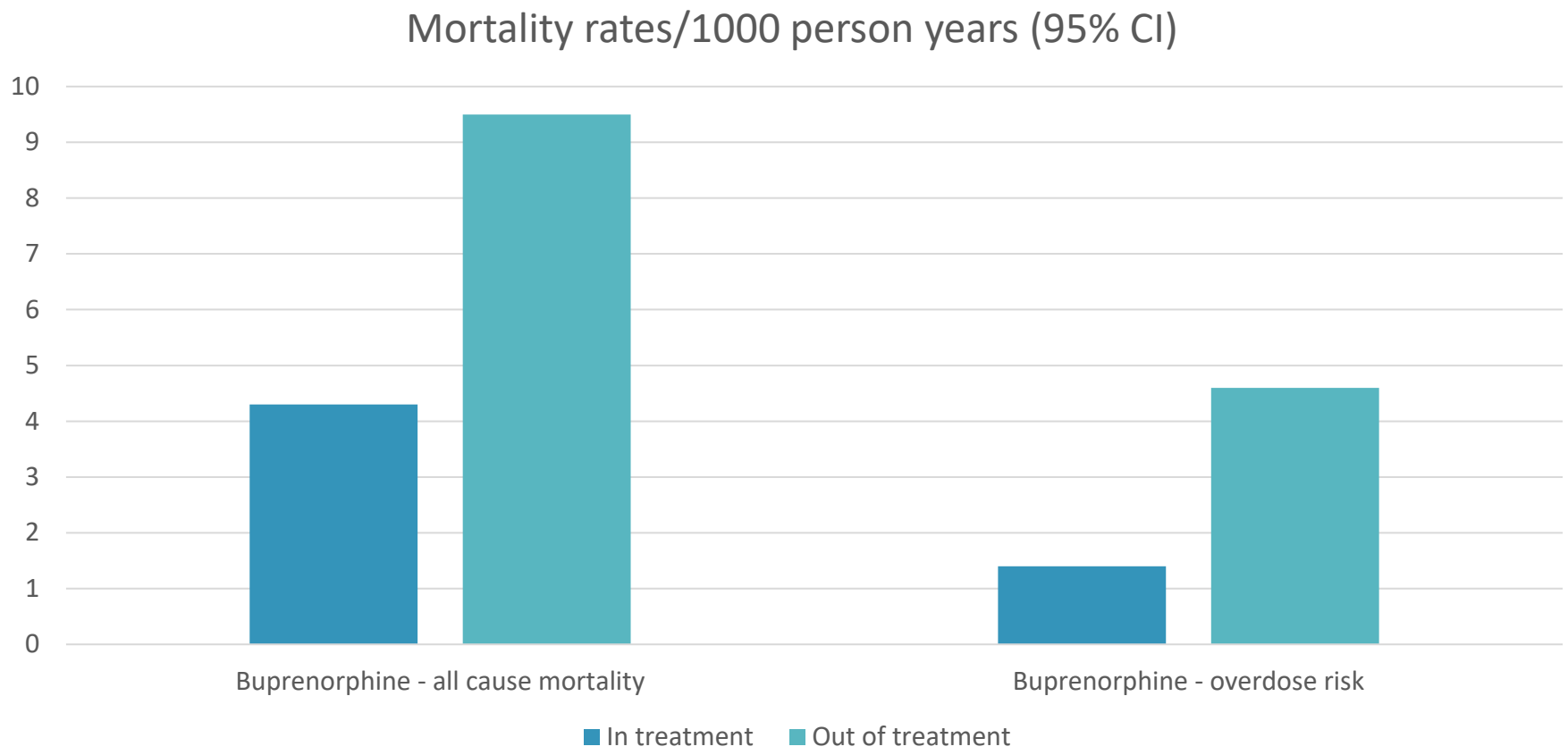
Patients taking buprenorphine are significantly more likely to engage and remain in treatment compared to those tapered off the medication.

Fiellen 2014; D'Onofrio 2017

Why is it so great?

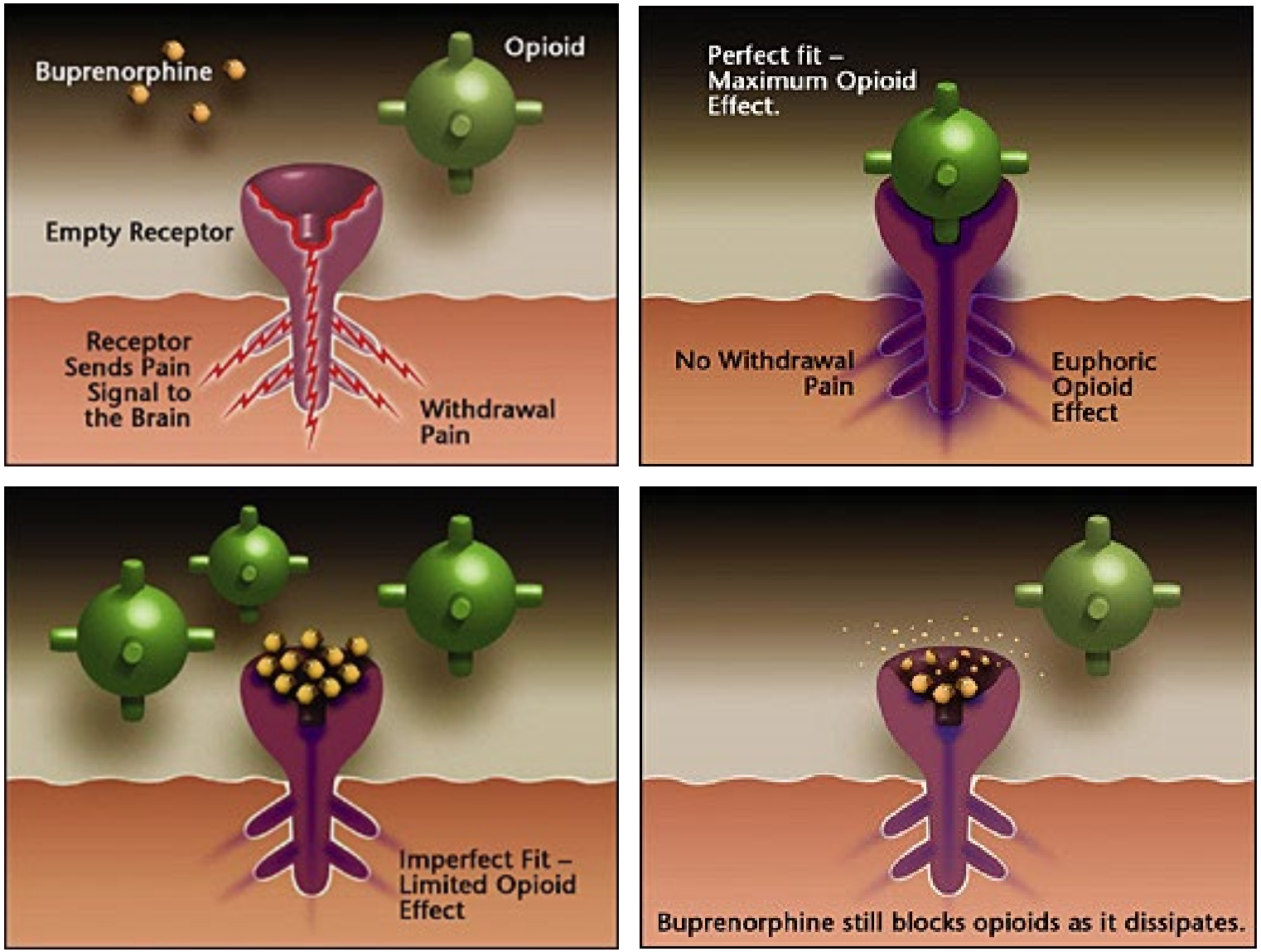
Most importantly, with buprenorphine in their systems, patients live.

Mortality Risk during and after buprenorphine treatment



Mortality Risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. Sordo, et al. BMJ 2017.

How does it work?


Buprenorphine
Opioid
Empty Receptor
Receptor Sends Pain Signal to the Brain
Withdrawal Pain
Perfect fit – Maximum Opioid Effect.
No Withdrawal Pain
Euphoric Opioid Effect
Imperfect Fit – Limited Opioid Effect
Buprenorphine still blocks opioids as it dissipates.

One “trick” to buprenorphine

- Buprenorphine is a high-affinity binder at the mu opioid receptors, which means it sits tightly on the receptor.
- It will kick off anything else that’s bound there.
- But it is a partial agonist at the receptor. That means it doesn’t activate the receptor completely.
- If it kicks full agonists off the receptors all at once, the difference between full agonism and partial agonism is big enough to cause “precipitated withdrawal.

“Traditional” inductions

- Instruct the patient to abstain from any opioid use for a minimum of:
  - 12-16 hours for short-acting opioids
  - 24 hours for sustained-release opioid medications
  - 36 hours for methadone

“Traditional” inductions

- Wait until the patient is in mild to moderate withdrawal as assessed by COWS (which means most receptors are empty)
- Begin buprenorphine and titrate up, as needed, over 3-4 days
- Could be done at home

If you followed the directions it was easy …

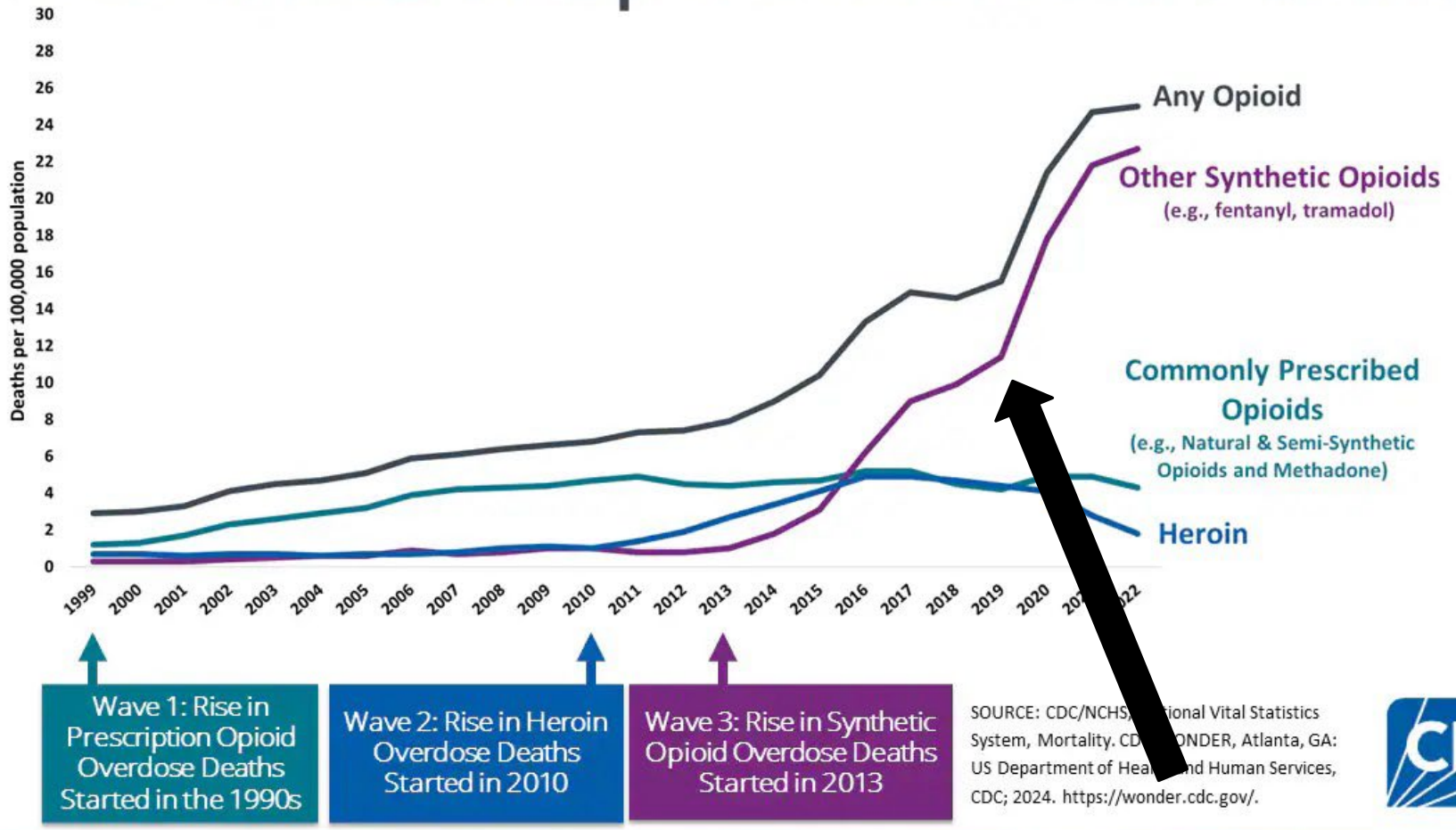
… and also felt like a true "miracle of modern medicine"

"It's amazing! I used to wake up and think about scoring [heroin]. It's all I thought about all day every day. Now I never think about it – I just live my life."

- Patient in Blackburn walk-in buprenorphine clinic, 2019

Fall 2020, Medical Director
De Paul Treatment Centers

Three Waves of Opioid Overdose Deaths



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2024. https://wonder.cdc.gov/.

CDC

How it showed up in Portland

How it showed up clinically

- Patients would start buprenorphine and then get sick again a few hours later or even the following day
- Patients would wait up to 72 hours to start buprenorphine and still feel worse after starting
- Patients would continue to have terrible cravings and withdrawal symptoms even on the maximum buprenorphine dose (then 24 mg)

How it showed up clinically

- Withdrawal looked different
- Profound restlessness, anxiety, and pain
- The term “precipitated withdrawal” no longer meant what it had
- COWS no longer reliable

How it showed up clinically

- Patients leaving due to distress & fear
  - Estimates from other facilities (~30% of patients leaving prior to induction)
- And potentially dying


WE TRUST
2008
THIS IS A PENNY
THIS IS AN
OVERDOSE

What was happening?

Fentanyl (pharmaceutical)

- High affinity and high efficacy at mu receptor
- Single use has a short half-life (fast on, fast off)
- Repeated use may lead to accumulation in adipose tissue, decreased renal clearance, more mu opioid receptor desensitization
- Fentanyl and buprenorphine were in a battle for the receptors in the brain

Fentanyl (community acquired)

- Over 200 analogues
- Mixed with unknown other substances
- No consistency in product

How did we move forward?

Decision: Prioritize Buprenorphine Initiation

How did we move forward?

First, we remembered that we weren't alone in addressing the crisis

- Emerging issues in addiction clinical group with Hooper, OHSU, Providence, Kaiser, VA (what were they seeing? How did they handle it?)
- Literature on approaches used by other states, systems, and other fields of medicine

We looked at and discussed

- Low dose inductions
- High dose inductions
- Using every tool to address restlessness, anxiety, and pain

Low dose (Micro) induction

… Trojan horse approach…

ORIGINAL RESEARCH

Low-dose Buprenorphine Initiation in Hospitalized Adults With Opioid Use Disorder: A Retrospective Cohort Analysis

Dana Button, BS, Jennifer Hartley, MD, PhD, Jonathan Robbins, MD, MS, Ximena A. Levander, MD, MCR, Natashia J. Smith, BS, and Honora Englander, MD

Objectives: Patients with opioid use disorder (OUD) can initiate buprenorphine without requiring a withdrawal period through a low-dose (sometimes referred to as "micro-induction") approach. Although there is growing interest in low-dose buprenorphine initia-

hospital discharge. We share a standard low-dose initiation protocol with potential modifications based on above scenarios.

Conclusions: Low-dose buprenorphine initiation offers a well-tolerated and versatile approach for hospitalized patients with OUD. We share

Low dose buprenorphine induction

- Many different protocols
  - Initial protocol “Bernese Method”
  - Usually start at 0.5 mg
  - Often 7-10 days
  - No universally accepted regimen
  - Can continue full agonists throughout the entire induction

Day	Dose
1	0.5 mg daily
2	0.5 mg bid
3	1 mg bid
4	2 mg bid
5	4 mg bid
6	4 mg tid
7	8 mg tid

Adapted from Yale protocol

[9]Opioid Use Disorder Practice Update (2022) British Columbia Centre on Substance Use

Rapid low dose inductions

Day	Full Opioid Agonist	Buprenorphine Dosing Instructions	Total Daily Dose of Buprenorphine
1	Continue	0.5 mg SL once	0.5 mg
2	Continue	0.5 mg SL bid	1 mg
3	Continue	1 mg SL bid	2 mg
4	Continue	2 mg SL bid	4 mg
5	STOP (if able to tolerate increase)	4 mg SL once. If tolerated take additional 4 mg in 10 mins. Continue to titrate prn for ongoing cravings or withdrawal symptoms for TDD of 16-24 mg	16-24 mg

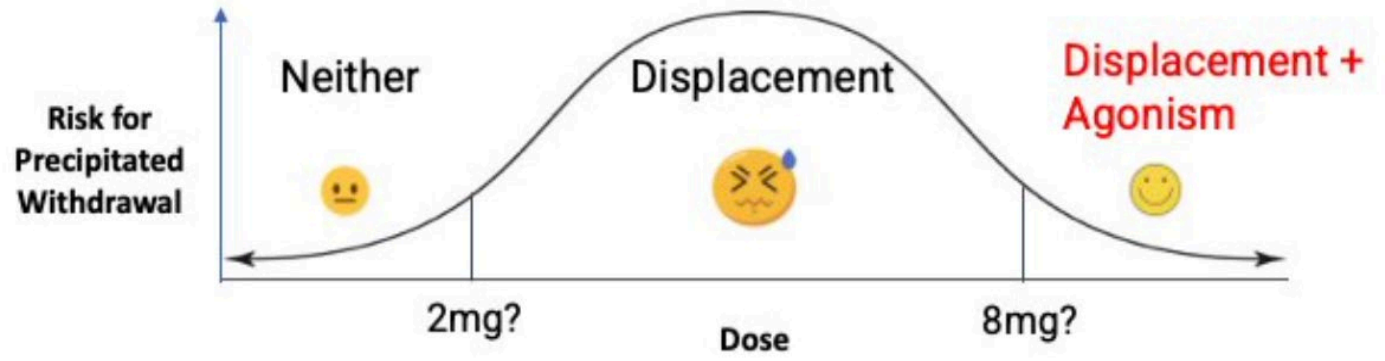
High Dose (Macro) Induction

"Houston, we have lift off"

What is it?

- **Higher doses** than used in standard inductions
- Wait until patient in withdrawal, same as standard inductions

- Start with 8-16 mg
- Idea is to get to agonism/relief of withdrawal symptoms quicker



Source: [11]Chen C. Buprenorphine Strategies in the Age of Fentanyl. Lecture presented at Rutgers New Jersey Medical School SUD MAT ECHO; April 1, 2022

JAMA Network Open

Original Investigation | Substance Use and Addiction

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

Andrew A. Herring, MD; Aidan A. Vosooghi, MS; Joshua Luftig, PA; Erik S. Anderson, MD; Xiwen Zhao, MS; James Dziura, PhD; Kathryn F. Hawk, MD, MHS; Ryan P. McCormack, MD, MS; Andrew Saxon, MD; Gail D'Onofrio, MD, MS

Abstract

IMPORTANCE Emergency departments (EDs) sporadically use a high-dose buprenorphine induction strategy for the treatment of opioid use disorder (OUD) in response to the increasing potency of the illicit opioid drug supply and commonly encountered delays in access to follow-up care.

OBJECTIVE To examine the safety and tolerability of high-dose (>12 mg) buprenorphine induction for patients with OUD presenting to an ED.

DESIGN, SETTING, AND PARTICIPANTS In this case series of ED encounters, data were manually abstracted from electronic health records for all ED patients with OUD treated with buprenorphine at a single, urban, safety-net hospital in Oakland, California, for the calendar year 2018. Data analysis was performed from April 2020 to March 2021.

INTERVENTIONS ED physicians and advanced practice practitioners were trained on a high-dose sublingual buprenorphine induction protocol, which was then clinically implemented.

MAIN OUTCOMES AND MEASURES Vital signs; use of supplemental oxygen; the presence of

Key Points

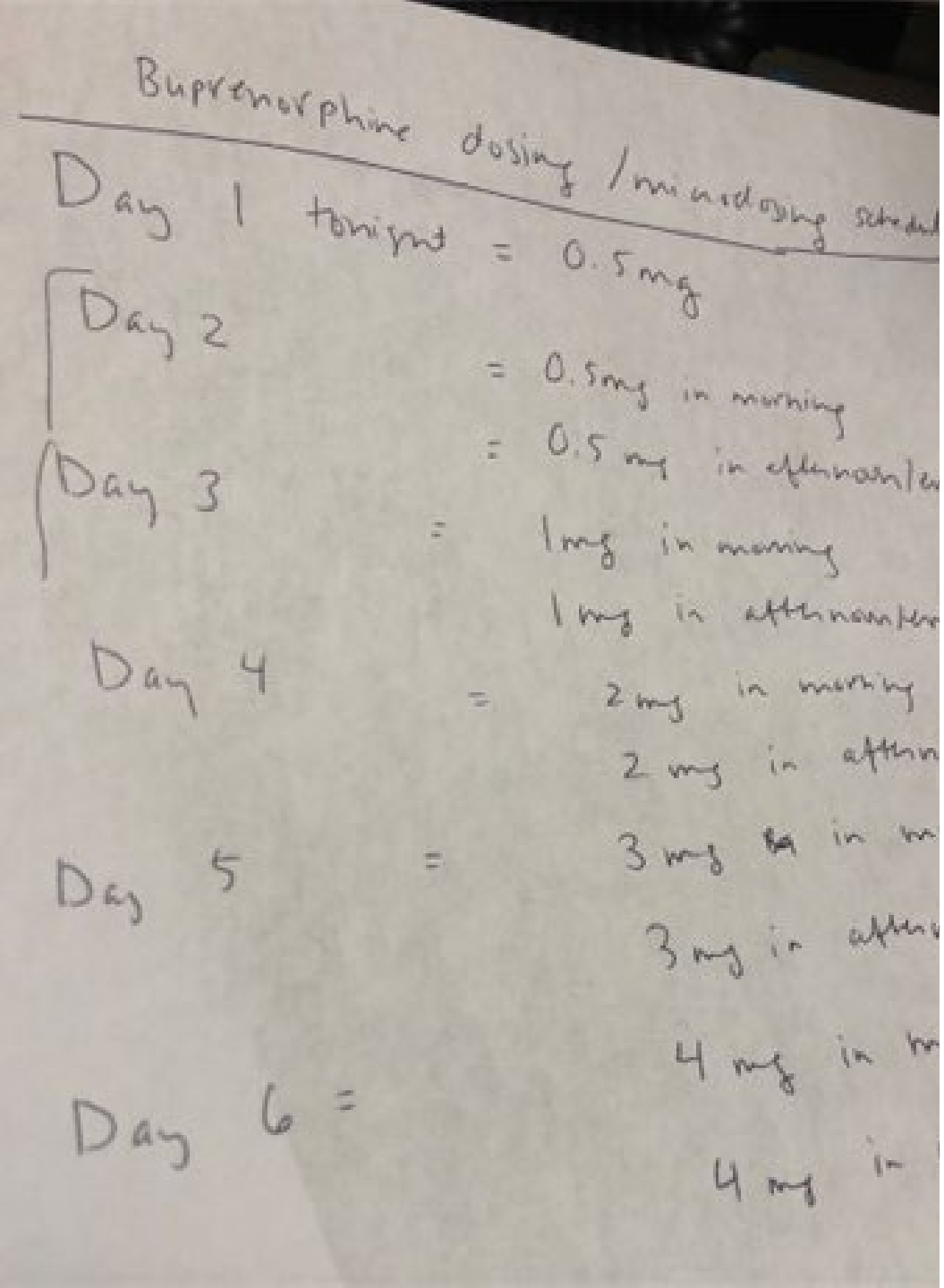
Question Is high-dose (>12 mg) buprenorphine induction safe and well tolerated in patients with untreated opioid use disorder who present to the emergency department?

Findings In this case series of 579 cases, 54 clinicians followed a high-dose buprenorphine (monoproduct) protocol. There were no documented episodes of respiratory depression or excessive sedation, and precipitated withdrawal was rare (0.8% of cases) and was not associated with dosing.

Meaning These findings suggest that high-dose buprenorphine induction, adopted by multiple clinicians in a single-site, urban emergency

How did we move forward?

- We embraced innovation
- Became “anthropologists of fentanyl”



Returned to a prior lesson:

In an absence of definitive data, use what you have and pay very close attention to your patients, listen & observe.

Optimized adjunctive medications

- Clonidine, tizanidine, methocarbamol, hydroxyzine, trazodone
- Ondansetron, promethazine, loperamide, dicyclomine
- Acetaminophen, ibuprofen
- Gabapentin
- Quetiapine, olanzapine

- Started 1 mg buprenorphine doses based on case reports from pain literature
  - Recognized psychological component
  - Physiological component – some evidence that even small buprenorphine doses help resensitize receptors

Micro-Macro protocol

Approach

- Low dose buprenorphine for physiological & psychological benefit
- Build a strong “container” around the experience
- Find the “sweet spot” for macro-induction
- Support sleep as much as possible to minimize discomfort and fear

Micro-Macro Protocol

Fora Health
TREATMENT & RECOVERY

Withdrawal Management Admission
Order Set Non-Pregnant Patients

☐ **Micro / Macro Induction Opioid Protocol STANDARD**

☐ Provider administered on admission 1 mg buprenorphine, 600 mg gabapentin, 0.1 mg clonidine.

Micro-Induction Phase 1	**1100 med pass:** • 0.1 mg clonidine • 50 mg diphenhydramine	**1600 med pass:** • 1 mg buprenorphine • 0.2 mg clonidine • 600 mg gabapentin • 50 mg diphenhydramine	**2100 med pass:** • 1 mg buprenorphine • 0.2 mg clonidine • 600 mg gabapentin • 50 mg diphenhydramine	**0200 med pass:** If patient sleeping, do not awaken If patient awake, give: • 1 mg buprenorphine • 4 mg tizanidine • 300 mg gabapentin • 50 mg diphenhydramine

- **IF PATIENT EXPERIENCING EARLY RESTLESSNESS PRIOR TO 1700, CALL PROVIDER FOR LORAZEPAM ORDER.**
- **May give 2 mg lorazepam PO ORN for restlessness/early withdrawal between 1700 and 2400. If patient restless after midnight call provider.**
- **If patient exhibits severe opioid withdrawal symptoms prior to 0600 med pass, RN / LPN may initiate Macro induction (16 mg buprenorphine + scheduled adjuncts) up to 2 hours early (0400)**

Macro-Induction Phase 2	**0600 med pass:** • 2 mg lorazepam • 600 mg gabapentin • 4 mg tizanidine • 16 mg buprenorphine DO NOT SPACE MEDICATIONS APART, HAVE PATIENT SIT UP AND FULLY DISSOLVE BUPRENORPHINE Hold all medications for sedation: RASS -2 or below. Notify provider on call.	**1100 med pass:** • 8 mg buprenorphine *(If patient has not yet received any PRN buprenorphine doses)* • 4 mg tizanidine • 600 mg gabapentin • 50 mg diphenhydramine	**1600 med pass:** • 4 mg tizanidine • 600 mg gabapentin

- MAY GIVE ADDITIONAL 8 MG BUPRENORPHINE PRN AT ANY TIME DURING THE DAY for TDD of 40 mg – Call provider if continued opioid withdrawal symptoms after 40 mg.
- ***For continued withdrawal after 32 mg please call provider for 1 mg lorazepam***

M/M Day 3	• At **0600 med pass** give 24 mg buprenorphine. May give additional 8 mg PRN for TDD 32 mg. Call provider if continued opioid withdrawal symptoms after 32 mg. (Patient may discharge if comfortable and wishing to leave.)
M/M Day 4	• At **0600 med pass**, give 24 mg buprenorphine and discharge with buprenorphine prescription.

May give additional PRNs from standard PRN adjunct menu as needed with standard hold parameters. Please give adjuncts as scheduled per protocol first and reassess for additional needs.

Successful Transition from Fentanyl to Buprenorphine in a Community-based Withdrawal Management Setting

To the Editor:

The presence of fentanyl and fentanyl analogs in the US drug supply presents new challenges to buprenorphine induction, including delayed time to induction, a higher risk of precipitated withdrawal, and idiosyncratic reactions, including intense dystonia and vomiting.[1–3] Recently, in this journal, Varshneya and colleagues[4] documented severe opioid withdrawal among patients induced from fentanyl onto buprenorphine in treatment settings across the United States

TABLE 1. Induction Outcomes

Induction	Patients	Lorazepam	AMA*	HLOC†
Low/High	40	4	3	0
Standard	42	6	6	3

*AMA = left against medical advice before stabilization.

†Sent by ambulance to a higher level of care (emergency department).

is followed by high-dose buprenorphine (up to 20 mg within the first hour) on day 2. Using this method, we have successfully inducted more than 50 patients who reported using fentanyl only or primarily since September 15, 2021.

Starting in mid-September, patients presenting with fentanyl use immediately before admission and not yet experiencing significant withdrawal symptoms were offered the low/high protocol, and their medical record numbers were entered into a secure tracking tool. In January 2022, we reviewed the charts of patients admitted through mid-December, examining buprenorphine formally evaluate this protocol and will track additional data, including age, specific withdrawal symptoms, length of stay, concomitant use of other substances, buprenorphine dose at discharge, and return visits. We will also collect qualitative data around patient experience with the protocol.

Jennifer Hartley, PhD, MD
Eowyn Rieke, MD, MPH
Christopher Blazes, MD
Benjamin Smith, MD, MPH
Jessica Gregg, PhD, MD

Also began to optimize non-pharmaceutical nursing interventions

- Showers
- Essential oils
- Hot water bottles
- Back/leg rubs
- Icy-Hot
- Fans
- Acupuncture
- Movement

Then the fentanyl supply changed …

How we moved forward

- Increased lorazepam
- Added droperidol
- Created collaborative protocol with OHSU Adventist ED

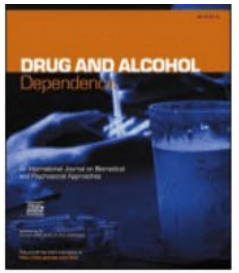
Reached limit of this management approach

How did we move forward?

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep



Check for updates

Bridge clinic implementation of "72-hour rule" methadone for opioid withdrawal management: Impact on opioid treatment program linkage and retention in care

Jessica L. Taylor [a,b,*], Jordana Laks [a,b], Paul J. Christine [a,b], Jessica Kehoe [a], James Evans [a], Theresa W. Kim [a,b], Natalija M. Farrell [c,d], Cedric S. White [c], Zoe M. Weinstein [a,b], Alexander Y. Walley [a,b]

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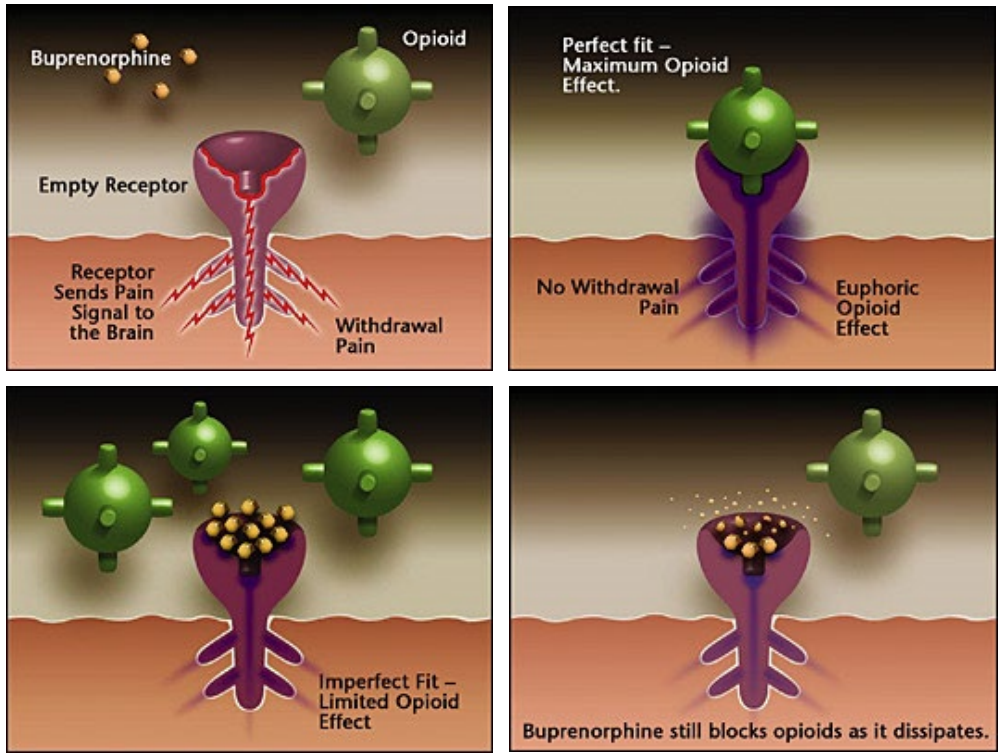
[c] *Department of Pharmacy, Boston Medical Center, Boston, MA, USA*
[d] *Department of Emergency Medicine, Boston University School of Medicine, Boston, MA, USA*

“72 Hour Rule” = 3 days of methadone dispensing

- This DEA exemption allows any setting that is not a hospital or Opioid Treatment Program (methadone clinic) to dispense 3 days of opioid medication to treat opioid withdrawal

What does this mean?

- Allows non-methadone clinic provider to administer “narcotic drugs to a person for the purpose of relieving acute withdrawal symptoms”[1]
- Permitted for up to 3 days while arranging ongoing treatment
- Medications must be administered, not prescribed
- No more than 1 day’s medication administered at one time*
  - New 2022 federal guideline can dispense 3 day supply
- 72-hour period cannot be renewed or extended
  - Slide courtesy of Dr. Mike Winer



1. Title 21, CFR, Part 1306.07b
* New Guidance in March 2022 allows providers to apply to dispense up to a 3-day supply

The challenges

- Setting up facility to store medication
- Records, inventory, destruction plan
- Staff education
- Purchasing medication (wholesalers don’t understand rules)
- Ordering medication (CSOS)

How we moved forward

- Collaborated with Hooper
- Met with programs on the East coast who were using this approach
- Met with wholesalers
- Nursing education

Methadone Bridge Protocol

Fora Health
TREATMENT & RECOVERY

Withdrawal Management Admission
Order Set Non-Pregnant Patients

☐ **Methadone Bridge to Buprenorphine Protocol**

➢ HOLD METHADONE FOR RASS -2 OR LESS AND REASSESS AT NEXT MED PASS OR GIVE DOSE WHEN PATIENT AWAKENS – WHICHEVER COMES FIRST

☐ Provider administered on admission 1 mg buprenorphine, 8 mg tizanidine, 1000 mg acetaminophen.

Admission Day 1			**1100 med pass:** • 30 mg methadone	**1600 med pass:** • 1 mg buprenorphine • 8 mg tizanidine	**2100 med pass:** • 1 mg buprenorphine • 10 mg methadone • 8 mg tizanidine
May give additional single 10mg methadone PRN for COWS >= 10. Separate by 2 hours minimum from other scheduled methadone doses. TDD of methadone NTE 50mg.					
Admission Day 2	**0200 med pass:** • 1 mg buprenorphine • 600 mg gabapentin	**0600 med pass:** • 1 mg buprenorphine • 8 mg tizanidine • 1000 mg acetaminophen • 40 mg methadone	**1100 med pass:** • 2 mg buprenorphine • 8 mg tizanidine	**1600 med pass:** • 2 mg buprenorphine • 8 mg tizanidine • 10mg methadone	**2100 med pass:** • 2 mg buprenorphine • 8 mg tizanidine
May give additional single 10mg methadone PRN for COWS >= 10. Separate by 2 hours minimum from other scheduled methadone doses. TDD of methadone NTE 60mg.					
Admission Day 3	**0200 med pass:** • 2 mg buprenorphine • 600 mg gabapentin	**0600 med pass:** • 2 mg buprenorphine • 8 mg tizanidine • 1000 mg acetaminophen • 50 mg methadone	**1100 med pass:** • 16 mg buprenorphine	**1600 med pass:** • 16 mg buprenorphine	**2100 med pass:** • 10 mg methadone
May give additional 8 mg doses of buprenorphine PRN for withdrawal/cravings to TDD of 48 mg. Call provider for COWS >= 10 for additional orders.					
Admission Day 4	**0200 med pass:**	**0600 med pass:** • 24 mg buprenorphine • 8 mg tizanidine • 1000 mg acetaminophen	**1100 med pass:** • 8 mg buprenorphine	**1600 med pass:** • Give PRNs as needed	**2100 med pass:** • Give PRNs as needed
May give additional 8 mg doses of buprenorphine PRN for withdrawal/cravings to TDD of 48 mg					
All patients have 300-600 mg Gabapentin available PRN Q6 hours					

Life changed overnight

“They’re sleeping”

- Fora Nurse

Simultaneous game-changers: Long-acting injectable buprenorphine

Brixadi


Brixadi™
(buprenorphine) extended-release injection for subcutaneous use
MONTHLY
For Subcutaneous Use Only
96 mg
0.27 mL
of a 356 mg/mL solution per syringe (Monthly)
WARNING: SERIOUS HARM OR DEATH COULD RESULT IF INJECTED INTRAVENOUSLY.
SINGLE-DOSE PREFILLED SYRINGE KIT
CONTENTS:
• One (1) sterile prefilled syringe with needle shield, 96 mg (buprenorphine) per syringe
• One (1) plunger rod
• Prescribing Information
• Instructions for Use
• Medication Guide
For Healthcare Provider Administration Only.
Do Not Dispense to Patient.
Attention: Dispense the enclosed Medication Guide to each patient.
Rx ONLY
Distributed by: Braeburn Inc., Plymouth Meeting, PA 19462
Properly dispose of BRIXADI® syringes per facility procedure for a Schedule III drug product, and per applicable federal, state, and local regulations.
Once-weekly subcutaneous injection for treatment of opioid use disorder. For questions, call 1-833-274-9234.
120434
BRIX-016-01A 12/18
NDC 58284-296-01
WEEKLY
24 mg
0.48 mL
of a 50 mg/mL solution per syringe (Weekly)
BRIX-013-01A 12/18
NDC 58284-224-01

What have we learned?

- No “one size fits all” approach to starting buprenorphine
- Both low and high dose approaches can help
- Optimizing comfort medications is important
- Access to methadone increases comfort and success

What have we learned?

- Take time to know your patient
- Talk through goals & options
- Have a game plan
- Have a “Plan B”
- Use non-pharmaceutical supports
- Kindness Matters

The work ahead

- Adapting the 72 Hour Rule for outpatient use
- Induction with LAI buprenorphine
- Expanded access to maintenance methadone remains an urgent need

The work ahead

- Increased access to supported housing
- Mental health care & primary care
- Connection & community in daily life

How do we keep moving forward?

- Courage
- Humility
- Curiosity
- LOVE

Be kind whenever possible. It is always possible.

- Dalai Lama

Questions??

Feel free to email me at jennifer.Hartley@forahealth.org