JCOIN Coordination and Translation Center

JCOIN Webinar:
Treatment Considerations in the Age of Fentanyl

April 5, 2023

12:00 – 1:30 pm Eastern Time

Speakers

Kathryn Cates-Wessel

Chief Executive Officer, American Academy of Addiction Psychiatry (AAAP)

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Dr. Tisha Wiley

Branch Chief, Associate Director for Justice Systems, National Institute on Drug Abuse (NIDA)

Jessica Hulsey

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Providers Clinical Support System

PCSS: Your Best Resource for Treating OUD/SUD

Kathryn Cates-Wessel
PCSS Principal Investigator and Project

John Mariani, MD
Columbia University, New York State Psychiatric Institute

Overall Mission: *provide training, educational resources and mentoring at no cost for health professionals in evidence-based practices in the prevention, identification, and treatment of opioid use disorders and other substance use disorders (SUD*).

Since 2008, nearly a half million clinicians have participated in PCSS trainings.

Funding for this initiative was made possible (in part) by grant no. 6H79TI081968 from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

PCSS is a SAMHSA-funded collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

Addiction Technology Transfer Center	American Society of Addiction Medicine
American Academy of Family Physicians	American Society for Pain Management Nursing
American Academy of Pain Medicine	Association for Multidisciplinary Education and Research in Substance use and Addiction
American Academy of Pediatrics	Council on Social Work Education
American Pharmacists Association	International Nurses Society on Addictions
American College of Emergency Physicians	National Association for Community Health Centers
American Dental Association	National Association of Social Workers
American Medical Association	National Council for Mental Wellbeing
American Osteopathic Academy of Addiction Medicine	The National Judicial College
American Psychiatric Association	Physician Assistant Education Association
American Psychiatric Nurses Association	Society for Academic Emergency Medicine

PCSS Providers Clinical Support System

PCSS is here to help

The *Providers Clinical Support System*, funded by the Substance Abuse and Mental Health Services Administration, has the resources and expertise to support health professionals' needs to overcome barriers to address substance use disorders with a focus on opioid use disorder and stimulant use. All resources are provided at no cost.

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LIVE AND ON-DEMAND WEBINARS
An array of topics pertaining to substance use disorders (SUD) and opioid use disorder (OUD).

MENTORING
Online discussions. Submit questions to clinical experts. Be matched with clinician to answer questions and discuss clinical cases.

ROUNDTABLES
Zoom call to discuss a specific topic with clinical expert. Submit clinical cases in advance of Zoom to expert to consider for discussion.

PCSS X-CHANGE
A course targeting prescribers and other allied health professionals in how to prescribe medications for treating OUD.

PCSS IMPLEMENTATION
Teams work with a clinical site to develop a system for treatment for OUD into their clinical practice.

SUD 101: Course on basics of identifying and treating SUDs.
Chronic Pain:
Course discusses treatment of OUD and the treatment of chronic pain.

What We Have Learned

- Stigma, stigma, stigma
- Training all staff from front desk, admin, clinical and CEO
- Health professionals need more education in the basics of SUD
- Access to behavioral health treatment
- Systems have to be integrated into clinical practice to include SUD
- Must address SUD and co-occurring psychiatric disorders concurrently.
- Clinicians need to be trained treating with all three FDA-approved medications for treating OUD: methadone, naltrexone and buprenorphine

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Opioid Response Network

ORN provides training and education in evidence-based practices in the prevention, treatment and recovery of opioid and stimulant use disorders with local *ORN* consultants in every US state and territories to meet locally identified needs—all at *no cost to the requestor.*

Opioid Response Network

ORN is funded through a SAMHSA grant awarded to the **American Academy of Addiction Psychiatry** in collaboration with the **Addiction Technology Transfer Center Network at the University of Missouri-Kansas City, Columbia University Division on Substance Use Disorders** and a coalition of over 40 national professional organizations **representing over 2 million constituents.**

Funding for this initiative was made possible (in part) by grant no. 1H79TI083343 from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

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Special Projects

Stand AGAINST Stigma Challenge

Opioid Response Network

Justice Involved Individuals with Substance Use Disorders:

Cultivating Law and Medicine Partnerships

Our Target

- **Everyone!** Our audience includes states, cities, organizations, community groups, health professionals, the justice system, law enforcement and even individuals.

- **Our goal is the goal of the requester.** All education and training is locally relevant, culturally responsive and tailored to the individual's, community's or organization's specific need.

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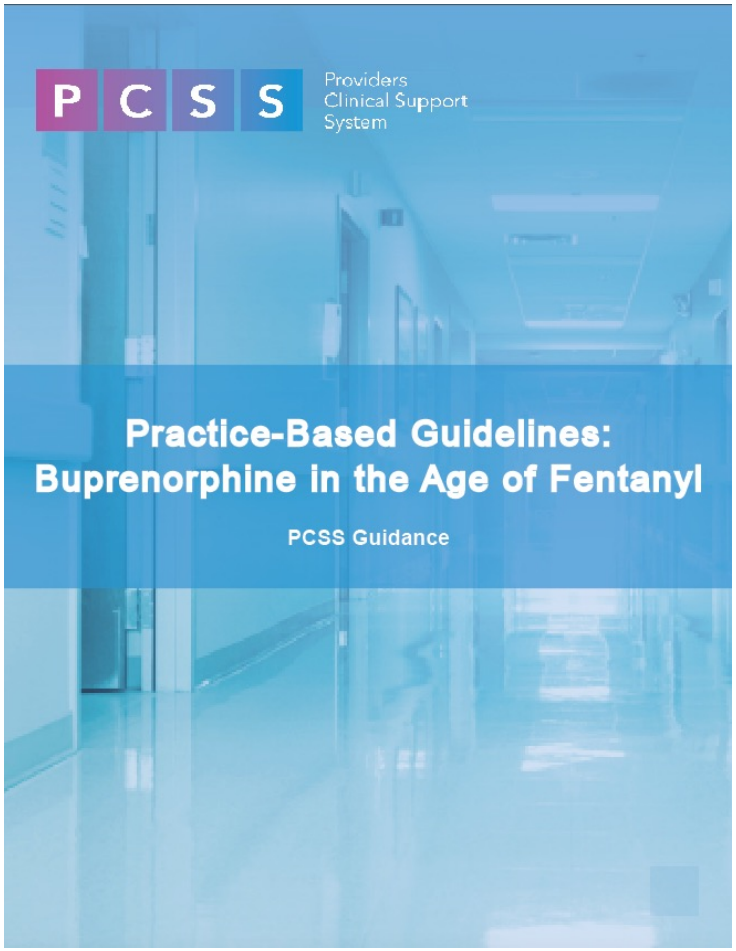
How to Submit a

- Those seeking education and training should submit a request via a form at www.OpioidResponseNetwork.org.
- Requests are forwarded to a designated Technology Transfer Specialist (TTS) for each state/territory. The TTS is the requester's point person.
- Once the request is submitted, the requester is contacted within one business day to discuss their needs and next steps.
- **Not sure what you need? Email orn@aaap.org.**

Treating Fentanyl Use Disorder



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Substance Treatment and Research Service | STARS

Treatment Considerations in the Age of Fentanyl

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Disclosures

- John Mariani, MD, has had a financial relationship with Indivior (manufacturer of Sublocade) in the past 24 months including payments for advisory board and speaker events
- The content of this activity may include discussion of off-label or investigative drug uses.
- Trade names are used to distinguish agents with the same generic designation (e.g., extended-release buprenorphine for injection)

Learning Objectives

- AT THE CONCLUSION OF THIS SESSION, PARTICIPANTS SHOULD BE ABLE TO:
  - Identify aspects of fentanyl pharmacology that complicate opioid use disorder (OUD) pharmacotherapy
  - Review the data supporting the use of medications for treating fentanyl-using patients, with an emphasis on extended-release injectable products
  - Discuss other clinical strategies for managing fentanyl-using patients

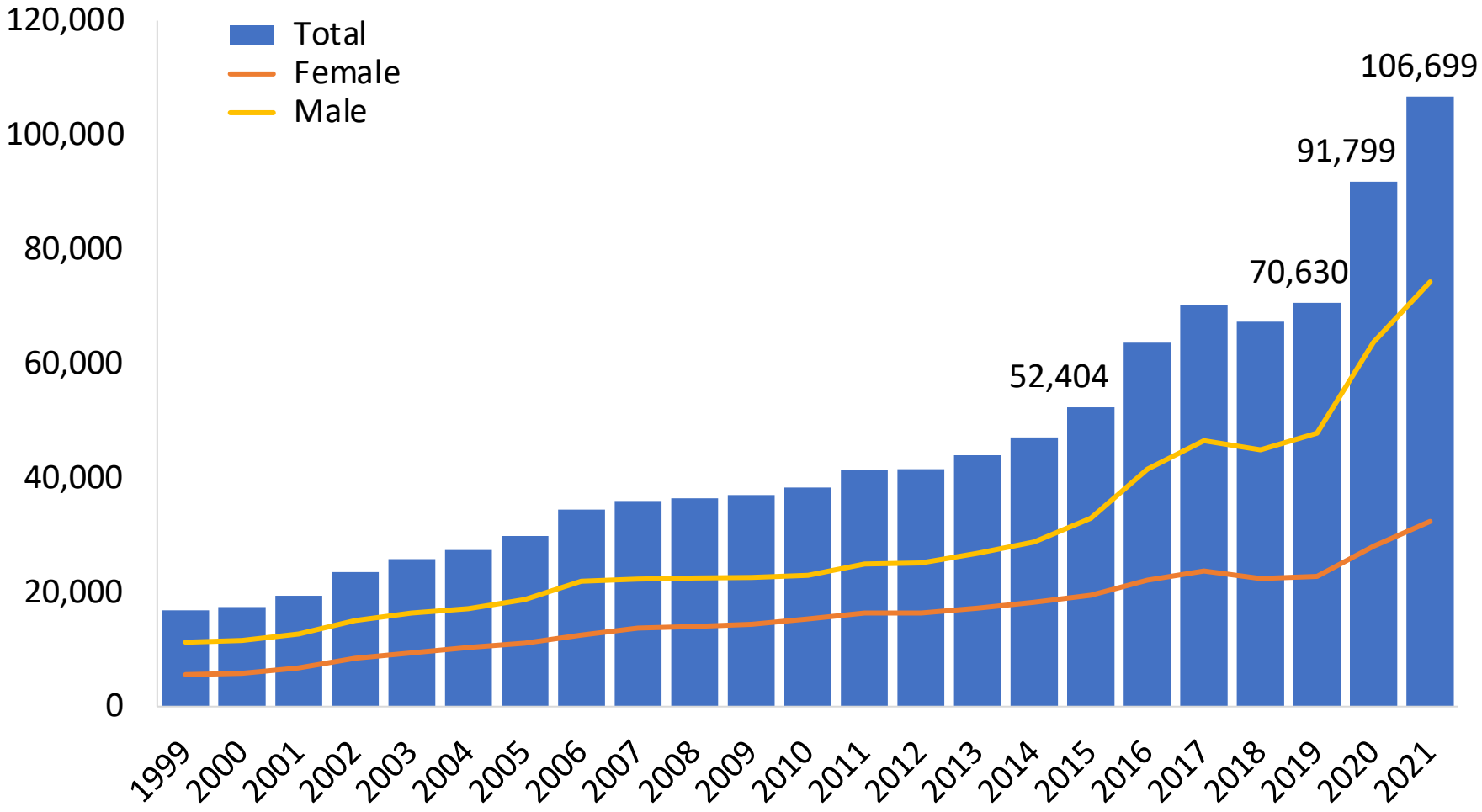
Why Talk About Fentanyl?

- Fentanyl use is a critical public health problem in the US leading to dramatic rises in overdose fatalities
- There has been a collective loss of confidence in proven treatment methods and this uncertainty is driven, in part, by a paucity of scientific evidence
- Clinicians, patients and their families, and policy makers are unsure of how to address this rapid and deadly change in the nature of the US illicit drug supply

Clinical Experience in New York City

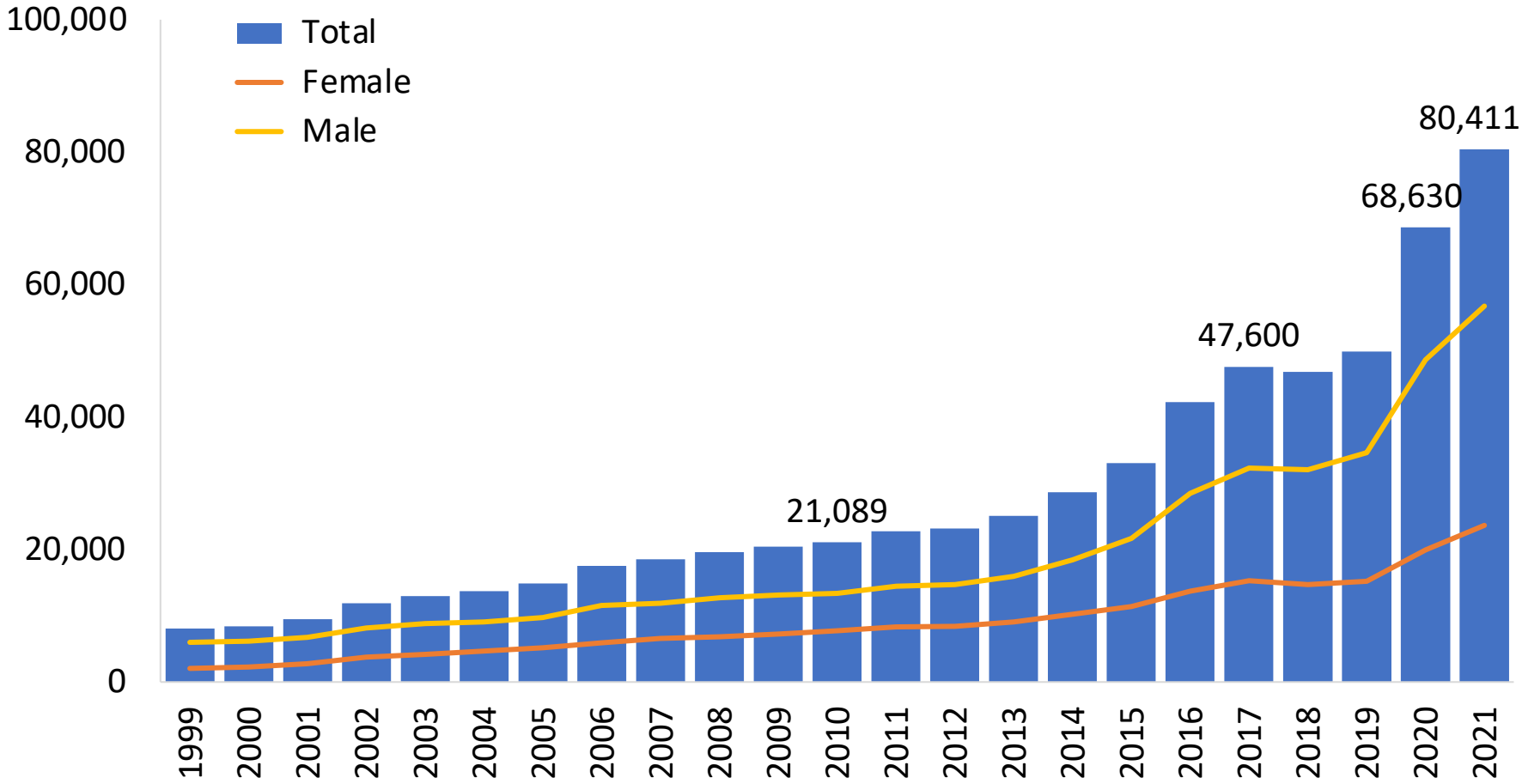
- September 2017
  - Private patient using heroin able to override Naltrexone XR injection despite Q 3 week dosing
    - Was able to re-establish blockade with Q 2 week dosing
  - Two private patients who are experienced with buprenorphine treatment report the same experience
    - Discontinued buprenorphine
    - Used heroin for several day period
    - Withdrawal symptoms did not start within usual time frame—delayed
    - Attempts to restart buprenorphine 48-72 hours after last use of heroin precipitated withdrawal
  - Research clinic
    - Staff discussions noting difficulty with first day of buprenorphine treatment for a clinical trial
  - Decision made to begin testing all patients in research clinic
    - ~90% of heroin users positive for fentanyl

National Drug-Involved Overdose Deaths*, Number Among All Ages, by Gender, 1999-2021



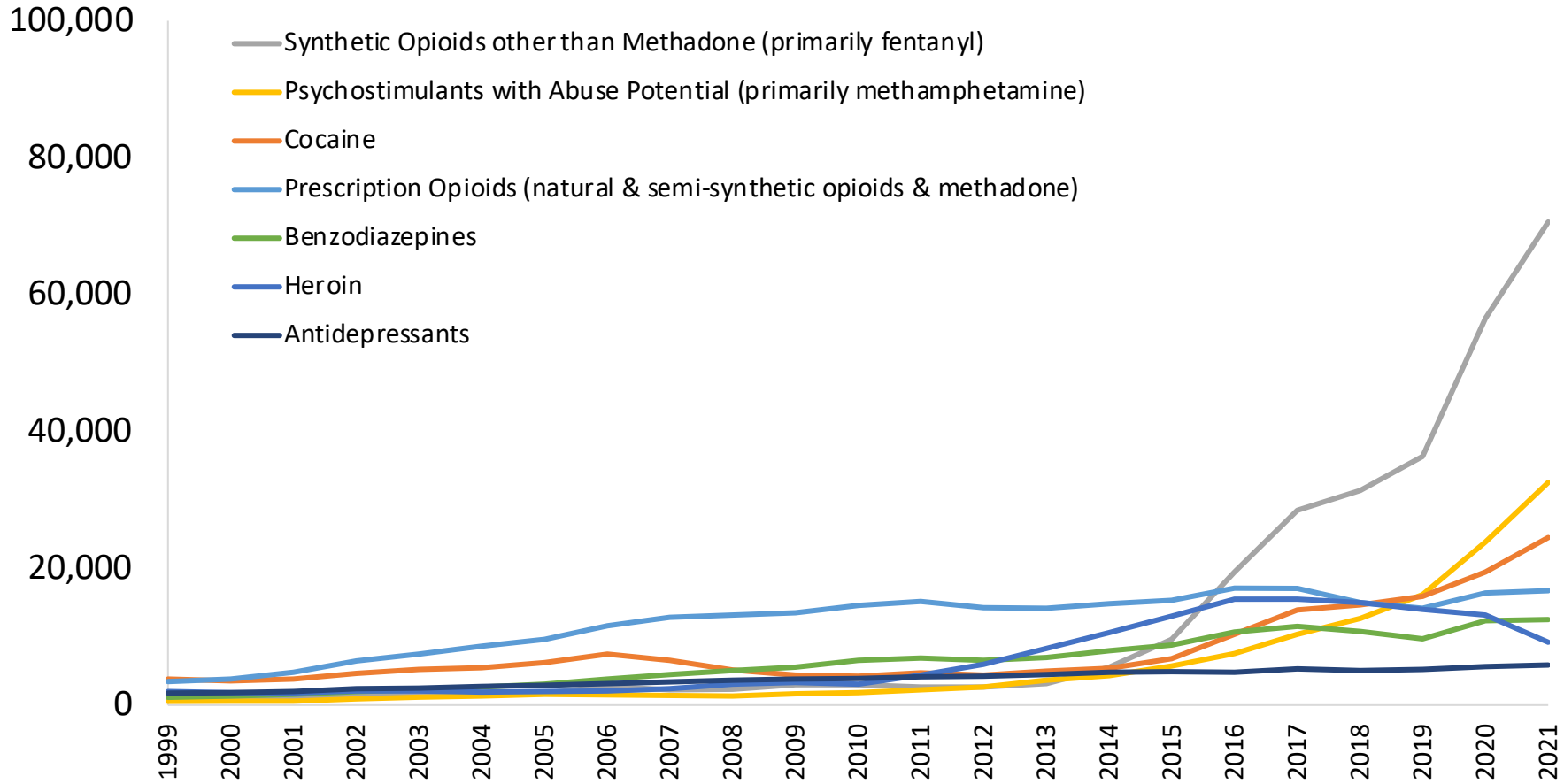
*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision.
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

National Overdose Deaths Involving Any Opioid*, Number Among All Ages, by Gender, 1999-2021



*Among deaths with drug overdose as the underlying cause, the "any opioid" subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2), methadone (T40.3), other synthetic opioids (other than methadone) (T40.4), or heroin (T40.1). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2021



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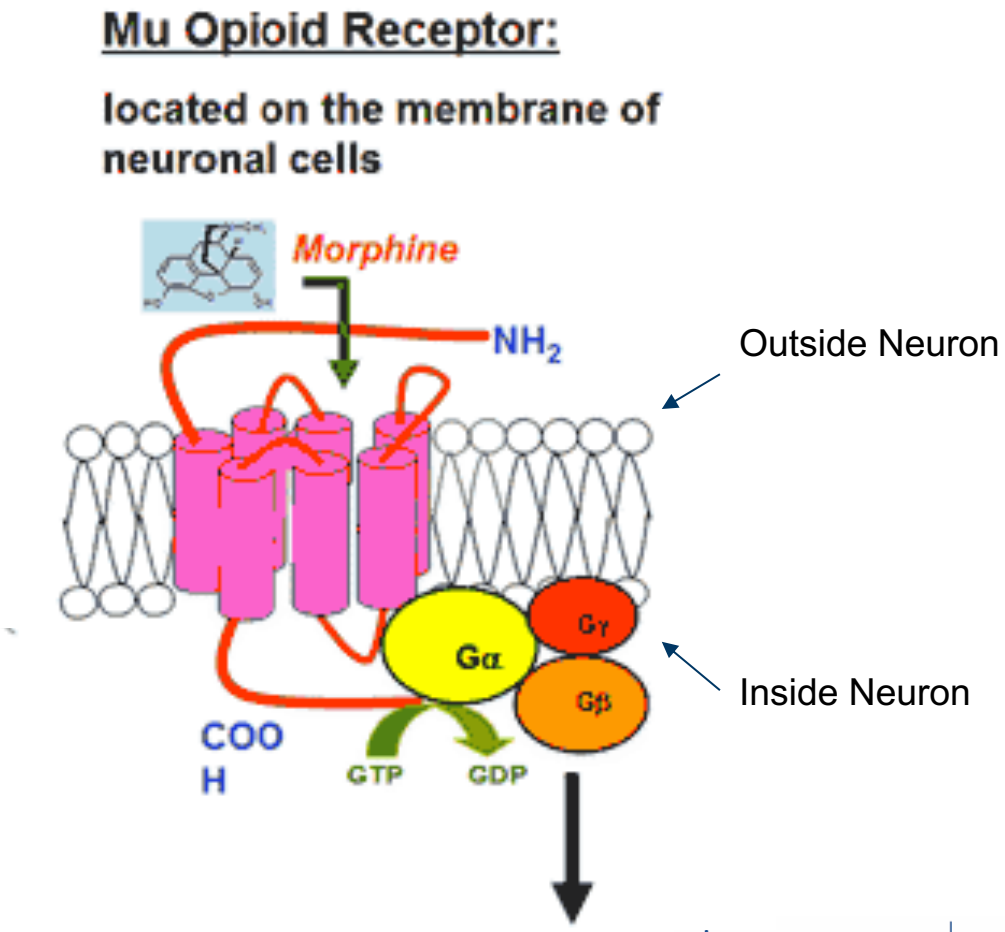
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

Why are so many people dying?

- Fentanyl and other Highly Potent Synthetic Opioids (HPSO) are substantially more potent than semi-synthetic or natural opioids
  - Fentanyl approximately 50-100 times more potent than morphine
    - Developed as a rapidly acting pain reliever
  - Carfentanil approximately 10,000 times more potent than morphine
    - 100 times more potent than fentanyl
- The high potency of fentanyl has implications for both overdose risk from use and the efficacy of standard Opioid Use Disorder treatment.

(Stanley 2014, Schug et al. 2017) (Armenian et al. 2018)

Mu Opioid Receptor



http://www-personal.umich.edu/~timaster/biopsych/pharm.html

Why is Fentanyl so Potent?

- Fentanyl and its analogues are highly lipophilic (“fat loving”)
- High lipophilicity results in:
  - Rapid crossing of the blood-brain barrier
  - Rapid distribution to the peripheral tissue and a slow return to the central compartment
- Highly “efficacious” μ-opioid receptor agonist
  - Differential changes in receptor conformation
- Similar μ-opioid receptor affinity as morphine
- Definitive human studies are lacking

(Chen, 1993)(Traynor 1995))(Volpe 2011)
(McClain 1980)(Maguire 1992) (Ricarte 2021)

Relative Potency

- Conceptually, fentanyl is more “efficacious” at μ-opioid receptor
  - If one molecule of morphine activating one receptor is 100 units of agonism
    - Then buprenorphine is 50 units
    - And fentanyl is 150 units
- Implications for standard dosing of current opioid use disorder pharmacotherapy
  - Treatment medication dosing is based on assumptions on what fraction of opioid receptors are occupied

Impact of Fentanyl on Existing Treatment Approaches

- Medication treatment is standard of care for Opioid Use Disorder treatment
- Main medication treatments (buprenorphine, methadone, naltrexone) all act on the mu-opioid receptor
- “Unoccupied” mu-opioid receptors are an opportunity for fentanyl to cause opioid effects
- Chronic use of fentanyl leads to accumulation in fat tissue and re-release back into systemic circulation
  - Relatively low serum levels may be clinically relevant due to high potency

Buprenorphine Treatment

- Administered sublingually or long-acting injection
- Buprenorphine is a “partial agonist” at the mu opioid receptor
- Buprenorphine has a relatively strong “receptor affinity” for the mu opioid receptor
- Key (buprenorphine) and lock (opioid receptor) analogy
  - Buprenorphine turns the cylinder partially and gets stuck
- Provides opioid agonism that reduces craving and withdrawal
- Blocks ability of other opioids to act on the opioid receptor

Clinical Difficulties Inducting Fentanyl-Using Patients Onto Buprenorphine

- Standard buprenorphine induction strategies can precipitate withdrawal (Shearer 2021, Varsheneya 2021, Spadaro 2022)
  - However, recent study (D'Onofrio, 2023) 1200 enrolled patients (~70% fentanyl positive) there were 9 cases of precipitated withdrawal
- Withdrawal time course is more protracted, likely due to "third space" accumulation of fentanyl in adipose tissue
  - Hospitalized patients positive 8 days after admission
- More failed initial inductions
- More failed "secondary inductions"—buprenorphine maintenance patients unable to restart buprenorphine on their own

Mechanism of Buprenorphine Induction Precipitating Withdrawal

- Ultimately unknown, but likely related to the differential pharmacokinetic and pharmacodynamic properties of fentanyl and buprenorphine (Olofsen 2022)
- Fentanyl is highly lipophilic and accumulates in adipose tissue
- Slow release back to circulation results in delayed onset of withdrawal symptoms despite short half-life
- Buprenorphine has a greater receptor affinity than fentanyl (Volpe 2011)
  - Administration of buprenorphine causes precipitated withdrawal when displacing more efficacious opioid agonist, fentanyl

Extended-Release Buprenorphine for Injection (BXR)

- Sublingual formulation of buprenorphine approved in US in 2002 for opioid use disorder
  - Effective and adopted widely
  - Main disadvantages are noncompliance and diversion
- 1st BXR approved in the US in 2017 (Sublocade™) for the treatment of moderate-severe OUD (available since 2019)
  - Two available strengths, 300 mg and 100 mg
  - SC abdominal injection every 4 weeks
- 2nd BXR approved in the US in 2018 (Brixadi™ US; Buvidal™ EU)
  - Not yet available in US; available in EU
  - Weekly (8, 16, 24 or 32 mg) or monthly (64, 96, 128) are planned to be available commercially

Buprenorphine XR Injection Pivotal Trials

- Sublocade (Haight 2019)
  - Placebo-controlled 3-arm trial (n = 504)(Haight 2019) comparing:
    - BUP-XR 300 mg/100 mg (2 x 300 then 4 x 100 mg)
    - BUP-XR 300 mg/300 mg (6 x 300 mg)
    - PBO
  - % negative urine sample/self-report from weeks 5 to week 24
  - BUP-XR 300 mg/300 mg (41.3%)/BUP-XR 300 mg/100 mg (42.7%)/PBO (5 %)
  - Retention 12 months 50.6% (Andorn 2020)
  - Labelling recommends 7-days SL BUP $\geq$ 8 mg daily before injection
- Brixadi/Buvidal (Lofwall, 2018)
  - Double-dummy design comparing injectable vs. SL buprenorphine formulations (n= 428)
  - Phase 1: 12 weeks weekly injection; Phase 2: 12 weeks monthly injection
  - On day of randomization, received 4 mg SL buprenorphine, followed by randomization to either SL or injection treatment arms
  - 1st Injection weekly injection equivalent to 8 mg SL
  - 2nd injection on day 3-4 equivalent to 4 mg SL
  - Non-inferiority as primary outcome was met

Comparison of Sublocade and Brixadi/Buvidal

- No direct efficacy comparisons available
  - Brixadi was “non-inferior” to SL buprenorphine
  - Sublocade was superior to placebo
- Brixadi available in weekly and monthly formulations in several formulations
  - Weekly (8 mg, 16 mg, 24 mg or 32 mg) or
  - Monthly (64 mg, 96 mg, 128 mg or 160 mg)
    - Good dosing flexibility
    - Unclear how weekly injection is an advantage
- Sublocade 300 mg and 100 mg monthly formulations available
- Great to have these options available, but much to be learned
  - Should all OUD patients being treated with buprenorphine be started on an injectable product?
  - No controlled studies (yet) on subgroups who would likely benefit from injectable formulation vs SL
- Many research questions remain to be answered to guide clinical decision making

Sublocade Pharmacokinetics

Comparison of Steady-state Buprenorphine Plasma Exposure Between Daily Transmucosal Buprenorphine and Once Monthly SUBLOCADE at Trough (C_{trough}), Average (C_{avg}) and Peak (C_{max}) Levels (Geometric Mean (CV%))

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)

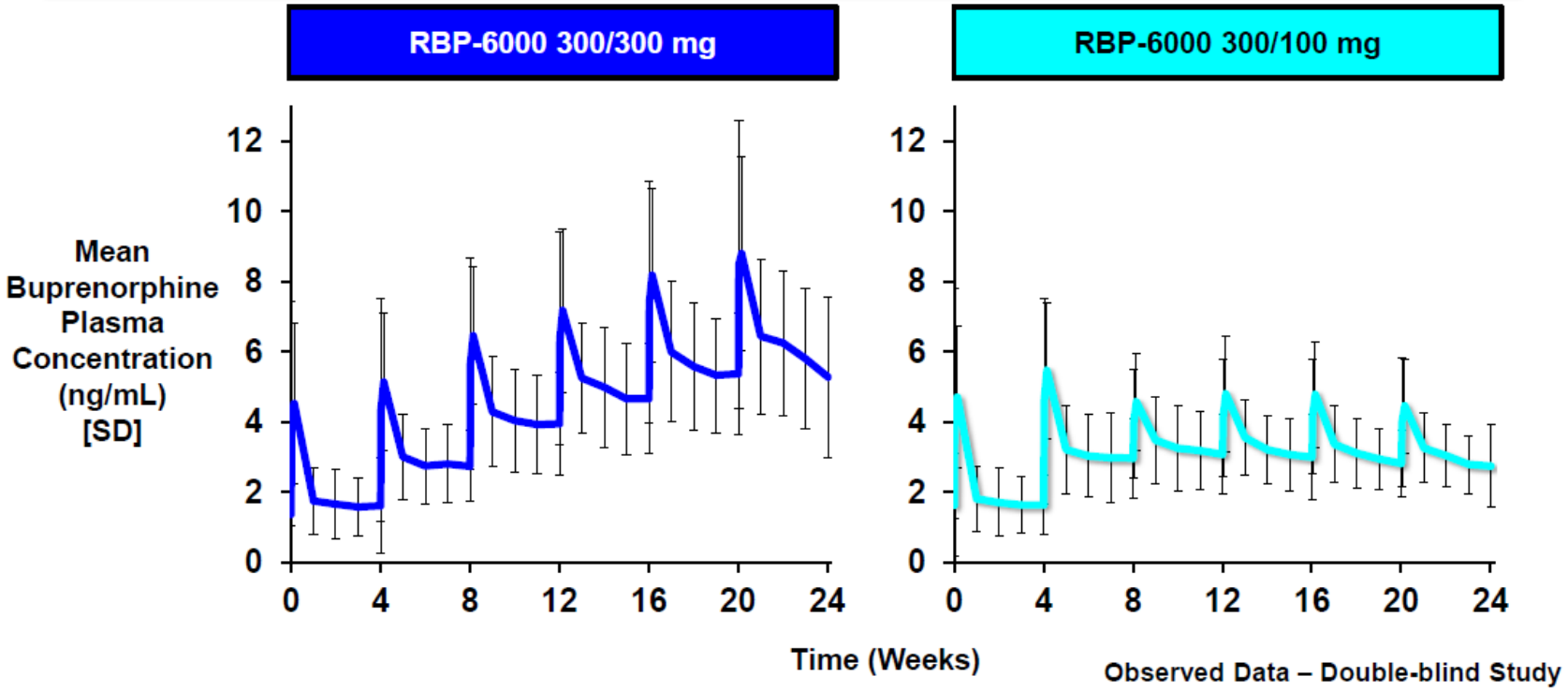
(Sublocade FDA Prescribing Information)

(Sublocade FDA Prescribing Information)

Sublocade PK in Phase 3 Double-Blind Study

CO-40

RBP-6000 PK in Phase 3 Double-Blind Study



(https://www.fda.gov/media/108382/download)

300/300 group received Sublocade 300 mg every month
300/100 group received Sublocade 300 mg for two months followed by 100 mg monthly

Methadone Treatment

- Methadone is an orally administered medication used to treat opioid use disorder
- Methadone is a full opioid agonist with a long half life
- By acting as an opioid agonist, methadone reduces craving and treats withdrawal
- Does not “block” the effects of other opioids, but rather raises the tolerance to opioids out of reach of other opioids
- Does not have “precipitated withdrawal” issue with fentanyl
- Minimal literature examining methadone treatment in the fentanyl era
  - Likely to be questions about adequacy of maintenance dose for fentanyl using patients

Extended-Release Naltrexone for Injection (XR-NTX)(Vivitrol™)

- Oral formulation of naltrexone approved 1984 for opioid use disorder
  - However, not shown to differentiate from placebo unless administration monitored
- XR-NTX approved in the US in 2010 for prevention of relapse to OUD following detoxification, in conjunction with psychosocial counseling
  - IM gluteal injection every 4 weeks
- XR-NTX shown to be associated with increased treatment retention, decreased relapse, and decreased cravings for opioids in outpatients and inpatients
  - (Krupitsky 2011, Nunes 2018, Lee 2018, Bisaga 2018)
- FDA prescribing instructions recommend an opioid-free duration of at least 7-10 days to avoid precipitated withdrawal
  - 5-day induction period may be feasible for outpatients (Sibai 2020)
  - Fentanyl user induction data unclear

Naloxone and Fentanyl

- Naloxone is a mu opioid antagonist (receptor blocker)
- When fentanyl became available in the community, reports of multiple doses of naloxone being required to reverse overdose
- Because the length of time between substance use and death is shorter with fentanyl, there have been more reports of unsuccessful attempts to revive with naloxone despite administration of multiple or escalating doses
- Some naloxone programs have begun providing more than the standard two doses of naloxone, and others have begun utilizing higher dose devices
- FDA has approved higher potency naloxone kit formulation
- Modifying naloxone to be more lipophilic
  - It is not clear whether these approaches are effective

(Somerville 2017)(Sutter 2017)(Fairbairn 2017)
(Voronkov 2021)(Moustaqim-Barrette 2021)

What Should Clinicians, Patients, and Families Do?

- We are in the midst of a rapid change of our illicit drug supply increasing the risks to drug users
  - Counterfeit opioids and benzodiazepines tablets have been found to contain fentanyl
  - Cocaine and other illicit drugs have contained fentanyl, leading to overdose deaths in opioid non-tolerant individuals
  - Patients with opioid use disorder are reluctant to start buprenorphine because of the fear of precipitated withdrawal
- There is limited evidence-based recommendations for how to treat fentanyl users
- Best approach is to use standard evidence-based approaches for opioid use disorder and modify based on clinical circumstances

Gradual-Low or Rapid-High Dose Buprenorphine Induction Approaches

- Several Case series using gradual low dose strategy (Ahmed 2020, Brar 2021, Suen 2022)
  - Adapted from strategies for buprenorphine induction from methadone (Antoine 2021)
- An alternative approach is rapid high dose strategy up to 20 mg on first day of the induction (Herring 2021; Quattlebaum 2022)
- Open-label uncontrolled pilot study to demonstrate feasibility and have flexibility to develop optimal induction method
  - 7-day stabilization period described in labelling was thought to be unnecessary
  - What about patients who can't tolerate SL induction?

Phase 1 (2- or 3-day induction)

Subject	Day 1	Day 2	Day 3	Day 4	Current Status
001	• COWS = 10 at start of induction • BUP-SL = 24 mg	• BUP-SL 16 mg • BXR 300 mg injection	• COWS = 7	• COWS = 4	• Received 3 BXR injections • Completed trial • No opioid use since day prior to start of induction
003	• COWS = 10 at start of induction • BUP-SL = 10 mg	• BUP-SL = 24 mg	• BUP-SL 16 mg • BXR 300 mg injection	• COWS = 0	• Received 3 BXR injections • Completed trial • No opioid use since receiving 1st BXR injection
004	• COWS = 16 at start of induction • BUP-SL = 24 mg	• BUP-SL 16 mg • BXR 300 mg injection	• COWS = 0	• COWS = 0	• Received 3 BXR injections • Completed trial • No heroin use since second BXR injection
005	• COWS = 12 at start of induction • BUP-SL = 24 mg	• BUP-SL 8 mg	• BUP-SL 16 mg • BXR 300 mg injection	• COWS = 2	• Received 3 BXR injections • Completed trial • Intermittent heroin use after 3rd injection
006	• COWS = 10 at start of induction • BUP-SL = 24 mg	• BUP-SL 8 mg	• BUP-SL 16 mg • BXR 300 MG injection	• COWS = 0	• Received 1 BXR injection; refused 2nd injection • Retained in trial 5 weeks • No heroin use after 1st injection

(Mariani, 2020)

Phase 2 (One Day Induction)

Participant	Day 1	Day 2	Day 3	Day 4	Clinical Status
#1 41 y/o Hispanic Male Intravenous heroin 13 bags/day Utox: +Fentanyl/+Morphine	• COWS = 11 at the start of the induction • Total BUP-SL = 24 mg in divided doses • BXR 300 mg injection • COWS = 9 at the end of the induction	• Missed Visit	• COWS = 0	• COWS = 1	• Received 3 BXR injections • Completed Trial • 4 days heroin use in first 28 days post-induction • 5 days heroin use in 28 day period after 2nd injection • 4 days heroin use in 28 day period after 3rd injection • Longest continuous heroin using period was 2 days
#2 33 y/o White Male Intranasal heroin 15 bags/day Utox: +Fentanyl/+Morphine	• COWS = 9 at the start of the induction • Total BUP-SL = 24 mg in divided doses • BXR 300 mg injection • COWS = 4 at the end of the induction	• COWS = 2	• COWS = 0	• COWS = 2	• Received 3 BXR injections • Completed Trial • No heroin use after receiving 1st BXR injection for remainder of the study
#03 26 y/o White Male Intravenous heroin 15 bags/day Utox: +Fentanyl/+Morphine	• COWS = 8 at the start of the induction • Total BUP-SL = 24 mg in divided doses • BXR 300 mg injection • COWS = 11 at the end of the induction	• COWS = 7	• COWS = 5	• COWS = 0	• Received 3 BXR injections • Completed Trial • 2 days heroin use in first 28 days post-induction • Longest heroin continuous using period was 1 day • No heroin use after receiving 2nd BXR injection for the remainder of the study
#4 29 y/o White Female Intravenous heroin 8 bags/day Utox: +Fentanyl/+Morphine	• COWS = 18 at the start of the induction • Total BUP-SL = 24 mg in divided doses • BXR 300 mg injection • COWS = 9 at the end of the induction	• COWS = 3	• Missed Visit	• COWS = 7	• Received 3 BXR injections • Completed Trial • 14 days heroin use in first 28 days post-induction • 8 days heroin use in 28 day period after 2nd injection • 3 days heroin use in 28 day period after 3rd injection • Longest continuous heroin using period was 5 days
#5 40 y/o Black Male Intranasal heroin 8 bags/day Utox: +Fentanyl/+Morphine	• COWS = 17 at the start of the induction • Total BUP-SL = 24 mg in divided doses • BXR 300 mg injection • COWS = 15 at the end of the induction	• COWS = 0	• COWS = 0	• Missed Visit	• Received 3 BXR injections • Completed Trial • 9 days heroin use in first 28 days post-induction • 7 days heroin use in 28 day period after 2nd injection • Longest heroin continuous period was 3 days • No heroin use after 3rd injection

(Mariani, 2021)

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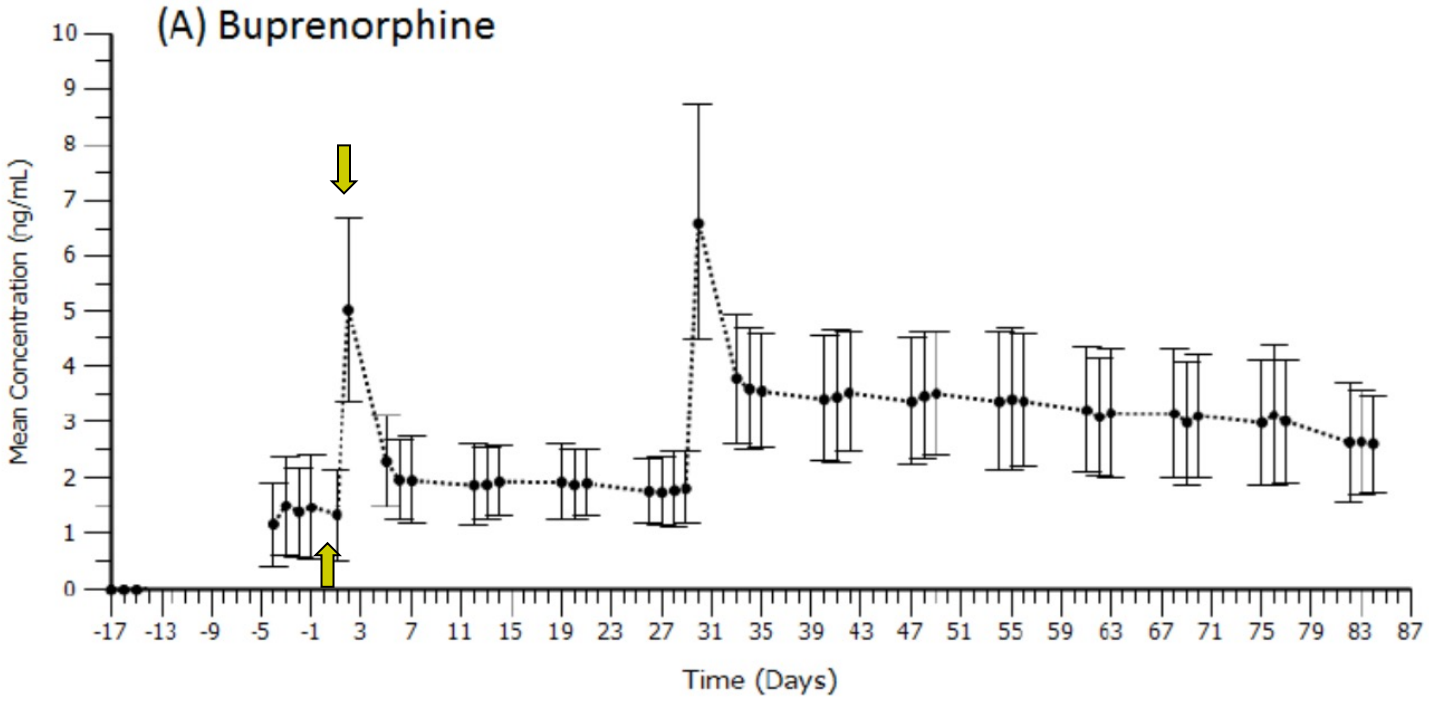
Sublocade 300 mg Serum Level Time Course



(Nasser, 2016)

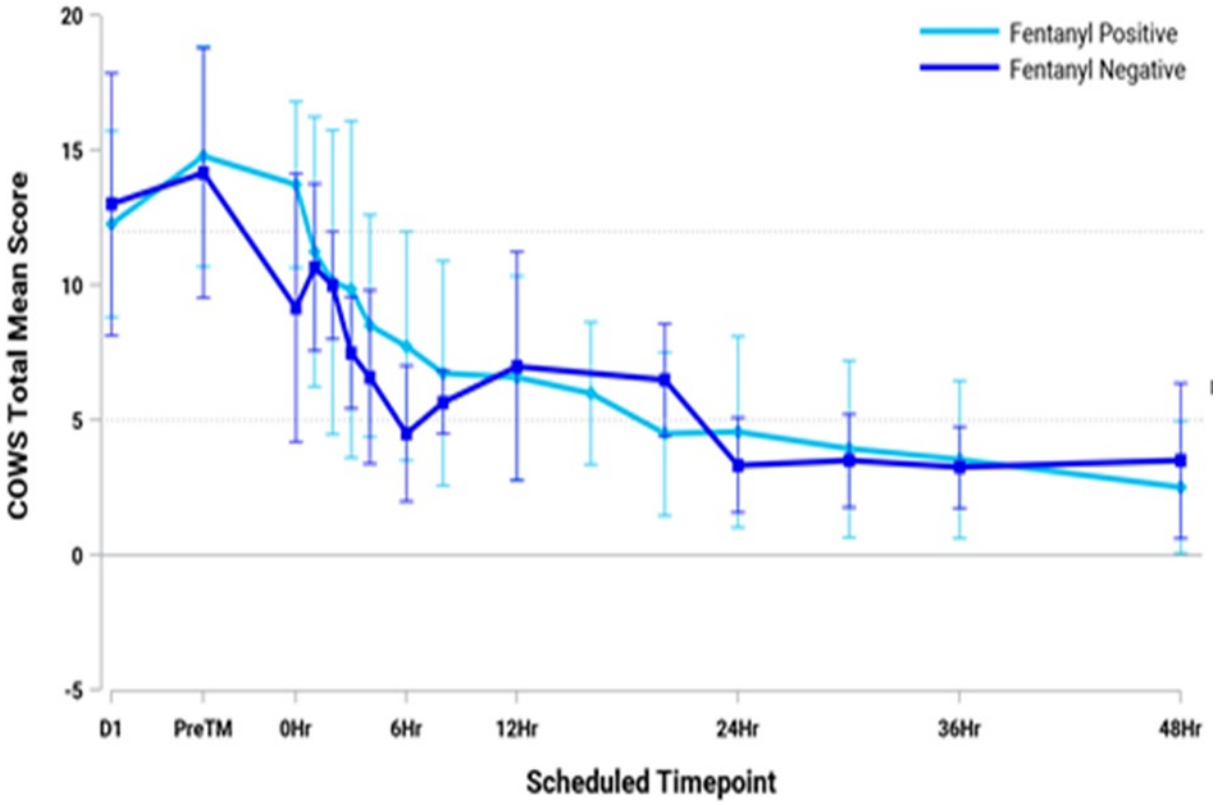
Rapid Initiation of XR-Buprenorphine in Fentanyl Using Patients

- Secondary analysis of (Hassman 2022)

- FEN+ (n=20)
- FEN- (n=6)

- COWS scores in FEN+ subjects decreased from a pre-BUP-XR baseline of 13.7±3.1 to 7.8±4.2 at 6h and to 4.6±3.5 at 24h
- 2 FEN+ subjects experienced precipitated withdrawal during initiation, but still completed all 6 injections

COWS Scores



D1= Day 1 Check-in, PreTM=Pre TM Buprenorphine, 0hr=time of injection

Mariani, et. al. Rapid Initiation of Extended Release Buprenorphine in Patients using Fentanyl and Fentanyl Analogs. Presenting at Canadian Society of Addiction Medicine - La Société Médicale Canadienne sur L'Addiction (CSAM-SMCA); October 21-23, 2021.

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Patient Selection for Extended-Release Injectable OUD Pharmacotherapy

- Key issue is that the ER-injectable medications reliably provide effective medication for a prolonged period of time, which should be an advantage for non or partially compliant patients and eliminate the risk of diversion
  - However, there are limited clinical trial data comparing oral/sublingual formulations to ER-injectable formulations
  - And no data comparing the different ER-injectable formulations
- Additional important clinical factor is the emergence of fentanyl analogs as the leading cause of overdose in the US
- Almost all clinical trial data was collected in the pre-fentanyl era, and how to best treat fentanyl using patients is mostly unknown.
- Limited data of ER-Bup use in pregnancy
  - Case series of 3 patients (Cleary 2020)
  - Potential concern over safety of non-buprenorphine components of ER-Bup injection

Injectable Naltrexone (XR-NTX) vs. Injectable Buprenorphine (BXR)

- No clinical trial data, but clinical experience suggests….
- Induction (favors BXR)
- Overdose Protection (likely favors BXR)
- Fentanyl/heroin users (likely favors BXR)
- Who is ideal XR-NTX patient?
  - Prescription painkiller user with low opioid tolerance
- Who is ideal BXR patient?
  - Sublingual buprenorphine treatment failure
  - Fentanyl/heroin users (regardless of treatment history)

Role for Injectable XR Buprenorphine for Fentanyl Era

- Advantages
  - All the pharmacodynamic advantages of SL buprenorphine
  - Assured compliance and clinical effects >5 weeks with monthly formulation
  - Maintains at higher serum level than patients would take sublingually
  - Induction may be easier than sublingual with fentanyl users
  - Diversion/compliance special populations (e.g., criminal justice system)
- Disadvantages
  - Cost
  - Accessibility (insurance prior authorization, shipping)
  - Nodules are noticeable on abdomen

Summary

- Fentanyl use continues to be a major public health problem in the US and evidence-based treatment recommendations are scant
- Clinicians and patients have experienced to some degree a loss of confidence in current treatment approaches
- Ongoing studies will help provide guidance for best practices
- In the meantime, the most prudent approach is to begin with standard evidence-based treatment recommendations and modify according to the clinical needs

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