HEALTH
UNIVERSITY OF UTAH

BUILDING BRIDGE: CREATIVITY IN TREATING OPIOID USE DISORDER

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CONFLICT OF INTEREST

- Sub-investigator CTN-100 for 3 years; NIH-funded MOUD study ("Retention, Duration, Discontinuation"), which uses buprenorphine and naltrexone products

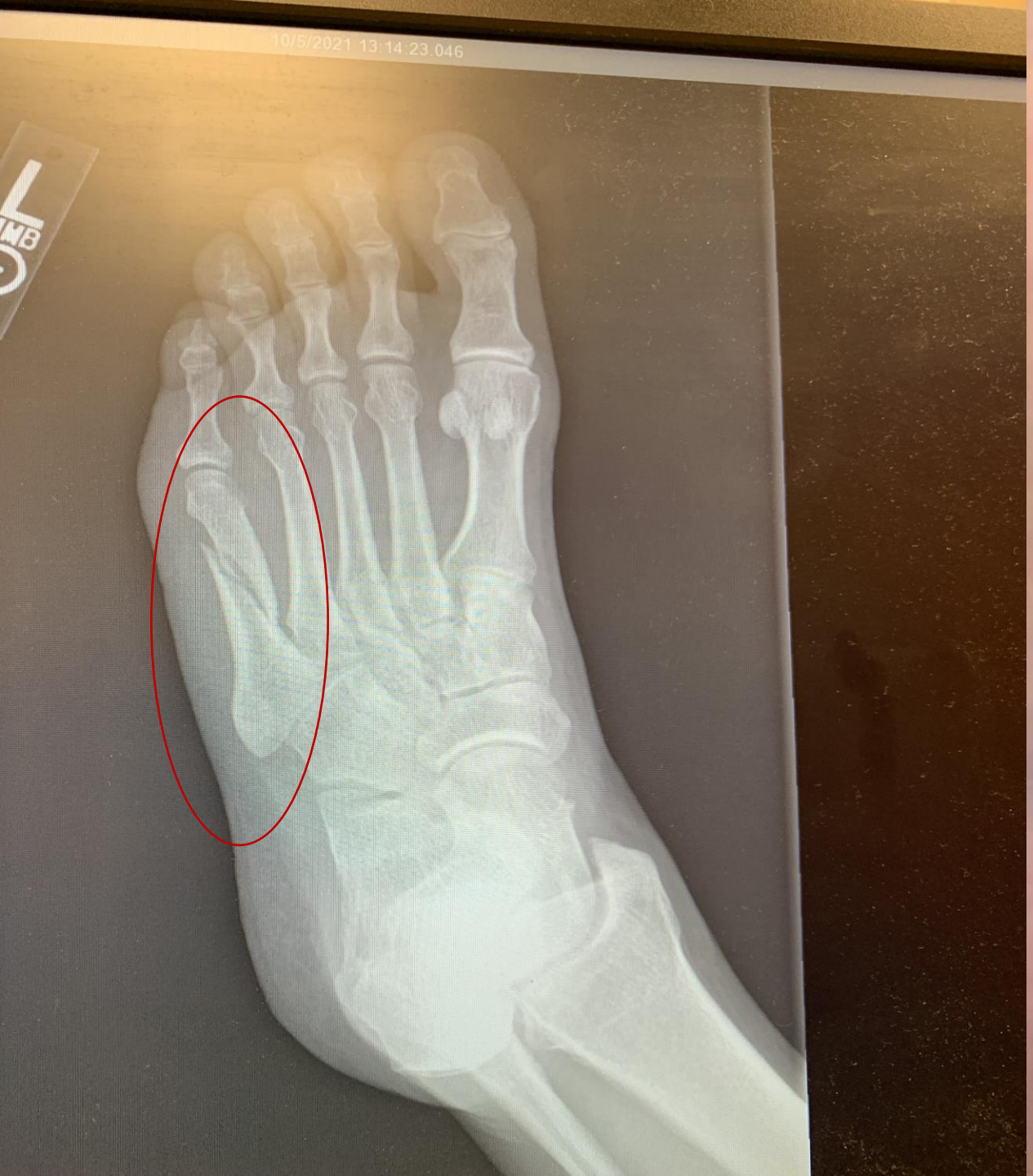
LEARNING OBJECTIVES

1. Describe need for MOUD and challenges in providing it to some Pt populations
2. Characterize adjustments required by onset of Covid-19
3. Describe key principles for delivery of MOUD in fentanyl era

DISCLAIMER:

"An expert is a person who has made all the mistakes that can be made in a very narrow field."

Niels Bohr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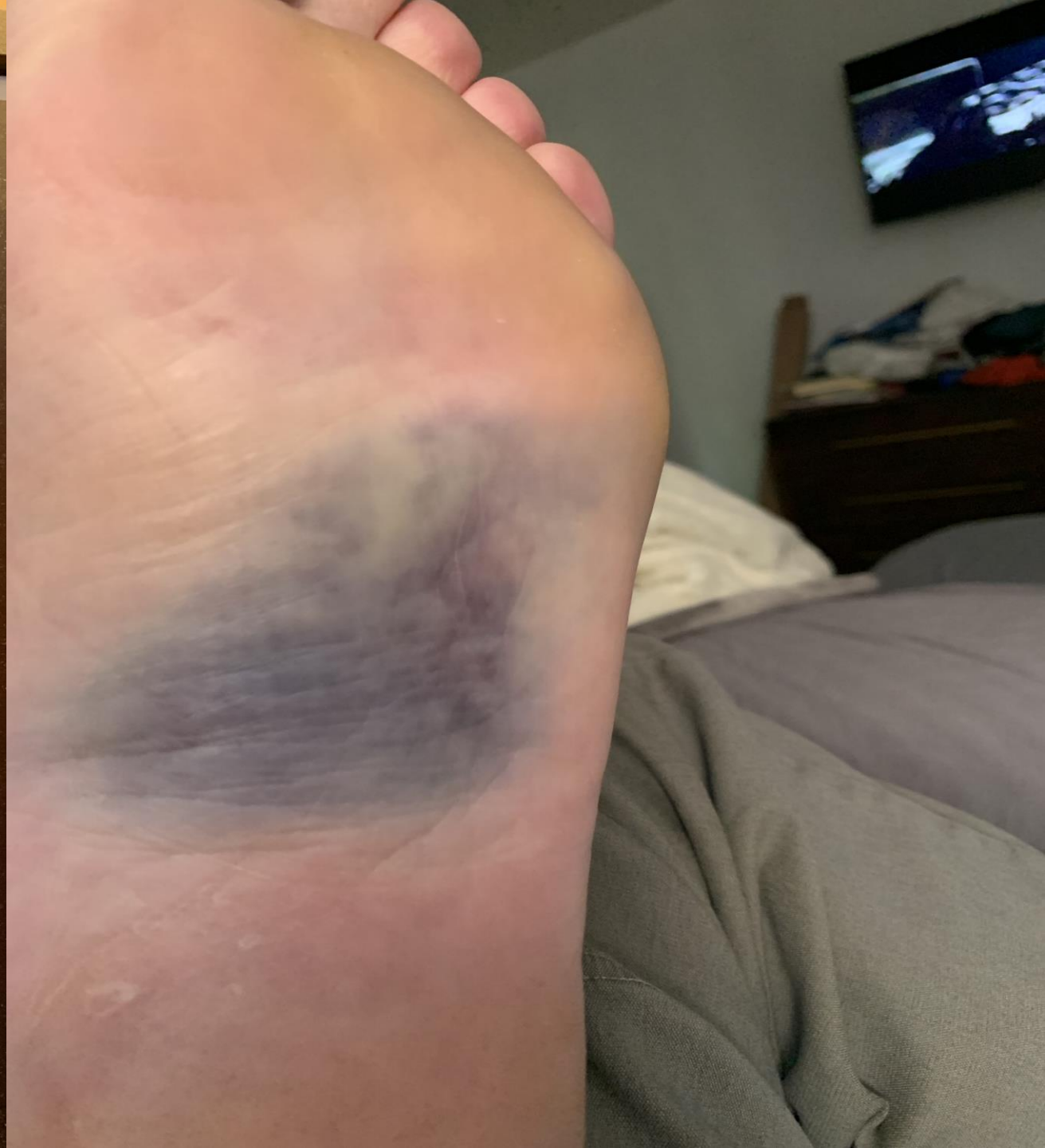
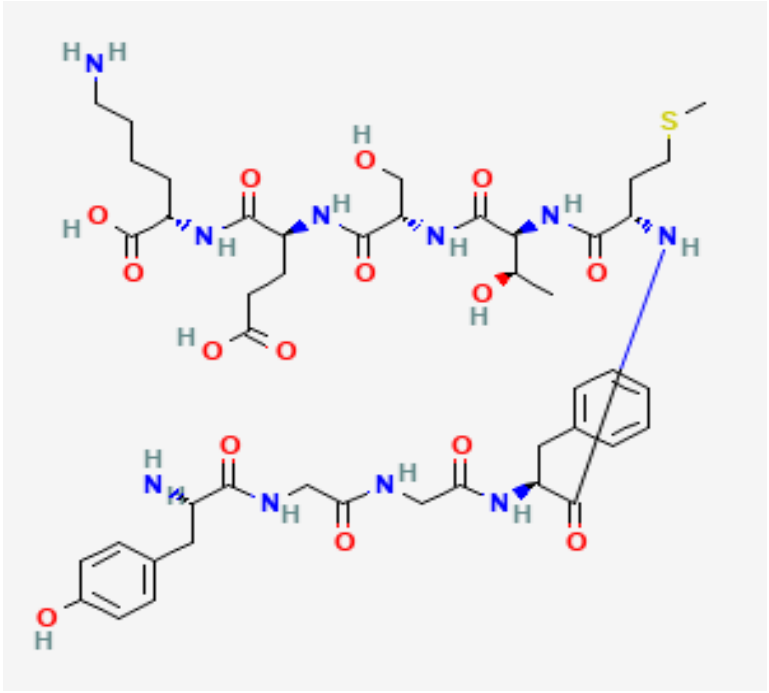
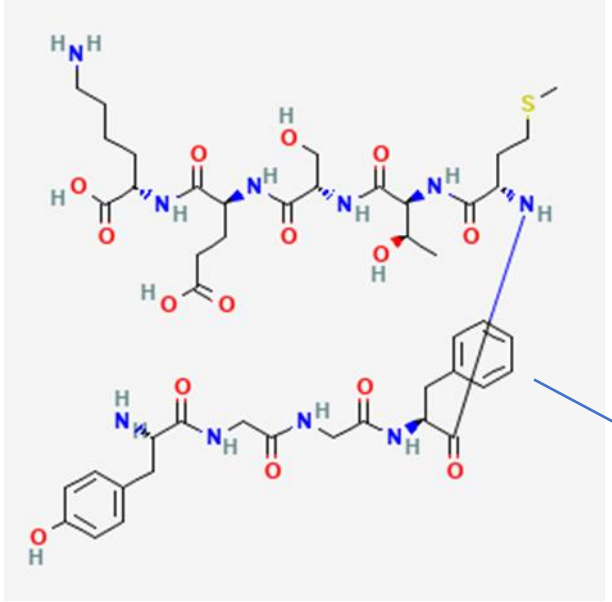
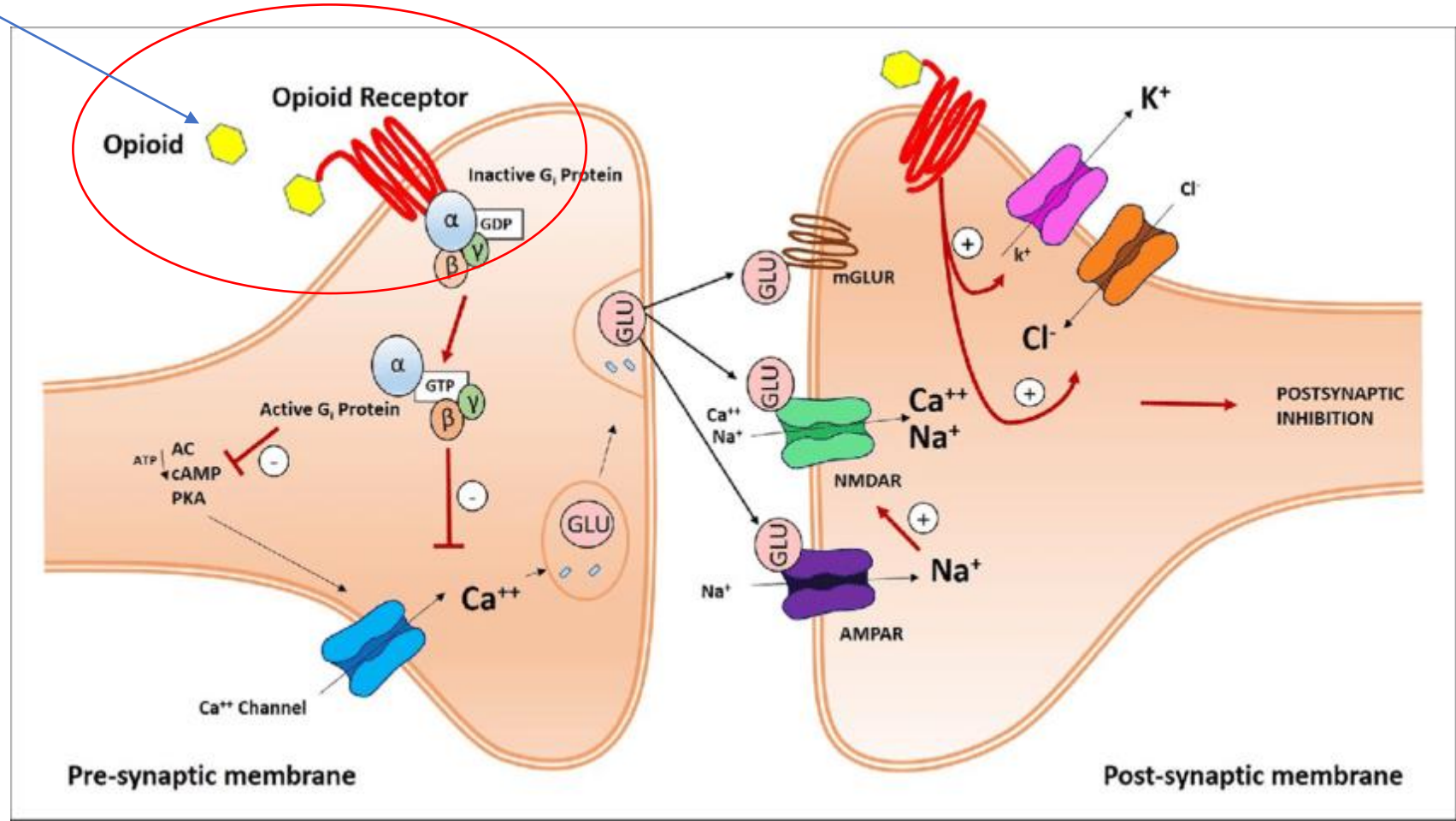


EVOLUTIONARY ANALGESIA: ENDORPHINS

- **En**d**orphin**= **en**dogenous + **morphine**
  - **Endo:** "from within" (Greek)
  - **Genous:** "generating", "yielding" (Greek)
  - **Beta-endorphin, dynorphin**






Opioid
Opioid Receptor
Inactive G, Protein
α
GDP
β
γ
GTP
Active G, Protein
ATP
AC
cAMP
PKA
Ca++
Ca++ Channel
GLU
mGLUR
NMDAR
AMPAR
Ca++
Na+
K+
k+
Cl-
POSTSYNAPTIC
INHIBITION
Pre-synaptic membrane
Post-synaptic membrane

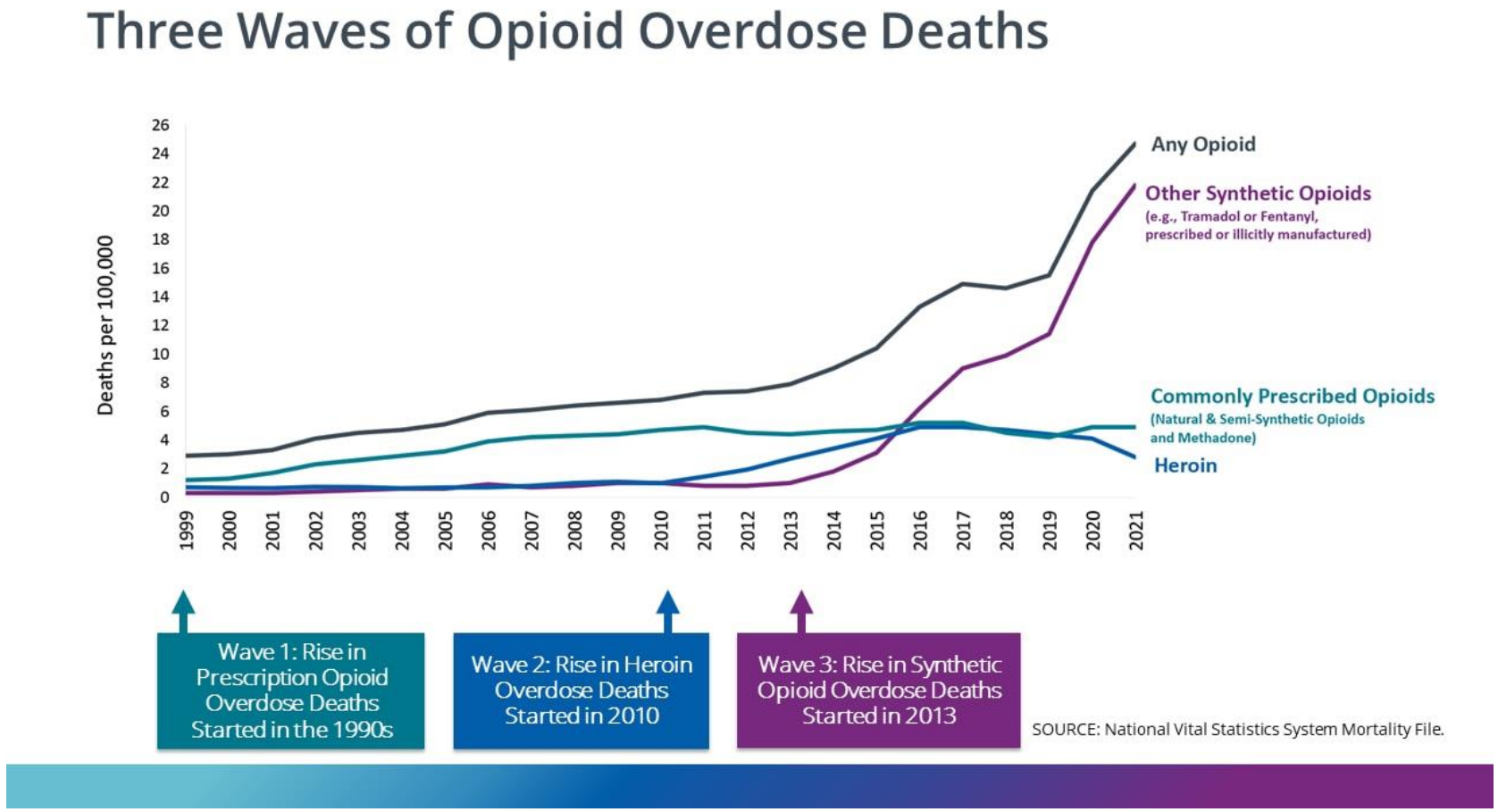
EXOGENOUS "NATURAL" OPIOIDS

- **Exo**= external
- Refined/concentrated: derived from plants
  - Morphine, codeine, oxycodone, heroin (diacetyl-morphine)
- Advanced medical care: acute pain, surgery

SYNTHETIC OPIOIDS

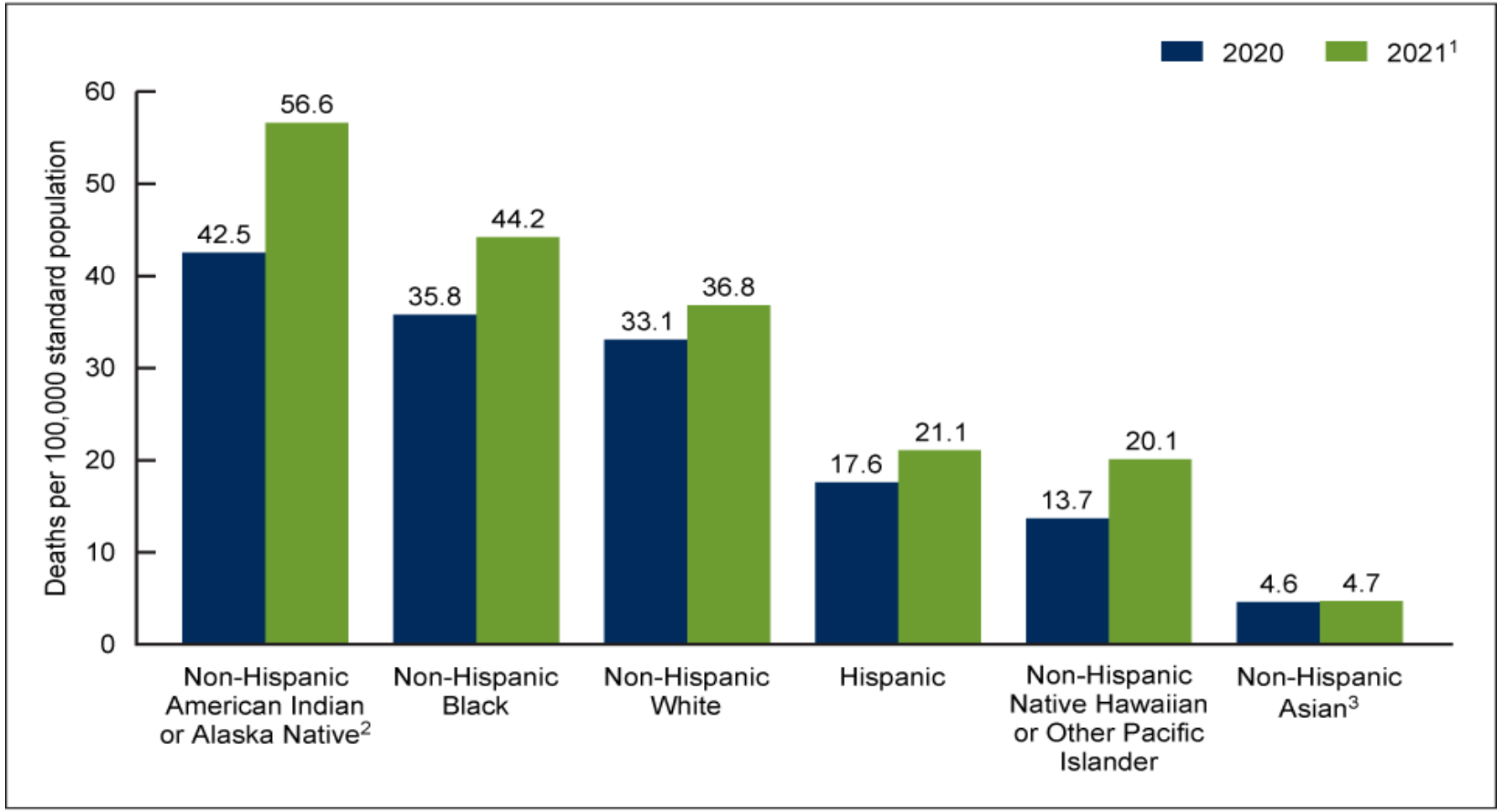
- Made in the lab (no plant precursor)
- Methadone, fentanyl (analogs), buprenorphine

RISE OF OPIOIDS



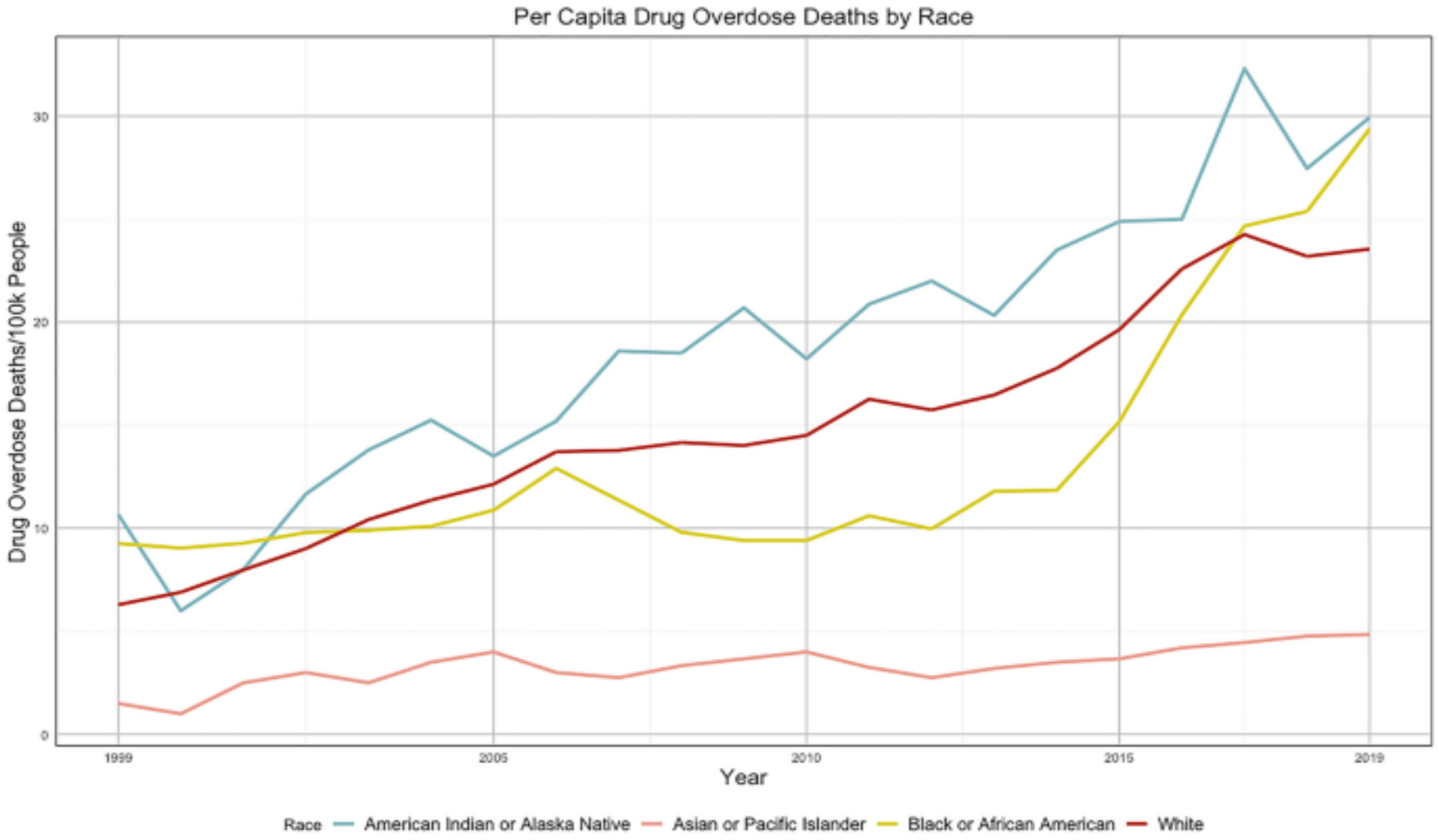
CDC, National Center for Health Statistics; 2021. Available at http://wonder.cdc.gov.

Figure 3. Age-adjusted rate of drug overdose deaths, by race and Hispanic origin: United States, 2020 and 2021



[1]Except for non-Hispanic Asian people, rates in 2021 were significantly higher than in 2020 for all race and Hispanic-origin groups, $p < 0.05$.
[2]Race and Hispanic-origin group with highest rate in 2020 and 2021, $p < 0.05$.
[3]Race and Hispanic-origin group with lowest rate in 2020 and 2021, $p < 0.05$.
NOTES: Misclassification of race and Hispanic origin on death certificates results in the underestimation of death rates by as much as 34% for American Indian or Alaska Native people and 3% for non-Hispanic Asian and Hispanic people. Drug overdose deaths were identified using *International Classification of Diseases, 10th Revision* underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Age-adjusted death rates were calculated using the direct method and the 2000 U.S. standard population. Access data table for Figure 3 at: https://www.cdc.gov/nchs/data/databriefs/db457-tables.pdf#3.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality File.

CDC: NCHS Data Brief No. 457, December 2022



Whelshula, M., Hill, M., Galaitsi, S.E. *et al.*

OPIOID USE DISORDER DSM-5

- Large amounts, longer than intended (dose, duration)
- Desire or difficulty controlling use (impaired control)
- A lot of time acquiring, using, recovering (impact)
- Craving
- Failure to fulfill major roles (home, work, school)
- Continued use despite social/interpersonal problems
- Social, occupational, recreational activities given up
- Recurrent use in physically hazardous situations
- Persistent use despite insight into the physical/psychological harm
- Tolerance and Withdrawal

ASAM 2020 OUD TREATMENT GUIDELINES

- *All FDA approved medications for the treatment of opioid use disorder should be available to all patients.*
- FDA Approved Medications for OUD
  - Methadone
  - Naltrexone long-acting injectable (*not PO Naltrexone*)
  - **Buprenorphine**

RETENTION

- Therapy can't work if you're not there
- Methadone > Bupe > Naltrexone > None
- Buprenorphine
  - 2-6mg daily: 1 in 4 pts retained
  - 7-16mg daily: 1 in 3 pts retained
  - >16mg daily : 1 in 2 pts retained

Timko et al., J Addict Dis. 2016; 35(1):22-35; Raleigh, Am Fam Physician. 2017 Mar 1; 95(5)

CASE 1: PT FROM ~2018

25 y/o male with OUD presenting to outpt clinic seeking assistance discontinuing heroin

- Rx opioids 3-4 times in teens; EtOH and THC
- Non-medical oxy @ 18, EtOH weekly
- Heroin smoked @ 19, IV @ 22, no other use
- Bupe initiation to 16mg, stable x 2 years

CHALLENGES TO OUTPT TREATMENT

- Social barriers (cost, transportation, etc)
- Difficult to time appt to withdrawal
- High "No Show" rate for 1st appt
- In-clinic vs home-initiation of bupe
- Overwhelming demand
- Low barrier, rapid access?

RECOVERY CLINIC

- Dual-diagnosis SUD training clinic
  - 4 part-time attendings, trainees, LCSW, RN, MA
  - Partnership with pharmacy (Rx billed to grant)
- **Low barrier, rapid access**
- Group triage, aggressive bupe initiation
  - Flexible enrollment, fewer No Shows
- An article and a chance conversation

Original Investigation

Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence
A Randomized Clinical Trial

Gail D'Onofrio, MD, MS; Patrick G. O'Connor, MD, MPH; Michael V. Pantalon, PhD; Marek C. Chawarski, PhD; Susan H. Busch, PhD; Patricia H. Owens, MS; Steven L. Bernstein, MD; David A. Fiellin, MD

IMPORTANCE Opioid-dependent patients often use the emergency department (ED) for medical care.

OBJECTIVE To test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention); and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine).

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial involving 329 opioid-dependent patients who were treated at an urban teaching hospital ED from April 7, 2009, through June 25, 2013.

INTERVENTIONS After screening, 104 patients were randomized to the referral group, 111 to the brief intervention group, and 114 to the buprenorphine treatment group.

MAIN OUTCOMES AND MEASURES Enrollment in and receiving addiction treatment 30 days after randomization was the primary outcome. Self-reported days of illicit opioid use, urine testing for illicit opioids, human immunodeficiency virus (HIV) risk, and use of addiction treatment services were the secondary outcomes.

RESULTS Seventy-eight percent of patients in the buprenorphine group (89 of 114 [95% CI, 70%-85%]) vs 37% in the referral group (38 of 102 [95% CI, 28%-47%]) and 45% in the brief intervention group (50 of 111 [95% CI, 36%-54%]) were engaged in addiction treatment on the 30th day after randomization ($P < .001$). The buprenorphine group reduced the number of days of illicit opioid use per week from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) vs a reduction from 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) in the referral group and from 5.6 days (95% CI, 5.3-5.9) to 2.4 days (95% CI, 1.8-3.0) in the brief intervention group ($P < .001$ for both time and intervention effects; $P = .02$ for the interaction effect). The rates of urine samples that tested negative for opioids did not differ statistically across groups, with

JAMA Report Video and **Author Video Interview** at jama.com

CME Quiz at jamanetworkcme.com and **CME Questions** page 1670

YALE MODEL

- Dr. Gail D'Onofrio et al
- OUD randomized: control vs bupe
- 30 days:
  - TAU: 37%
  - Bupe + appt: 78%
- 2 months: 74%
- 12 months: 49%

D'Onofrio et al. *J Gen Int Med* 2017;32 (6):660

ED-INITIATED BUPRENORPHINE

- Usage of illicit opioids in past 7 days
  - Referral: 5.4 days → 2.3 days
  - Bupe + appt: 5.4 days → **0.9 days**

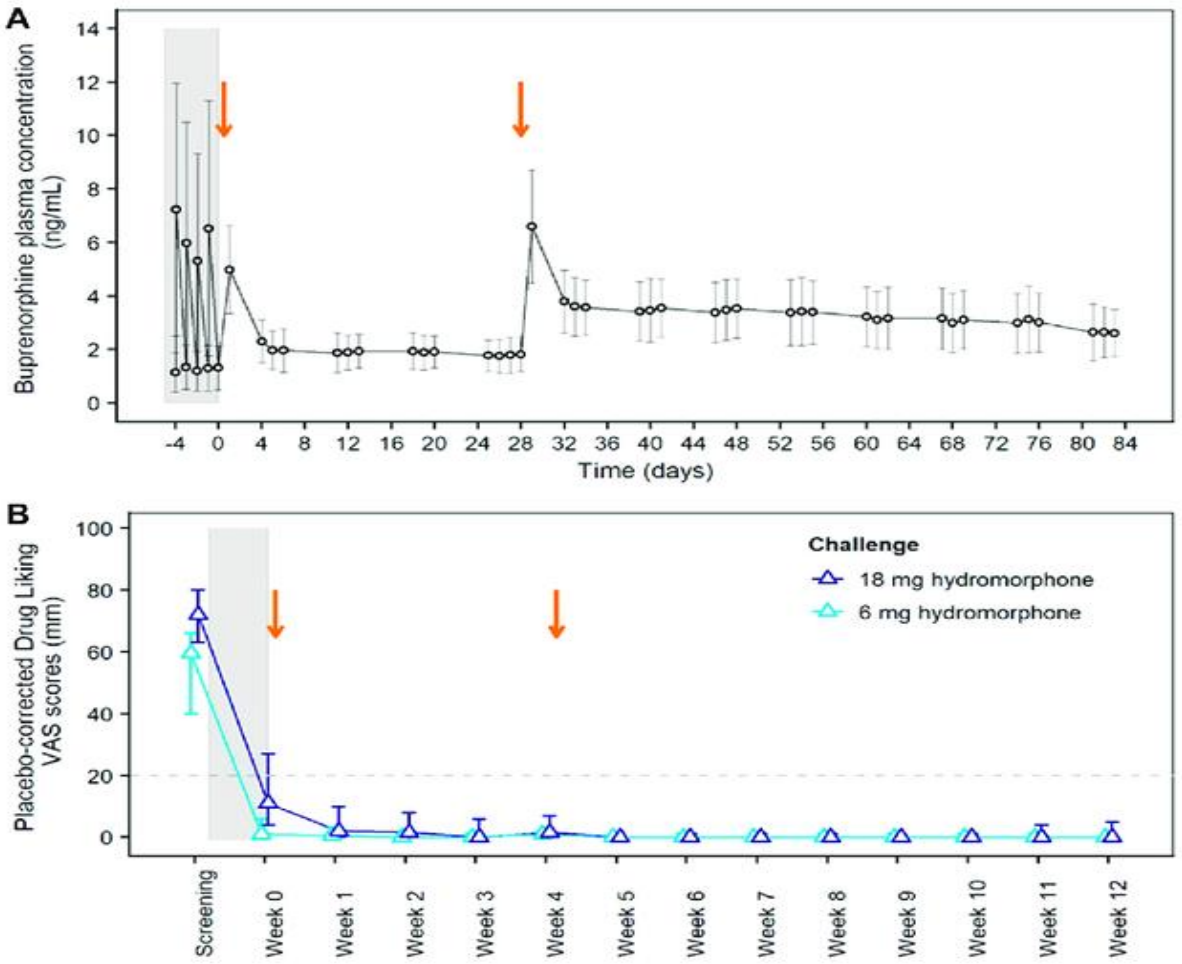
- Buprenorphine → lower rates of inpatient detox and fewer repeat ED visits

D'Onofrio et al JAMA 2015

WHY WOULD THIS BE?

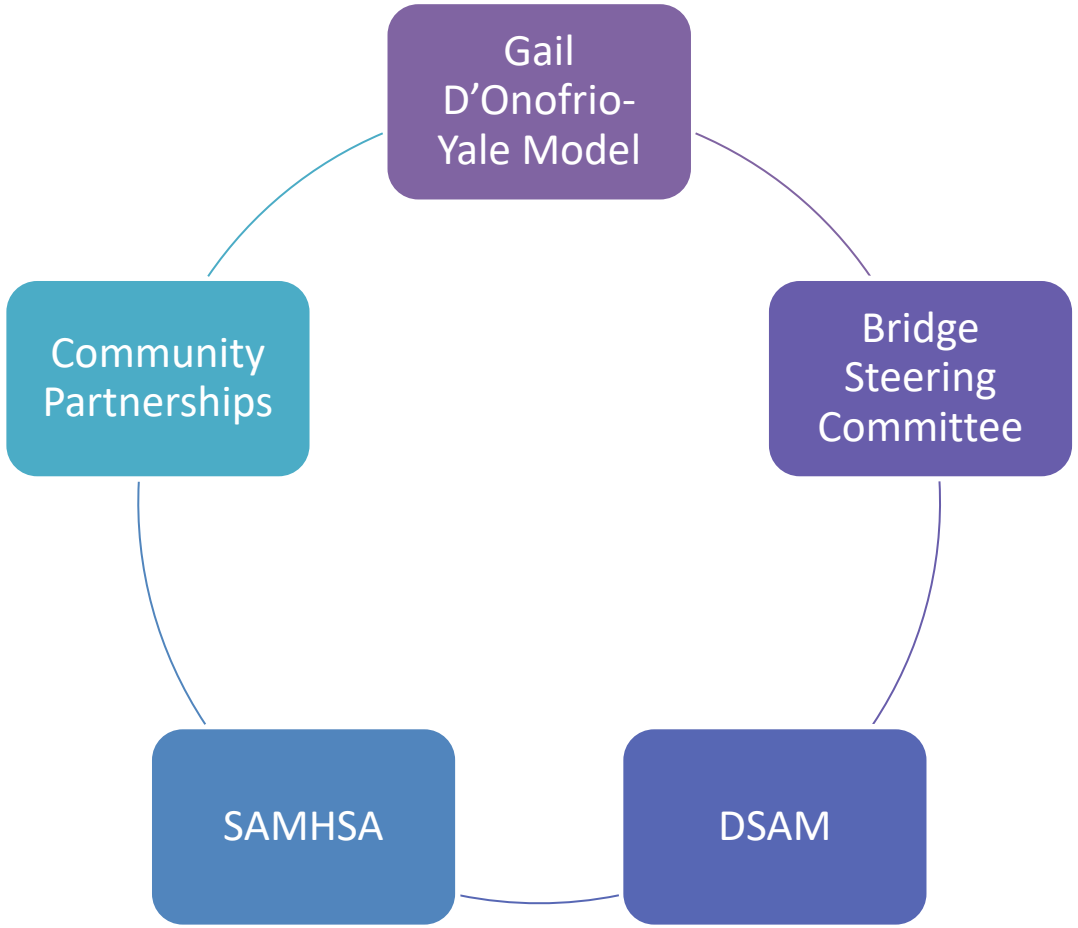
- Withdrawal management
- "Blockade" of opioid receptors
- Bupe is:
  - High **affinity**
  - Medium **intrinsic activity**
  - Slow **dissociation**
- Stays on those receptors!

WHY DO WE CARE?

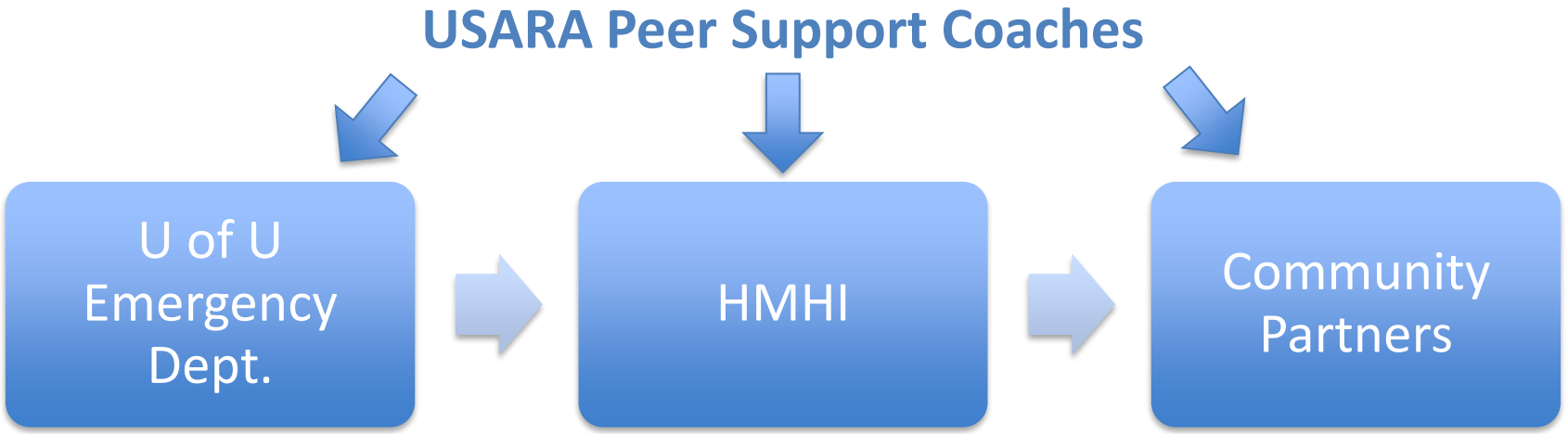


Laffont et al 2022

BUILDING BRIDGE PROGRAM



U OF U 3-PHASE PROGRAM



Grant Funding Provided by:
Utah Division of Substance Abuse and Mental Health
Utah Department of Human Services
(State Opioid Response Grants)

BRIDGE INCLUSION CRITERIA

- OUD Criteria (DSM-5)
- At least 16 years old
- Not on methadone maintenance
- Not in Bridge for previous 6 months

WHAT'S COVERED

- Initial ED visit
- Buprenorphine Rx's (dispensed weekly)
- Urine Drug Screens
- Clinic visits/groups
- Some transportation reimbursement
- CMs, 0.15 FTE for data analyst

PATIENT FLOW FOR BRIDGE 1.0

- Pt with OUD in the ED or Hospital
- Crisis LCSW: initial assessment
- Peer Support: makes contact, provides naloxone
- Simple ED order set:
  - Inclusion criteria, UDS, bupe Rx
- Peer Support and Case Management are the "glue"
- Bridge CM call/text to schedule 1st appt within 4 days
- "Up to 30 days" transition to Community Partners

CONTINGENCY MANAGEMENT APPROACH

- Complete ED visit → UUH 5-day Rx of bupe
- Initial clinic Group → HMHI 7-day Rx of bupe
  - Data collection for grant
  - Medicaid enrollment
- First 1:1 appt → HMHI 7-day Rx
- 2nd Group → 7-Day Rx
- 2nd 1:1 appt → 7-day Rx
- 3rd Group → 7-day Rx
  - Confirm follow-up w/ long-term clinic and naloxone kit

ADMINISTRATIVE DISCHARGE CRITERIA

- Behavioral problems
  - zero tolerance for disruptive/aggressive behavior (rare)
  - shop-lifting from gift shop (not as rare)
- Diversion
  - Word will get around
  - UDS
- Did **NOT** discharge for:
  - Continued/concurrent use (next slide)
  - Missed appt's/groups

FDA WARNING 2017

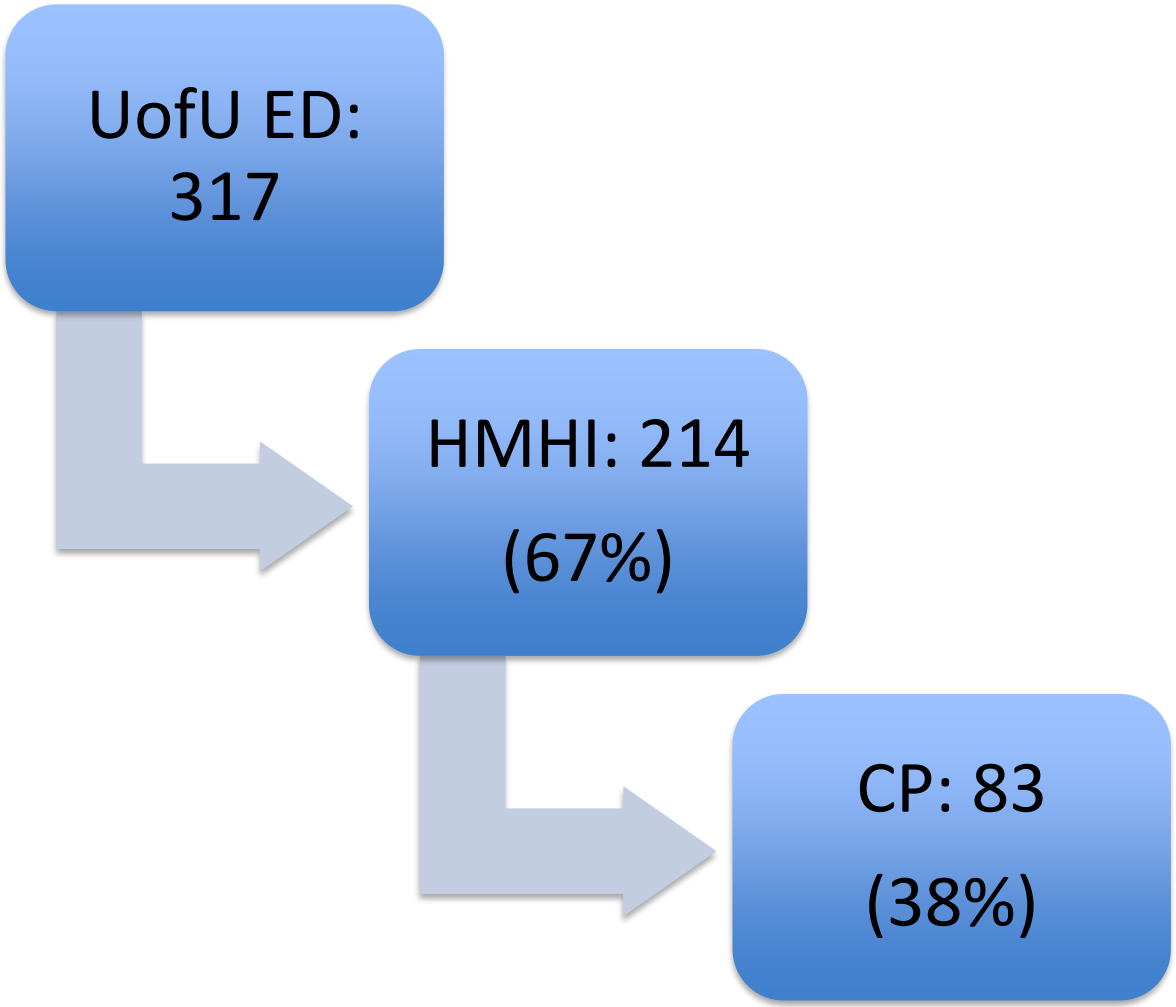
"Based on our additional review, the U.S. Food and Drug Administration (FDA) is advising that the opioid addiction medications buprenorphine and methadone **should not be withheld** from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks."

FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks | FDA

CASE 1 CONTINUED

- Pt lost his job, tried to wean bupe himself, relapsed
- Smoking 1g heroin/day, calls the clinic asking for help
- Sent through Bridge (because he didn't have insurance)
- Gets on bupe again, stabilizes quickly
- Able to get his job (and insurance) back
- Does well on 16mg bupe daily

PATIENTS TREATED APRIL – SEPTEMBER 2019



Unpublished Bridge data

COVID-19

- Built as a group-based program in a small clinic
- Most pt's relying on public transit
- Many began avoiding the ED
- Internal opposition to Bridge
- Desperate times…

BRIDGE 1.2

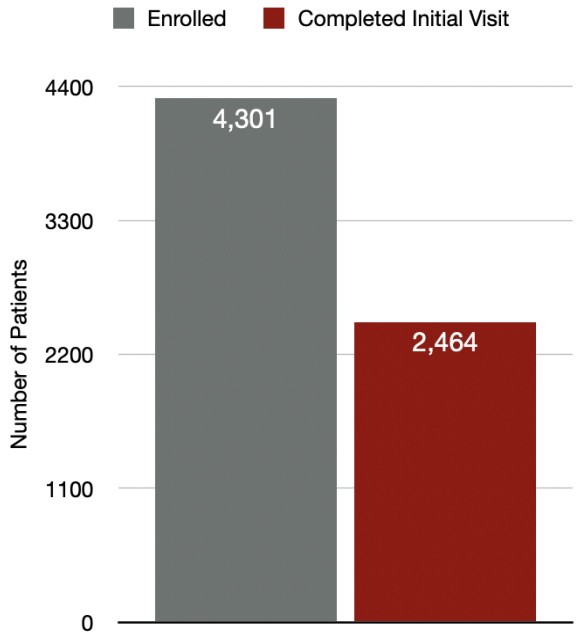
- Gymnasium at HMHI: socially-distanced stations
- UDS at the lab
- Rx at HMHI pharmacy
- Revise the grant language
- Move to **phone-based only** in April of 2020

BRIDGE 2.0

- In-person, group-based → 1:1 telephone visits
- UDS prior to Rx dispense → For-cause UDS w/ transport $
- Likely under-detecting other substance use
- Change in diversion risk
- Broader access
- No negative changes in retention/referral
- UUH Addiction C/L service can enroll

TOTAL BRIDGE PATIENTS SINCE INCEPTION

Total # Bridge Referrals Since Inception		
# ED to Bridge Referrals from Inception through 3/31/24	4,301	+244 enrollees
# ED to Bridge Referrals from Inception through 3/31/24 who Completed Initial Visit	2,464 (57%)	Same as last quarter



POST-COVID-19

- ED → HMHI: ~59%
- HMHI → Community: ~39%

- Bridge to-date: 4,470
  - Bridge 1.0 (in-person): 904
  - Bridge 1.1-3.0: (telephone): 3,566

- **NO SIGNIFICANT CHANGE** in outcomes w/ phone-visits
  - Some of this is "anec-data"

EXTENDED METAPHOR

- Endorphins = rainy-day savings
- Plant-derived opioids for acute pain = Credit Card with no balance (paid off monthly)
- Non-medical use = high-interest short-term loan
- Methadone = forbearance, mortgage
- Buprenorphine = reconsolidation at lower interest or shorter maturity

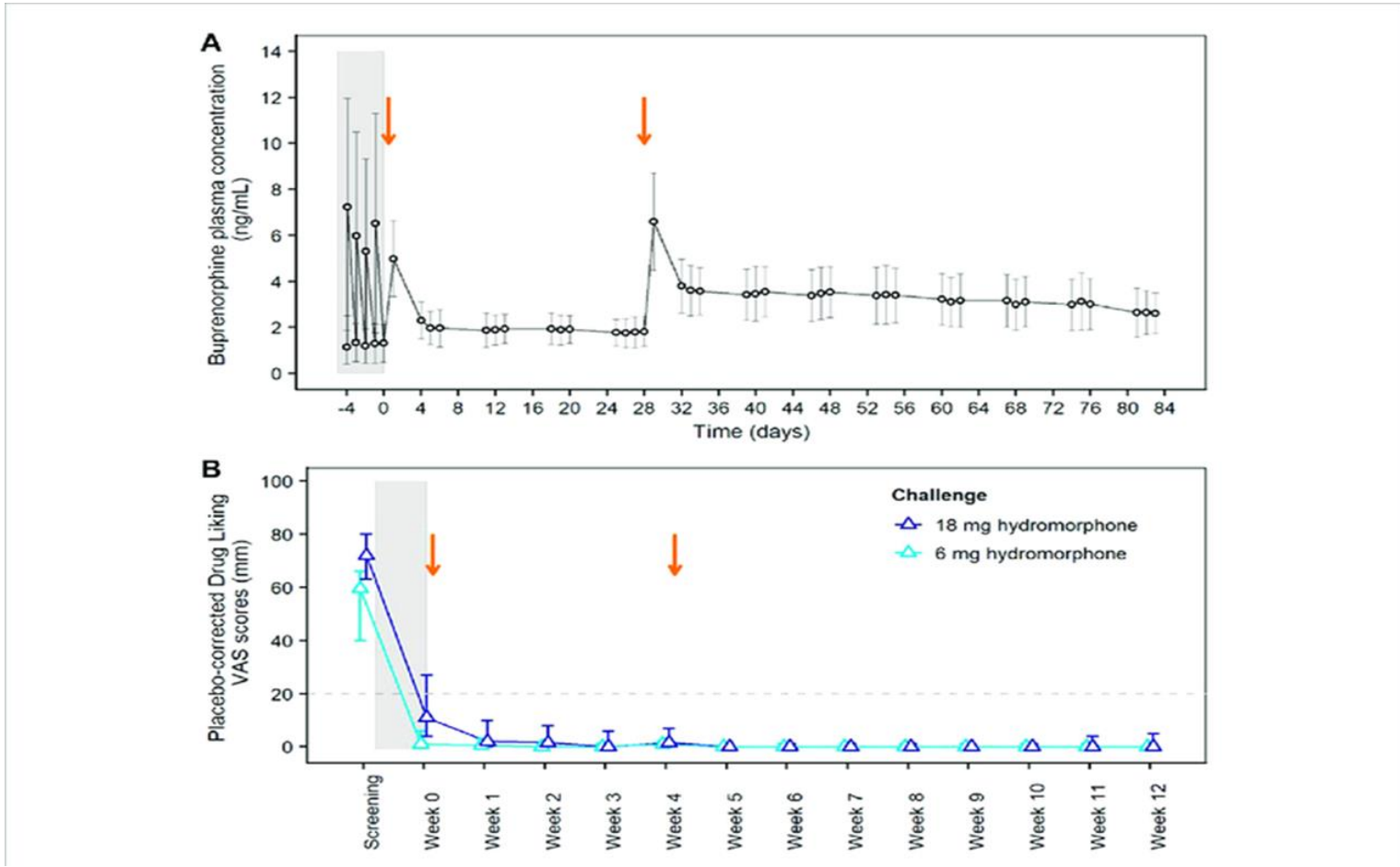
CASE 1

- Relapse after 2 yrs on bupe
- Thought he was taking “oxy 30s”, but really fentanyl (“blues”)
- Was at 10-15 “blues” per day in 6 weeks
- 2-4mg of fentanyl/pill
- Tries to quit “cold turkey”; hospitalized

CASE 1

- Ends up sedated, intubated in the ICU
- "I've never felt like that."
- Started back on bupe inpatient
- Relapsed within a few days
- Re-enrolled in Bridge, gets on a **long-acting injectable (LAI)**

WHY LONG-ACTING INJECTABLES?



MOVE TO BUPRENORPHINE-XR LAI

Clinical Pharmacokinetics
https://doi.org/10.1007/s40262-020-00957-0

ORIGINAL RESEARCH ARTICLE

Check for updates

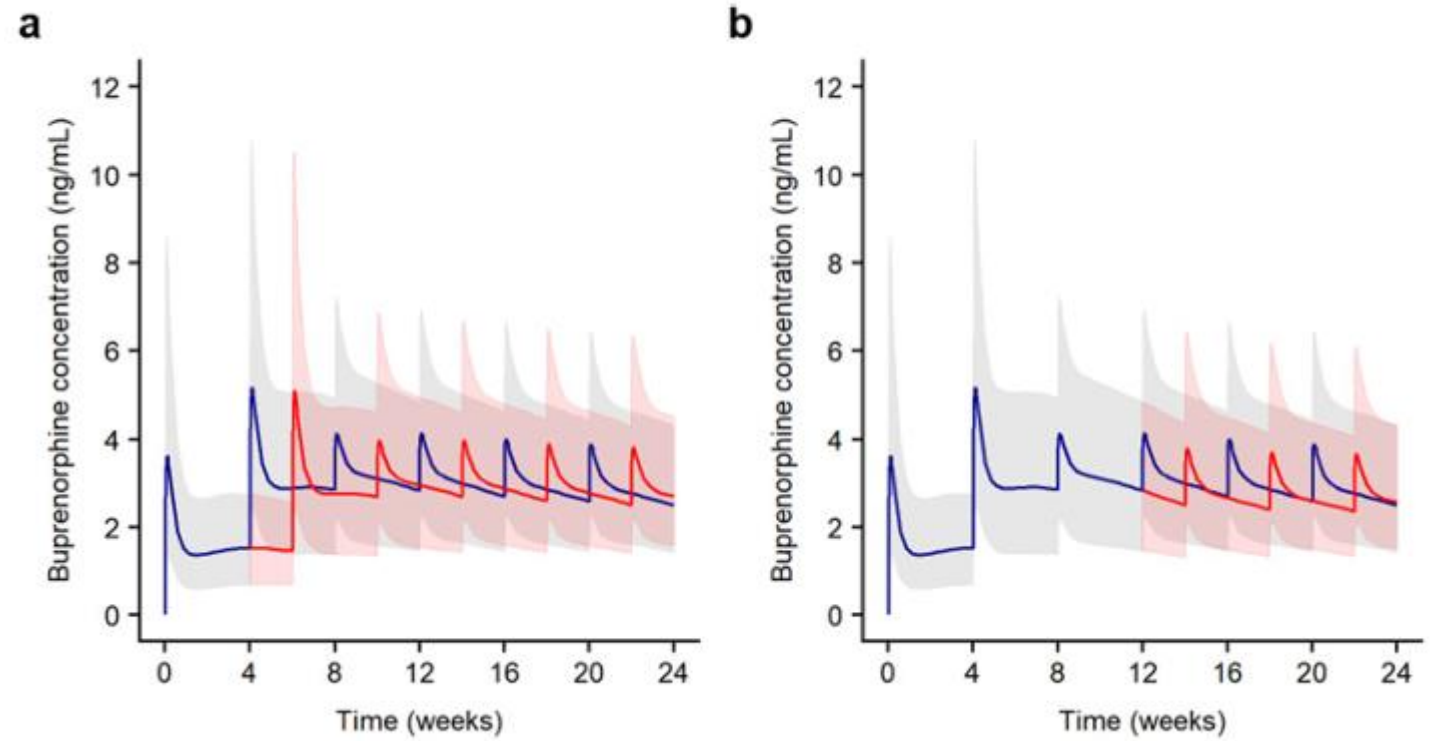
Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase II and Phase III Trials

Aksana K. Jones[1] · Eliford Ngaimisi[2] · Mathangi Gopalakrishnan[2] · Malcolm A. Young[1] · Celine M. Laffont[1]

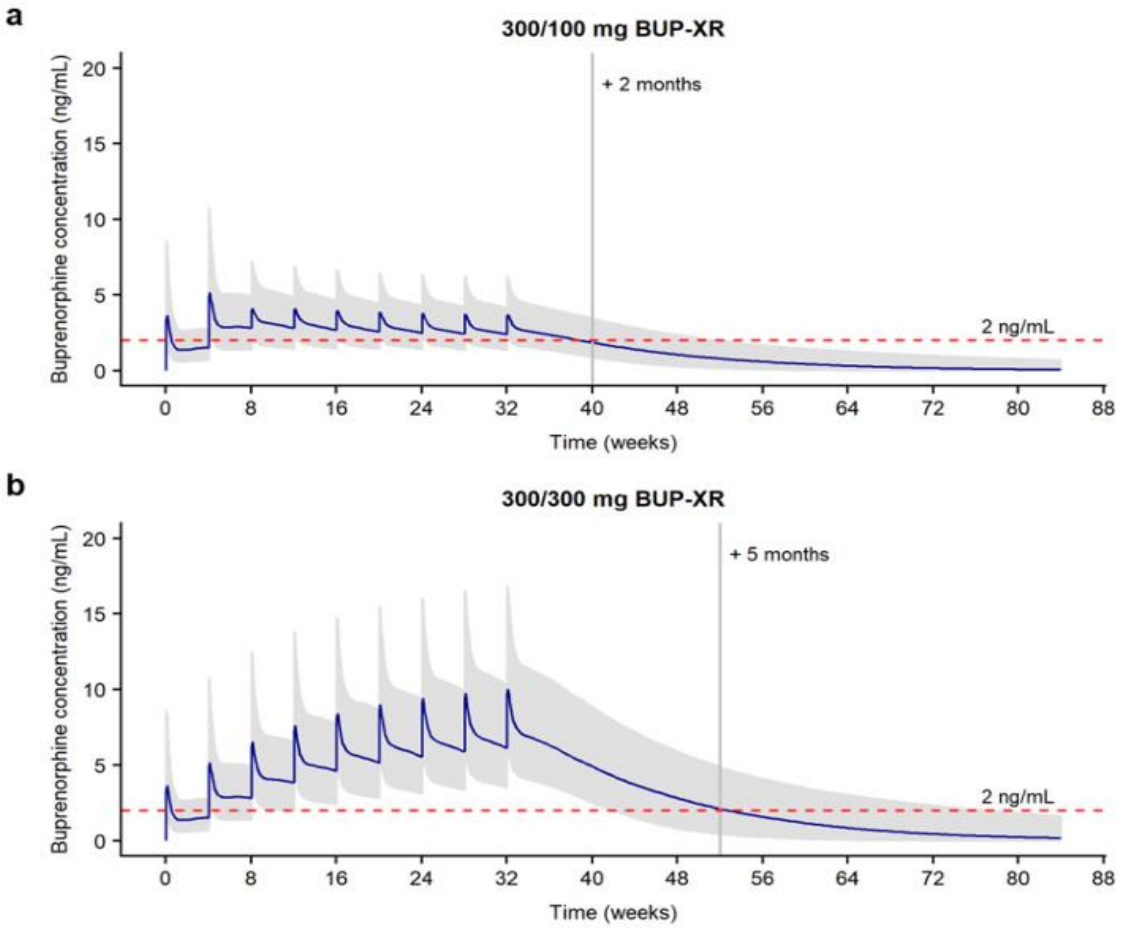
Accepted: 16 October 2020

BUPE DOESN'T WORK IF YOU DON'T TAKE IT

A. K. Jones et al.



BUPRENORPHINE-XR (LAI)



BRIDGE 3.0

- Can enroll from most UofU clinics and hospitals
- Rx at any UofU pharmacy
- Long-acting injectable (LAI) bupe-XR (Sublocade, Brixadi)
- PO Naltrexone available
- Community Bridge—pilot program
- De facto MOUD safety net for Salt Lake area
- "Competitors" replicating the program
- Spread the model

COMMUNITY BRIDGE

- Leveraging success and relationships
- Building new relationships
- First dose of bupe offered by paramedic after OD
- Peer Support goes to the scene to connect to Bridge
- First Rx sent in after consultation with ED attending
- Bridge CM connects with pt for clinic portion of Bridge

CLINIC PORTION OF BRIDGE

- Bridge CM collects data: phone, ED notes, schedules pt
- 3 groups, 2 individual appointments over 30 days
- Groups always Mon/Thurs (never exceeded ED Rx)
- Appt alternating every week (group, 1:1, group, 1:1, etc)
- Flexible scheduling

PT CHARACTERISTICS

- ~80% already on Medicaid/Medicare
- ~20% unfunded
- 1%> commercial insurance

- ~1/3 unhoused, marginally housed
- Many without cell phones
- Many without transportation
  - Creative solutions

BRIDGE "BONUSES"

- Re/start psychotropics
- Test for HCV/HIV and refer
- Referral for other services
  - Housing/shelter/detox
  - Primary care
  - Funding/research options
  - Basic necessities

CTN-99 AND CTN-100

- Bupe-XR injectable in Bridge-like model
- Bupe SL vs bupe-XR vs NTX-IM
- 5-year, multi-site RCT to answer some of the questions

FUTURE CHALLENGES TO SOLVE

- Additional MOUD: methadone, NTX
- Other substances (EtOH, benzos, stimulant)
- Health maintenance
  - Home meds, screening, vaccines, etc
- HCV treatment
- PrEP
- Medical Home

IN SUM

- No Recovery for the deceased
- No wrong door to treatment
- A day with bupe makes OD less likely
- How do I defend NOT giving this med?
- Progress > perfection
  - What is my pt up against? > What is my pt up to?
  - Trust, but verify

LESSONS CONTINUED

- Change “That won’t work because…” to “maybe if we did _____ this could work.”
- Make the ask. “No” isn’t that bad
- ‘No’ to ‘yes’ if possible
- For-cause UDS > Random/scheduled UDS
- Start small, but swing for fences as well—still a crisis

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THANK YOU!

Q&A

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