



Novel Approaches to Address Opiate Addiction in Timmins

Pan Northern Clinical Rounds
Dr. Louisa Marion-Bellemare & Dr. Julie Samson
October 5, 2022.

DISCLOSURE OF FINANCIAL SUPPORT

- This program has received no financial support
- This program has received no in-kind support
- Potential for conflict(s) of interest: none



PRESENTER DISCLOSURE

- Relationship with financial sponsors
 - Speaker Honorarium:
 - Indivior CSAM Conference October 2021
 - Master Clinician Alliance Harley Street Talk: Nov 2021 & Feb 2022

MITIGATING POTENTIAL BIAS

- CONTENT REPORTS ON CLINICAL EXPERIENCE
AND AS SUCH INCLUDES OFF-LABEL USES

LEARNING OBJECTIVES

Identify

- Identify treatment options for patients with opiate addiction.

Discuss

- Discuss novel approaches to treat opiate addiction.

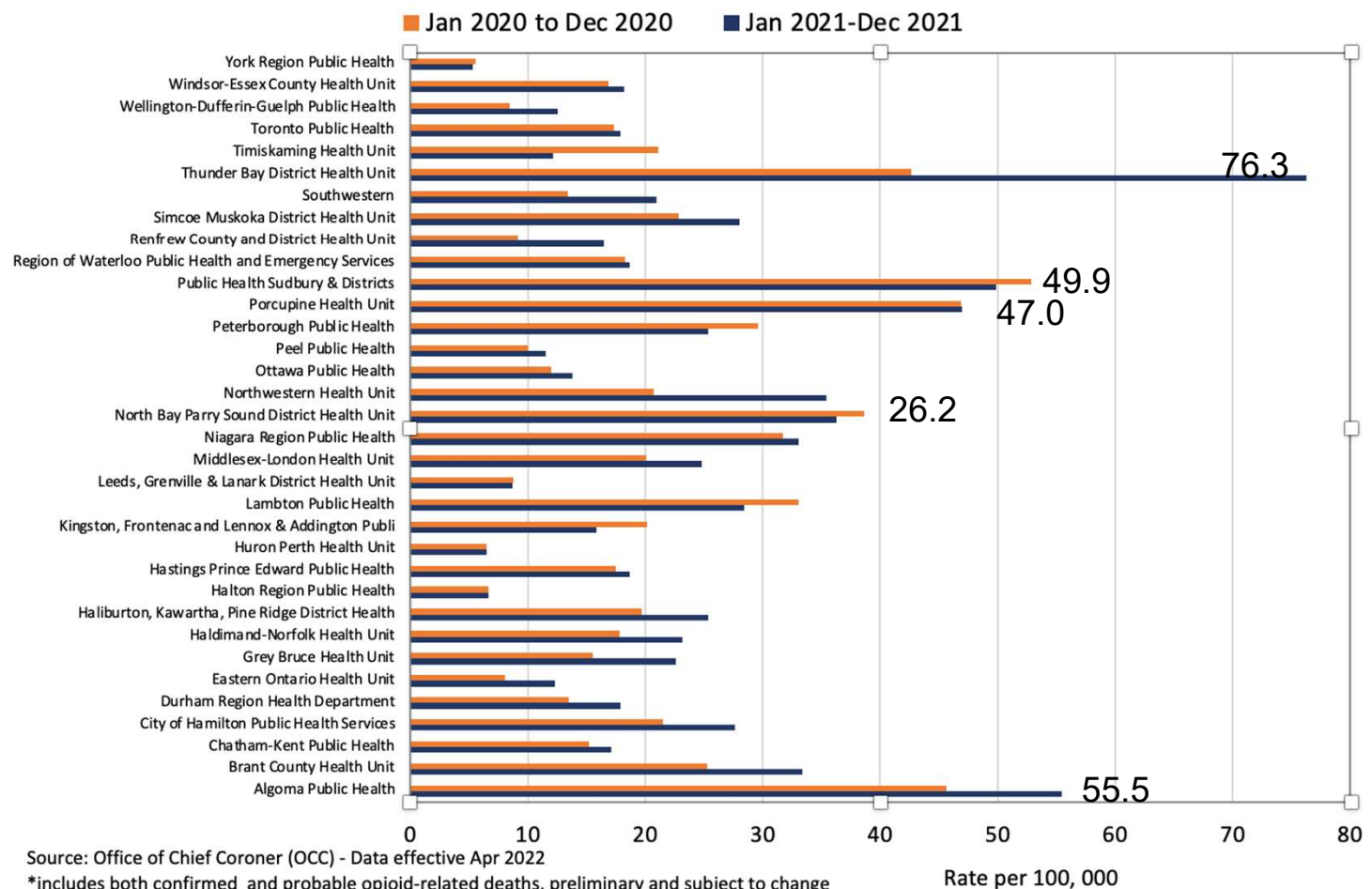
Explain

- Explain effective communication strategies to help those with an opiate addiction.

OUR CRISIS AND TIME FOR CHANGE



Opioid-related deaths per 100, 000 by PHU Region, Jan 2020-Dec 2020 and Jan 2021-Dec 2021



LOCAL CRISIS

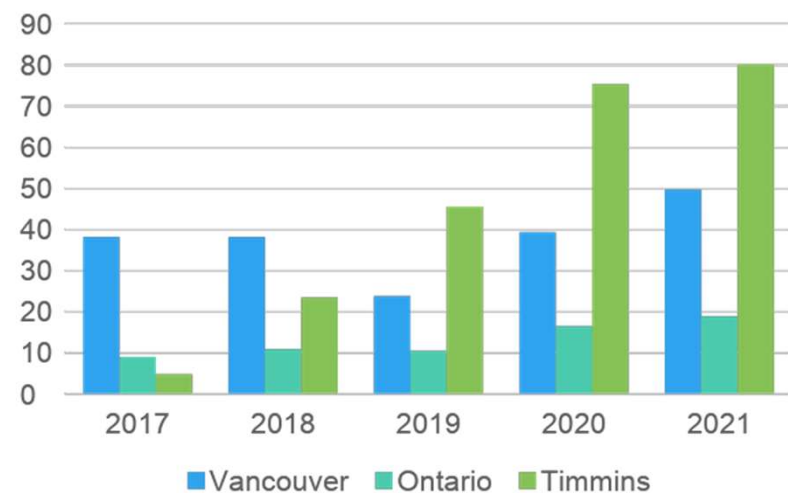
- Data Source:

<https://www.publichealthontario.ca/en/data-and-analysis/substance-use/interactive-opioid-tool>

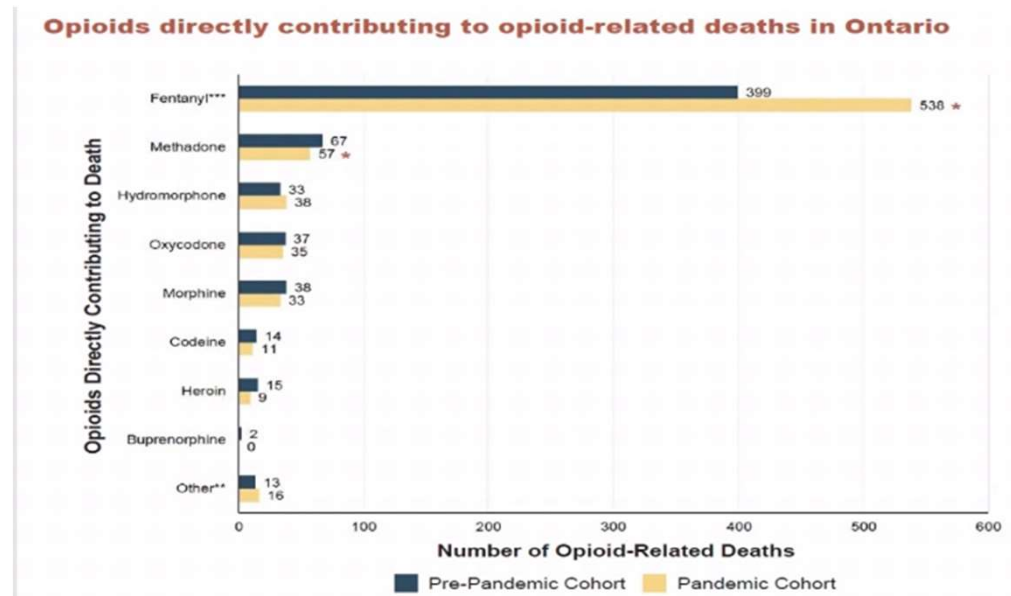
• <https://www2.gov.bc.ca/assets/gov/birth-adoption-death-marriage-and-divorce/deaths/coroners-service/statistical/illicit-drug.pdf>

- *2021rates are preliminary and subject to change

OPIATE RELATED DEATH RATES
PER CITY
2017 to 2021



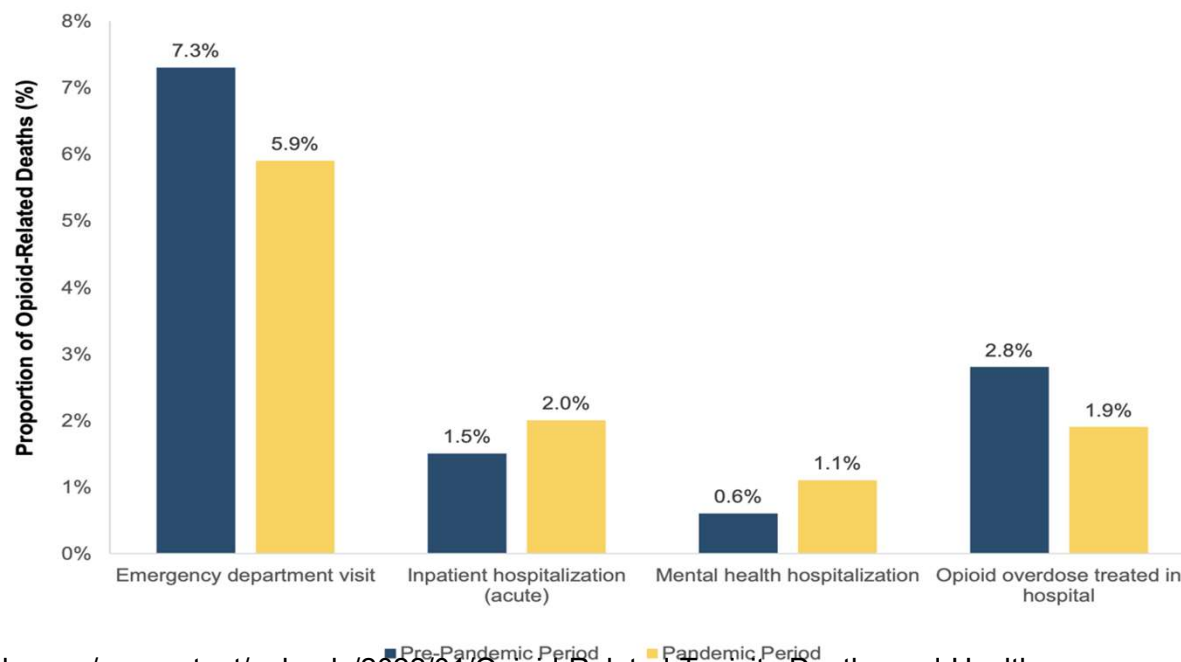
ONTARIO OPIOID RELATED DEATHS 2020



<https://www.publichealthontario.ca/en/data-and-analysis/substance-use/interactive-opioid-tool>

Healthcare Use among People who Died of Opioid-Related Toxicity During Pandemic- 2020

Figure 11: Recent hospital encounters in the seven days prior to opioid-related death in Ontario

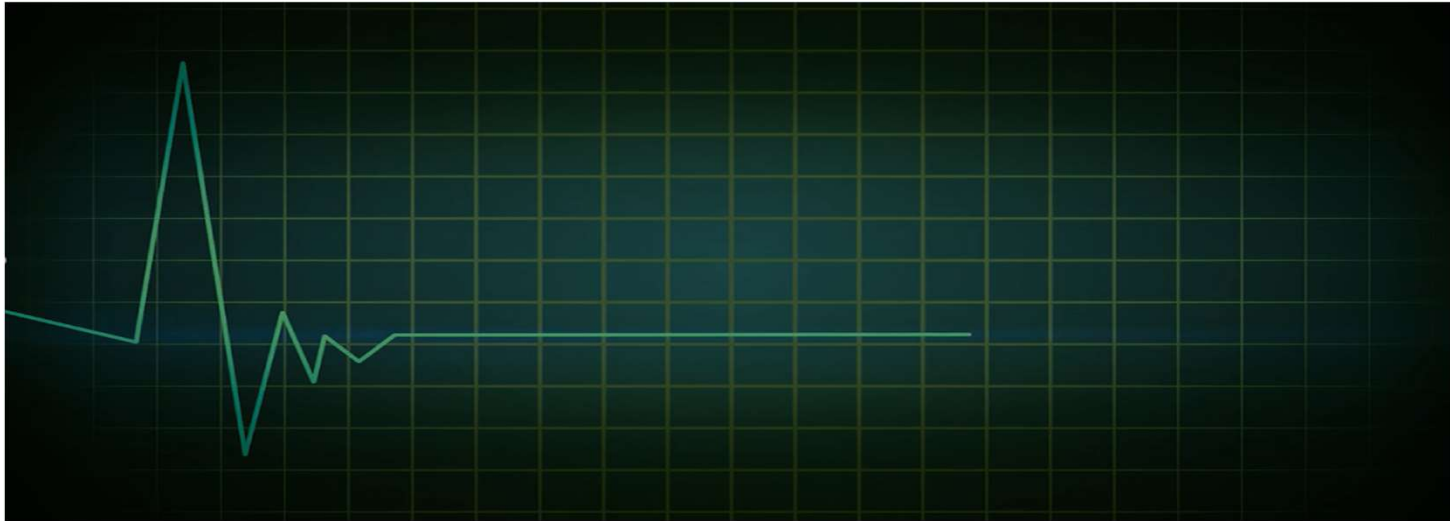


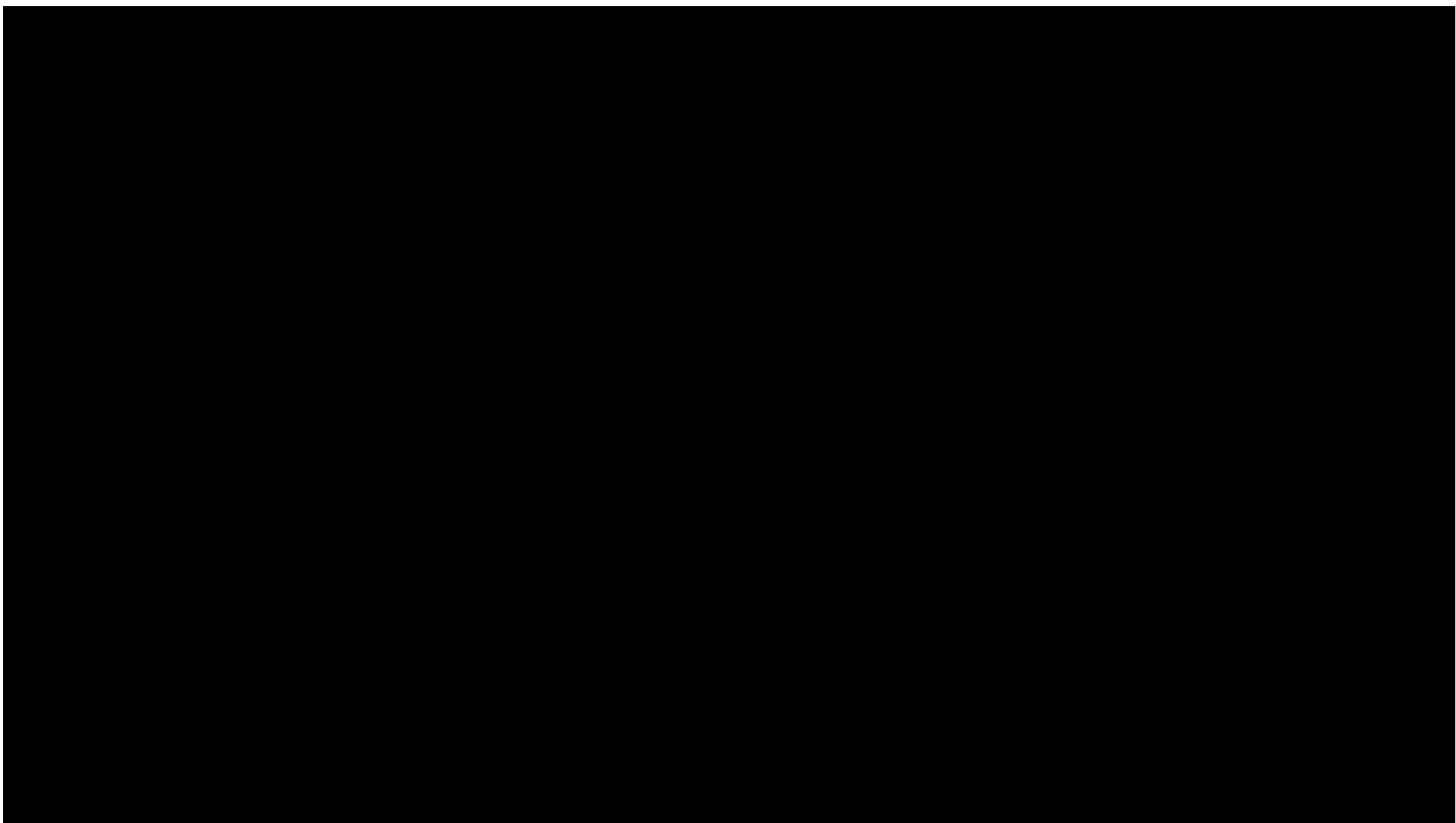
<https://odprn.ca/wp-content/uploads/2022/01/Opioid-Related-Toxicity-Deaths-and-Healthcare-Use-Report.pdf>

TOXIC
TWIN



THE EYE OPENER FOR CHANGE



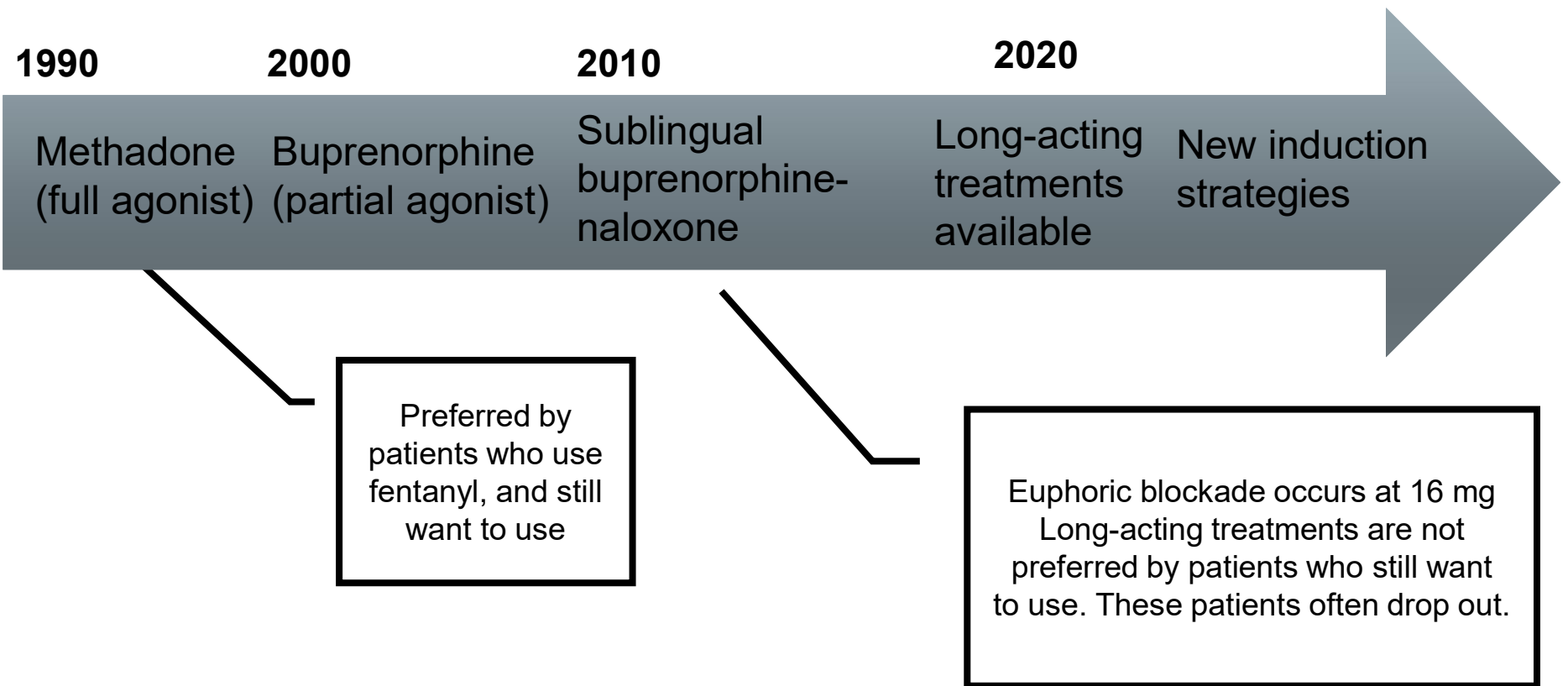


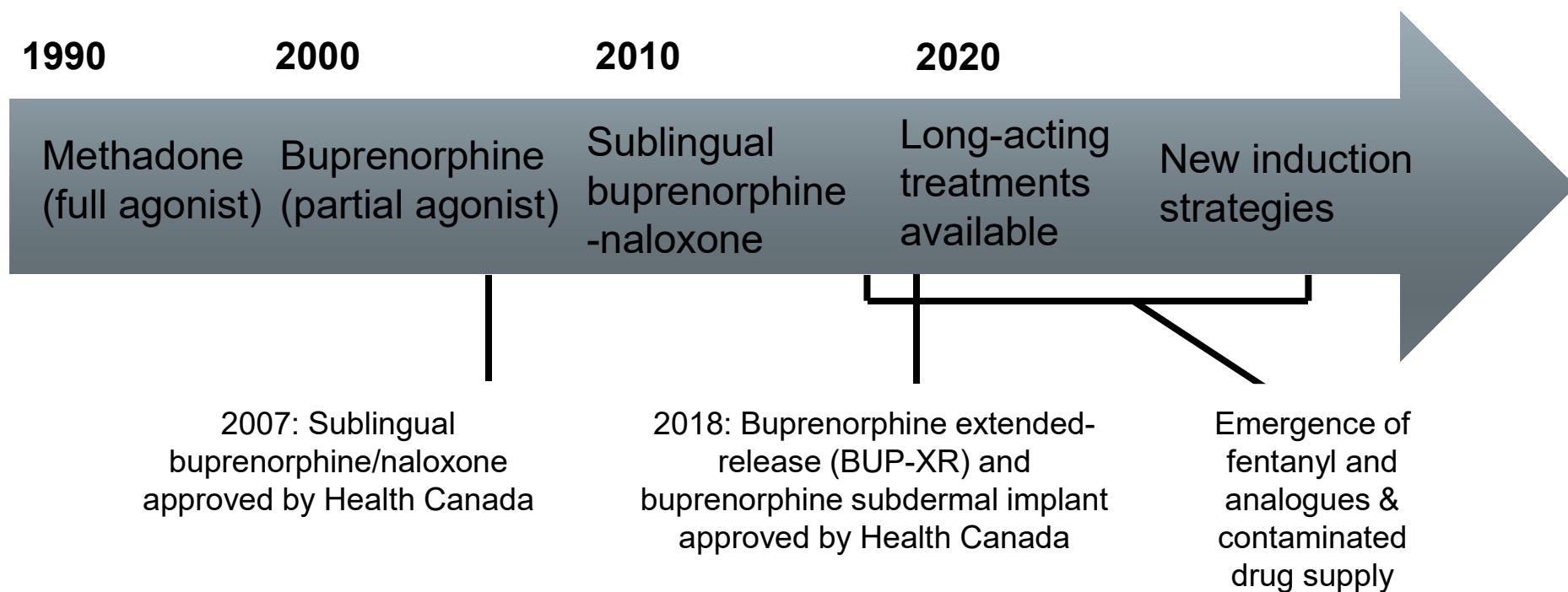
CASE PRESENTATIONS

34 yo female presenting to ER last used IV fentanyl 6 hrs ago asking for help with her opioid use (also uses IV Crystal Meth). Uses 0.5-1 g IV fentanyl daily x 5 yrs

25 yo male presenting to ER fully reversed with naloxone in severe withdrawals unsure if he wants help for his opioid use but wants to feel better immediately. Smokes fentanyl and crack x 2 years approximately 1-1.5 grams per day.

40 yo female in withdrawals and last used fentanyl 22 hours ago asking for help with her opioid use. Uses “a few points per day” of fentanyl, IV and smoked x 5 years. Use speed, cocaine, CM also IV and smoked.

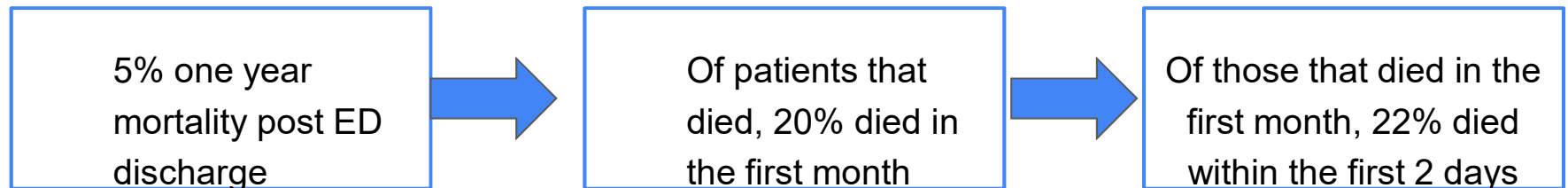




Canadian Agency for Drugs and Technologies in Health (CADTH). Buprenorphine/Naloxone Versus Methadone for the Treatment of Opioid Dependence: A Review of Comparative Clinical Effectiveness, Cost-Effectiveness and Guidelines [Internet]. Ottawa, ON; 2016 .

OVERDOSE & SHORT TERM MORTALITY

ED PATIENTS WITH NON FATAL OPIOID OVERDOSE:



Source: Weiner, Scott et al..One-Year Mortality of Patients After Emergency Department Treatment for Nonfatal Opioid Overdose. Annal of Emergency Medicine. April 2, 2019

PRACTICE GUIDELINES FOR TREATMENT OF OUD

For Mod & Severe Withdrawals Bup/Nal offered **WITHIN 2 HRS**

HQO Opioid Use Disorder Quality Statements 2018

First Line Treatment Option for Withdrawals & OUD: **BUP/NAL**

Management of OUD: A National Clinical Practice Guideline (CMAJ 2018)

If Not in Withdrawals but Requesting Treatment: should be offered within **MAX 3 DAYS (1st line BUP/NAL)**

HQO Opioid Use Disorder Quality Statements /18

If a person enters an inpatient facility, OAT should be continued without disruption

HQO Opioid Use Disorder Quality Statements 2018

WHERE CAN
WITHDRAWALS
BE TREATED
WITHIN 2
HOURS?

THE
HOSPITAL



PRACTICE GUIDELINES FOR TREATMENT OF OUD

While on Treatment: Minimum **6 months** of concurrent psychosocial treatment, support & monitor

Management of OUD: A National Clinical Practice Guideline (CMAJ 2018)

Withdrawal Management alone (“**Cold Turkey**”) will be avoided because it is associated with increased rates of **relapse** (60-90%), morbidity & death

Management of OUD: A National Clinical Practice Guideline (CMAJ 2018)

Discussion about Harm Reduction Strategies offered (Naloxone, clean drug paraphernalia, SCS, never use alone, smoking better than IV etc.)

Management of OUD: A National Clinical Practice Guideline (CMAJ 2018)

TREATING ADDICTIONS IN THE ER IS A STANDARD OF CARE

Expands opportunity
for initiating treatment
of OUD



Bup/Nal blocks
craving & withdrawals
symptoms




Bup/Nal prevents
relapse & reduces OD
& mortality



CAEP Position Statement: Emergency department management of people with opioid use disorder

October 2020

Justin J. Koh , MD, MPH^{*}; Michelle Klaiman, MD^{†‡}; Isabelle Miles, MD^{§||}; Jolene Cook, MD^{**}; Thara Kumar, MD^{††}; Hasan Sheikh, MD, MPA^{††§§}; Kathryn Dong, MD, MSc^{||||***}; Aaron M. Orkin, MD, MSc, MPH^{§§†††}; Samina Ali , MDCM^{||||††§§§}; Elizabeth Shouldice, MD, MPH^{|||||}

Managing Opioid Withdrawal in the Emergency Department With Buprenorphine



Andrew A. Herring, MD; Jeanmarie Perrone, MD; Lewis S. Nelson, MD*

**Corresponding Author. E-mail: lewis.nelson@rutgers.edu, Twitter: @LNelsonMD.*

0196-0644/\$-see front matter

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<https://doi.org/10.1016/j.annemergmed.2018.11.032>

Untreated opioid withdrawal commonly results in return to high-consequence opioid use, with high risk of OD death after discharge from the ED

“TREAT THEM AND STREET THEM” APPROACH IS NOT EFFECTIVE IN THE ER

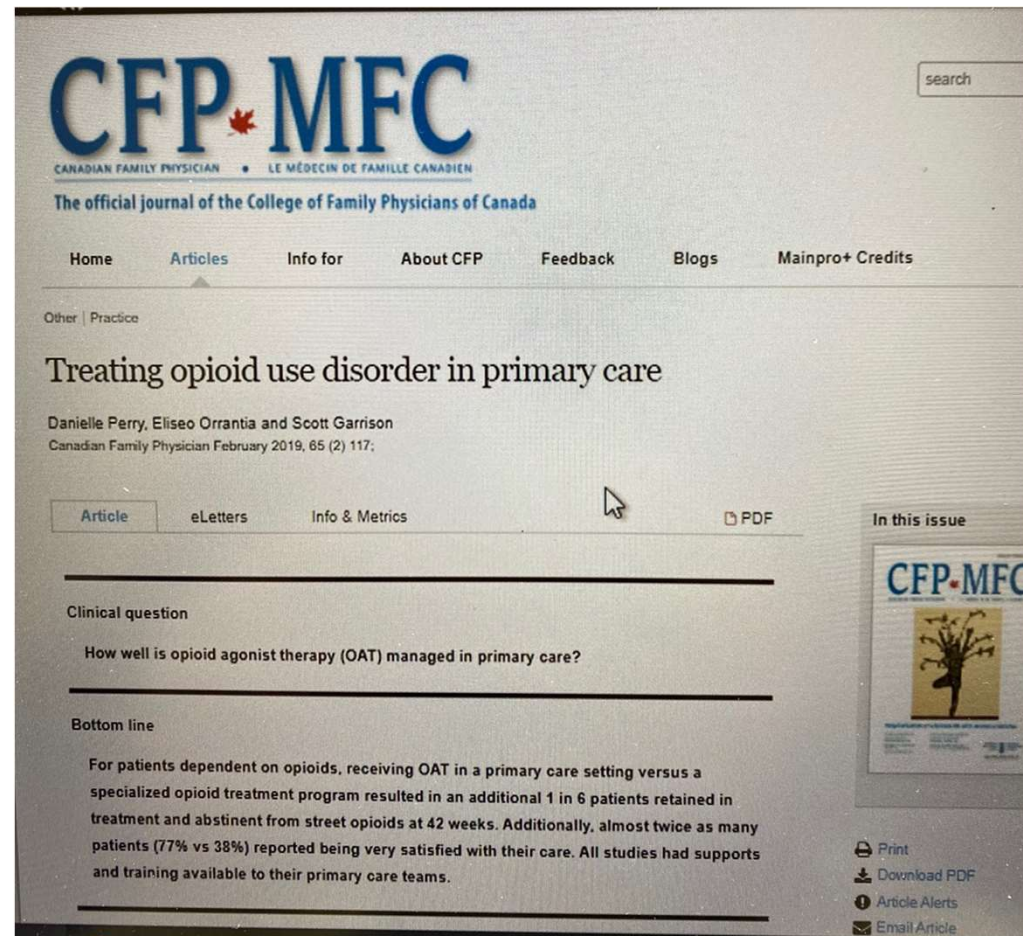
- < 20% of patients in need of OAT with OUD presenting to ER were started on OAT despite its strong evidence
- When Bup/nal is administered in ER & continued via primary care 74% remain in treatment after 2 months
- No other setting replicates the all-hours access & wrap around services in EDs (access point for the most vulnerable) & availability of same day treatment of OUD

<https://cabridge.org/wp-content/uploads/CA-Bridge-Impact-Report-2018-2021.pdf>
<https://www.healthaffairs.org/doi/10.1377/forefront.20211208.799414/full/>

ED improves access to OAT for many patients who would otherwise not seek help (levels the playing field)

Increase in ED visits coupled with the growing evidence for the effectiveness of bup/nal means addictions treatment cannot be a niche industry operating on the fringes of the fractured health care system

PRACTICE GUIDELINES FOR TREATMENT OF OUD



WHY BUPRENORPHINE/NALOXONE?

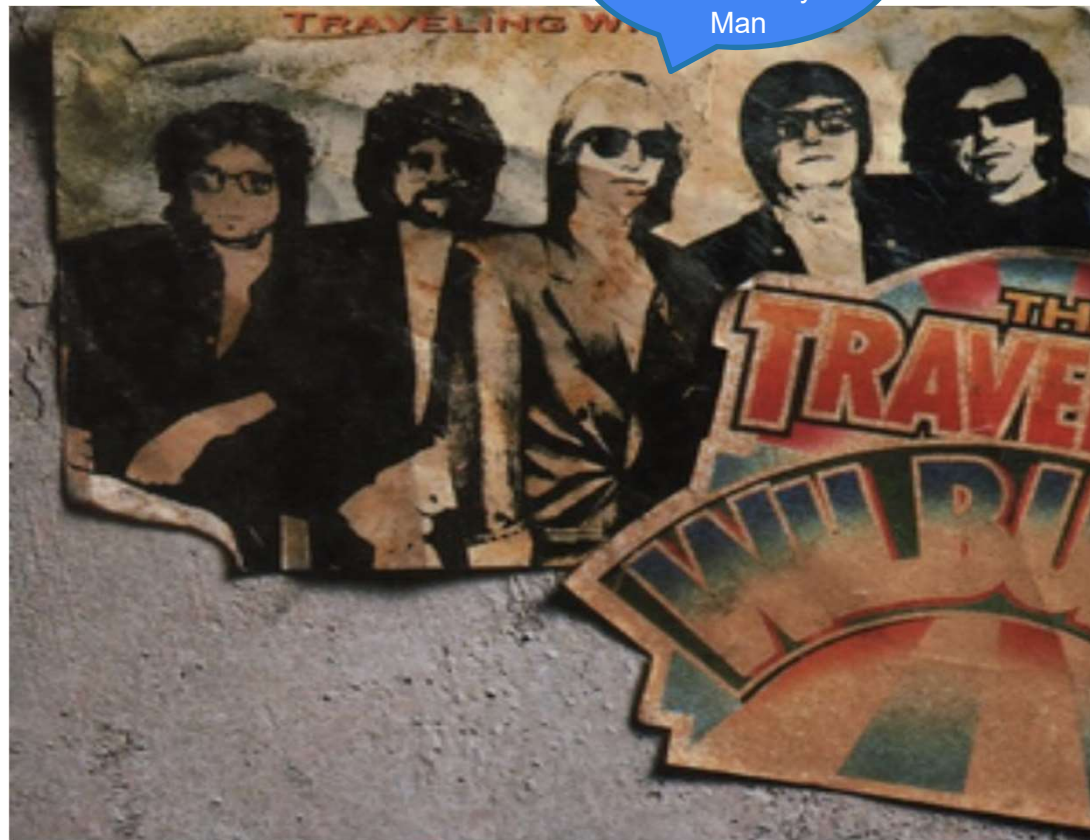
Thrombolytics for
STEMI
NNT 43

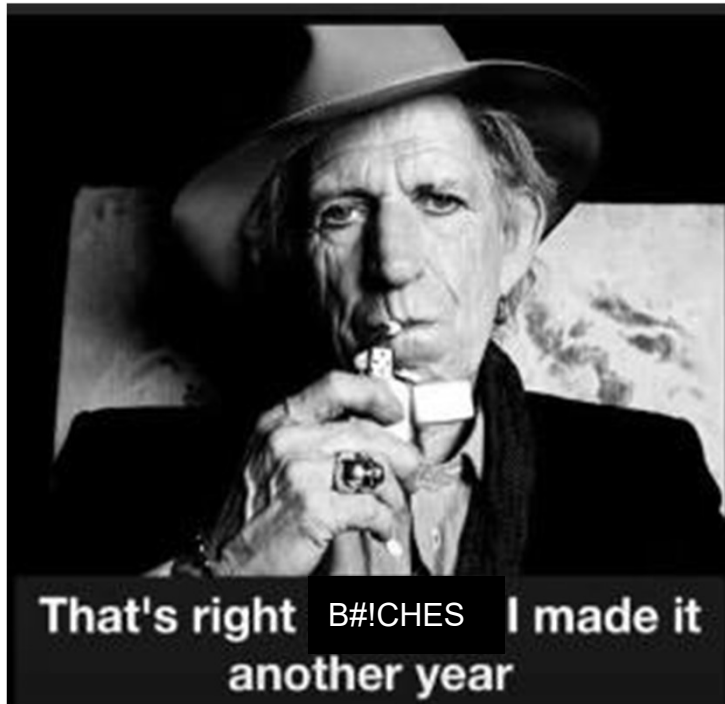
ASA for Acute
Ischemic Stroke
NNT 79

ASA for STEMI
NNT 42

BUP/NAL (>16 mg)
NNT 2

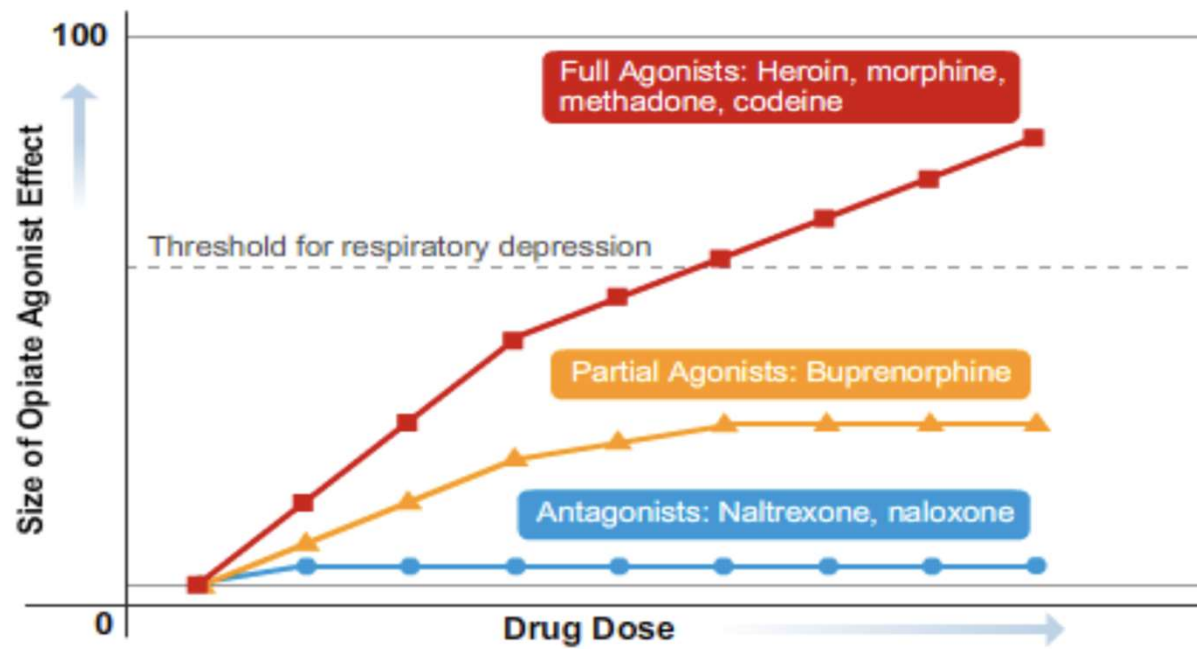
Gone are the
days of
Tweeter and
the Monkey
Man





That's right B#ICHES I made it
another year

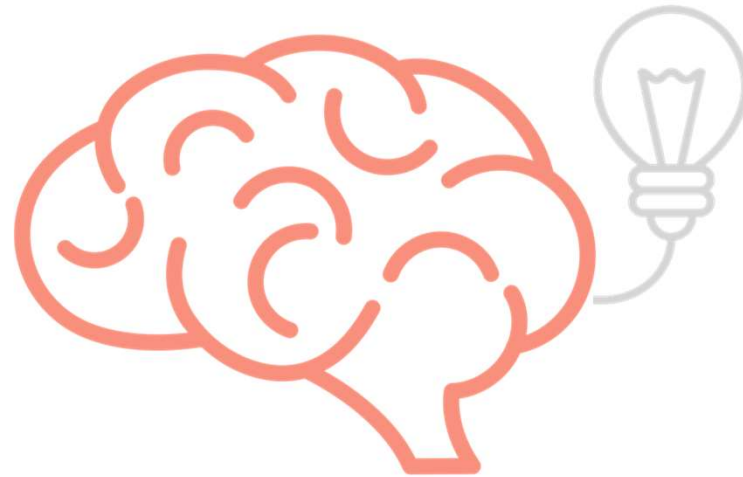
HOW SAFE IS BUPRENORPHINE?



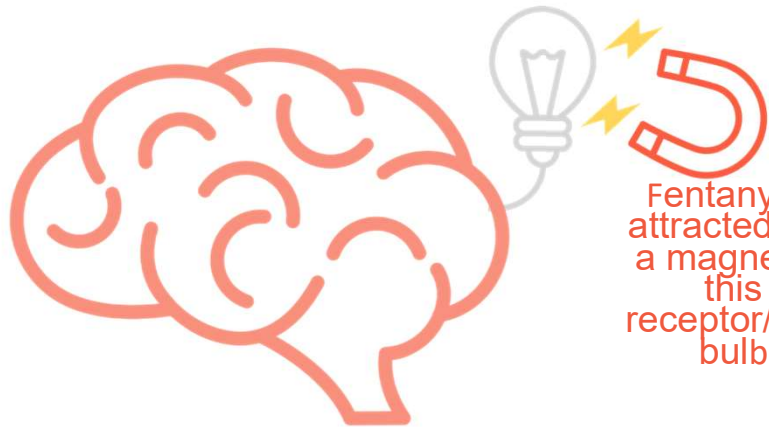
DURATION OF ACTION OF BUPRENORPHINE/NALOXONE

- DURATION OF ACTION IS DOSE DEPENDENT

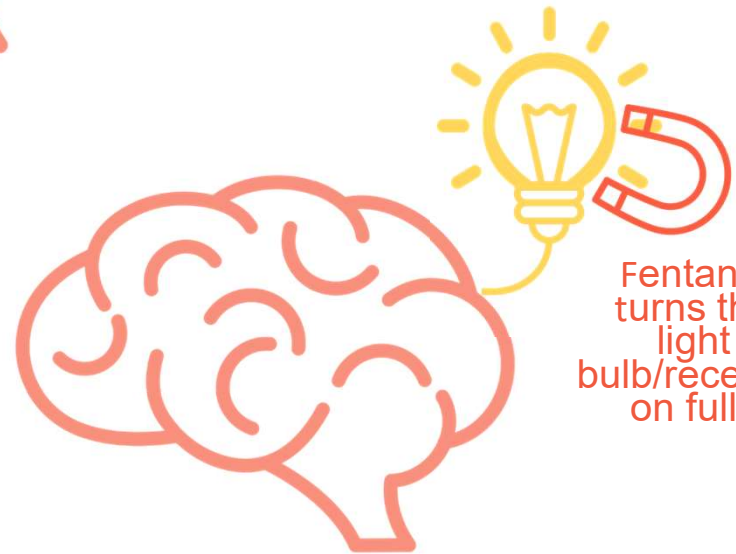
Dose	Duration of action
4-6 mg SL	4-12 hours
8- 12mg SL	24 hours
> 16 mg SL	24-48 hours
Sublocade 300mg/100 mg (injection every 28 days)	2-6 weeks up to months after steady state



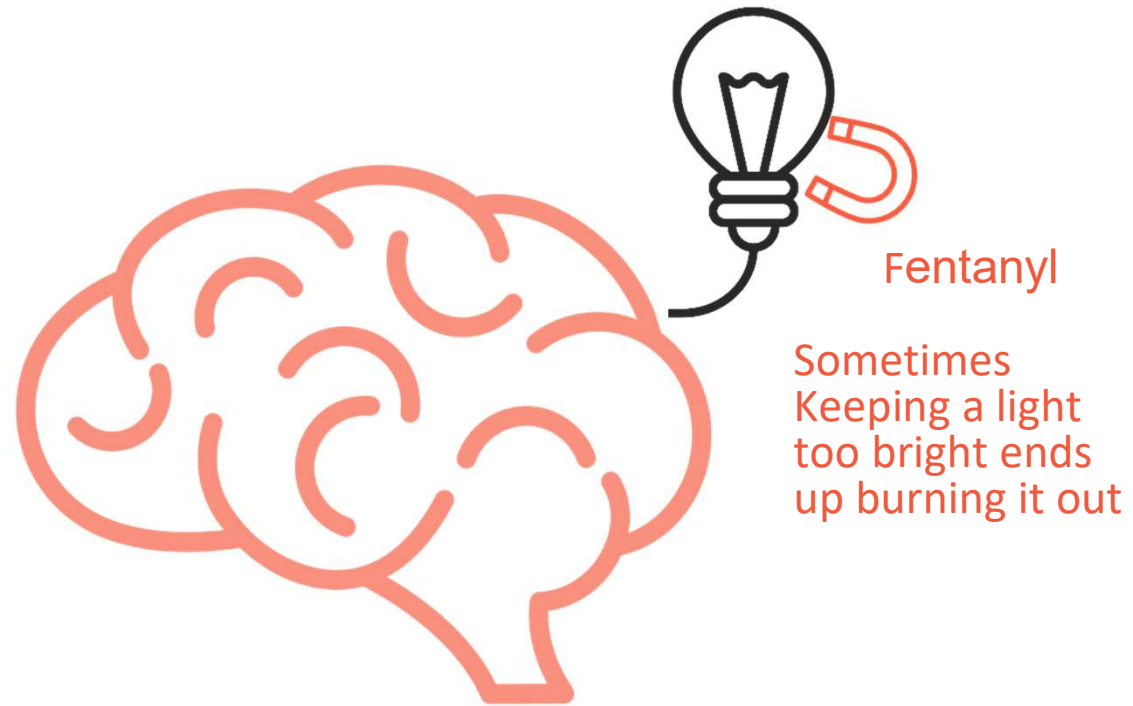
The light bulb is
like an opioid
receptor in your
brain

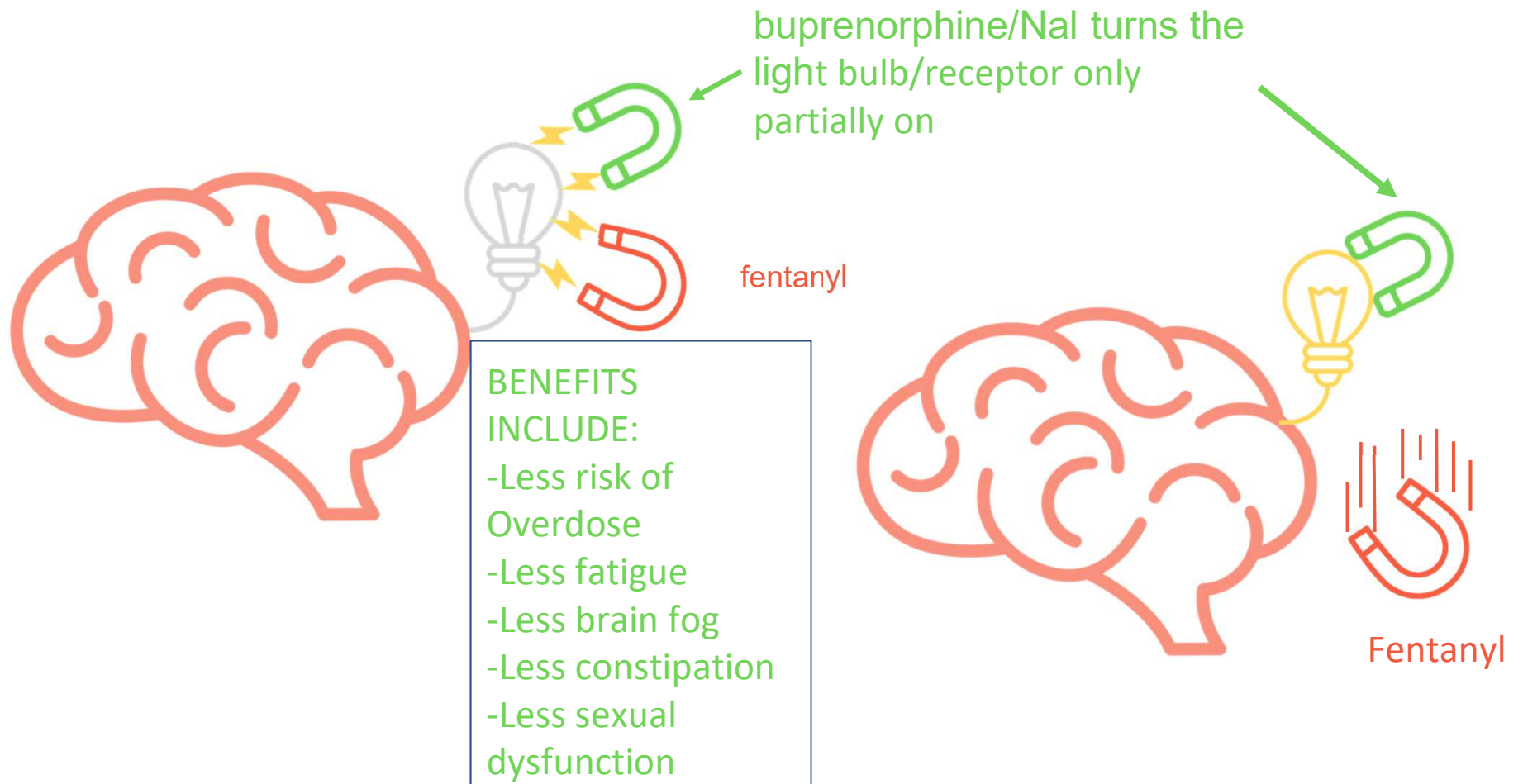


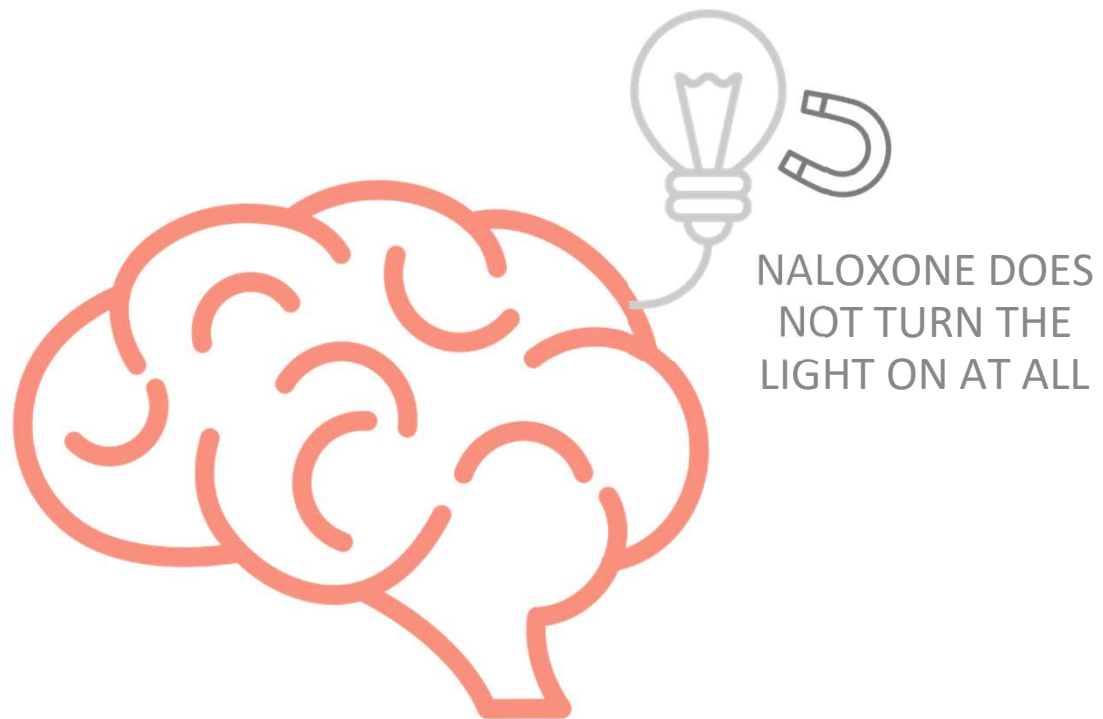
Fentanyl is
attracted like
a magnet to
this
receptor/light
bulb



Fentanyl
turns the
light
bulb/receptor
on fully



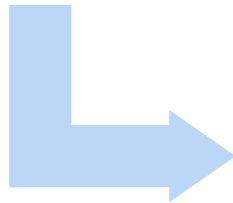




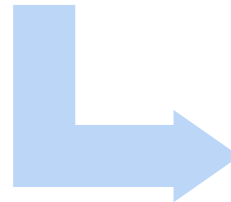
NALOXONE DOES
NOT TURN THE
LIGHT ON AT ALL

WHAT IS BUP/NAL INDUCED PRECIPITATED WITHDRAWAL?

Sudden onset of severe withdrawal symptoms if BUP/NAL is administered too soon after a sufficient dose of full opioid agonist (ie. fentanyl) has been taken

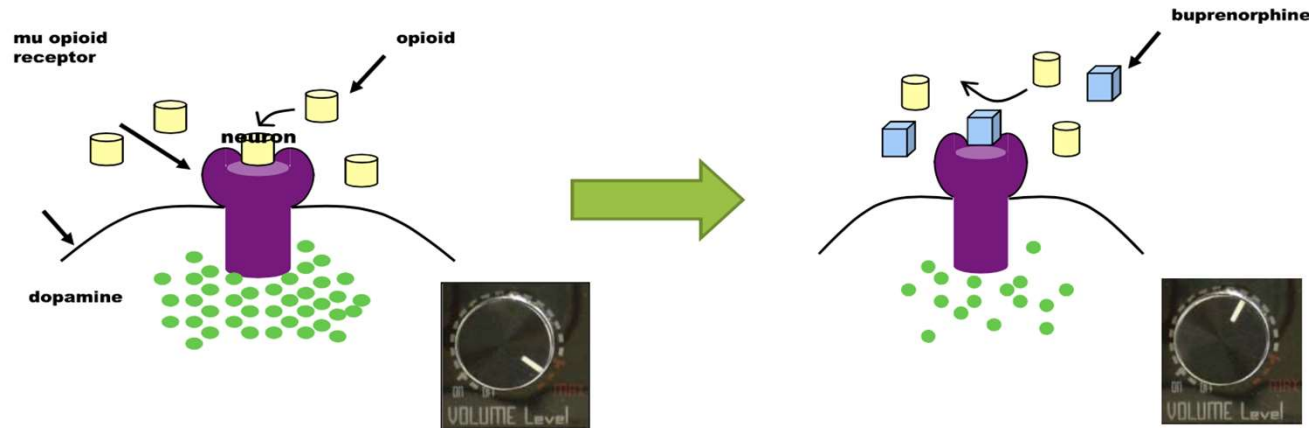


The full agonist (ie. fentanyl) is rapidly displaced from mu receptor



BUP/NAL (partial agonist) causes rapid loss of agonist effects of displaced opioids →
WITHDRAWALS

PRECIPITATED WITHDRAWAL FROM BUP/NAL



Intoxication

Significant amount of opioid bound to receptors

"Volume" on max

Buprenorphine

Binds preferentially to receptors

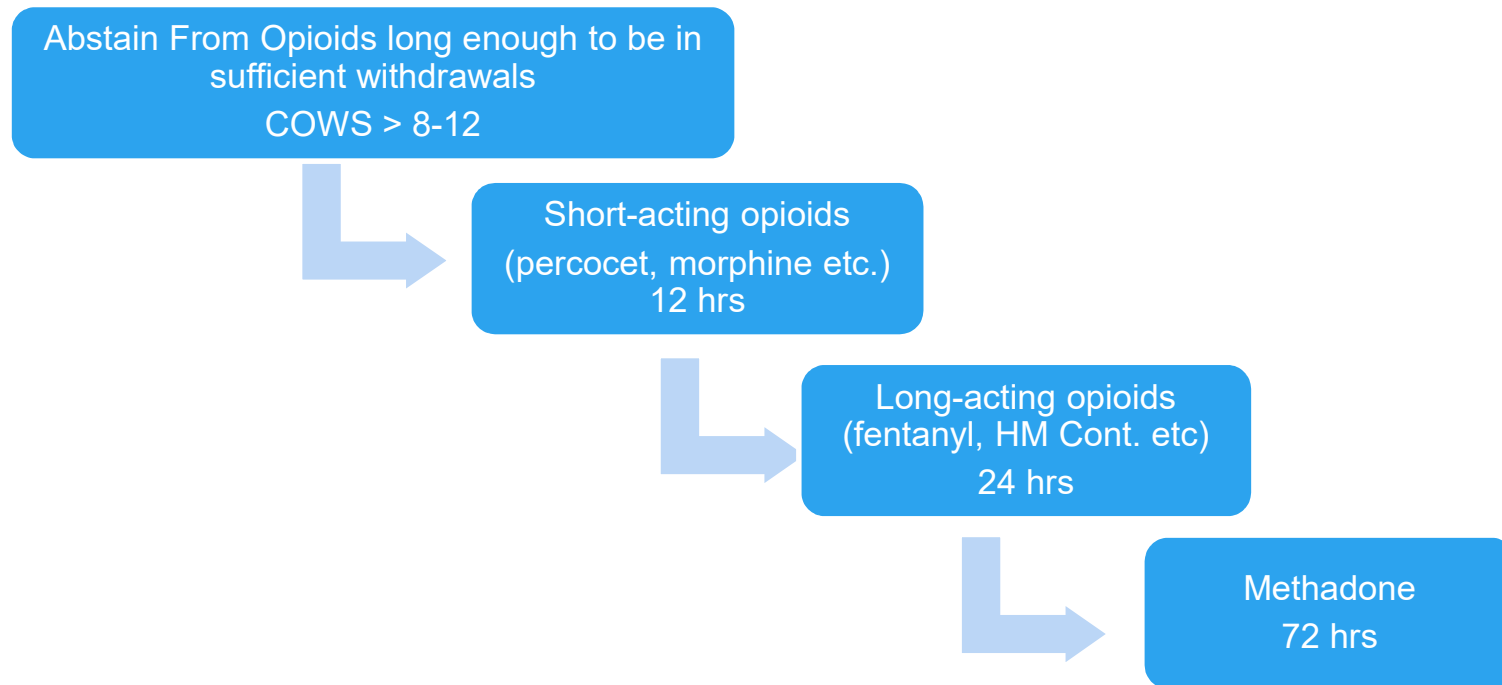
"Volume" on medium

Precipitated Withdrawal:

Relative to intoxication, Buprenorphine "turns on" receptors less so patients feel withdrawal

Graphics adapted from NAABT, Inc. (naabt.org)

PREVENTING PRECIPITATED WITHDRAWAL



TREATMENT OF PRECIPITATED WITHDRAWAL

- FIRST LINE
 - Continue with BUP/NAL induction (may need doses > 32 mg until stabilized)
 - For short-term symptomatic relief consider clonidine, Seroquel, Imodium, Zofran, NSAIDS
 - Also consider for severe agitation Ketamine, Haldol or Olanzapine (or statex)

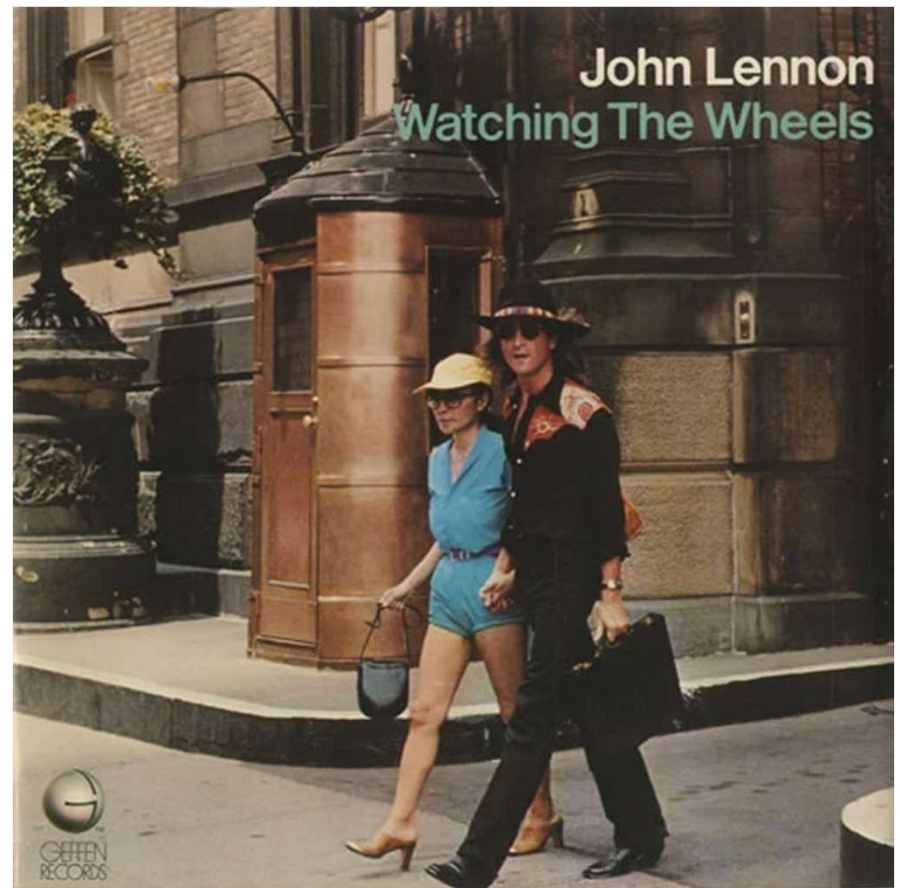
CABridge.org

COCAINE & BUPRENORPHINE IN PREGNANCY

SAFE IN PREGNANCY



People askin' questions
Lost in confusion
Well, I tell them there's no problem
Only solutions



BREAKING DOWN BARRIERS: OUR INNOVATIVE APPROACH TO SYSTEM CHANGE



- BREAKING DOWN SILOS AMONGST COMMUNITY ORGANIZATIONS & IMPROVING PARTNERSHIPS
- OFFERING IMMEDIATE CARE AT HOSPITAL FOR THOSE REQUESTING TREATMENT FOR OUD
- SEAMLESS ACCESS TO THE FULL CONTINUUM OF ADDICTIONS TREATMENT
- DEVELOPING A PROGRAM TO MEET THE NEEDS OF OUR PATIENTS

Known as the whistleblowers

INNOVATION AND IMAGINATION AT THE HOSPITAL

HOSPITAL IS A KEY PLAYER IN SYSTEM CHANGE

- FIRST CHANGING HOSPITAL CULTURE, REDUCING STIGMA, AND IMPROVING COMFORT LEVELS (including ED)
- PROVIDING IMMEDIATE TREATMENT FOR THOSE PRESENTING TO ER REQUESTING HELP
- OPENING OF MEDICAL WITHDRAWAL MANAGEMENT BEDS
- EDUCATION TO COLLEAGUES & STAFF
- IMPLEMENTING AMCS & CWMS TEAMS
- PROVIDING WRAPAROUND CARE



TIMMINS AND DISTRICT HOSPITAL
L'HÔPITAL DE TIMMINS ET DU DISTRICT



OUR TEAM

- COMMUNITY WITHDRAWAL MANAGEMENT SERVICE
- ACUTE MEDICINE CONSULT SERVICE
- TIMMINS POLICE SERVICE COMMUNITY OUTREACH SAFETY PROGRAM
- AND WE WORK VERY CLOSELY WITH MOBILE CRISIS

WITHDRAWAL MANAGEMENT BEDS

TIMMINS AND DISTRICT HOSPITAL

- WiMU (Acute Withdrawal Management Unit) 7 BED UNIT LOCATED IN OUR HOSPITAL
 - Initially started as 2 beds(Dec 2020) in the ICU
 - STAFFED BY RNS
 - AMCT RN AND HOSPITAL SW
- PHYSICIAN ON CALL 7 DAYS A WEEK

OUTPATIENT COMMUNITY WITHDRAWAL MANAGEMENT SERVICES

- RN
- NP
- SW

INITIAL INPATIENT BUP/NALX INDUCTION PROTOCOLS

- THE “EARLY” DAYS OF BUPRENORPHINE DOSING:
 - SLOW TITRATION OF SUBLINGUAL BUPRENORPHINE-NALOXONE
 - LONG-ACTING BUPRENORPHINE GIVEN ON DAY 7 (AFTER HOSPITAL DISCHARGE)

Max Daily Dosing:

Day 1:

- Dose #1: 4 mg
- Dose #2: 2-4 mg
- Subsequent dosing : 2 mg q1h prn

Max:

- Day 1: 12 mg
- Day 2: 16 mg
- Day 3: 20 mg
- Day 4: 24 mg

PROBLEMS:

- 7 days of inpatient stabilization on BUP/NAL > 8mg as per product monograph was too long
 - Patients would just leave
- Discharged patients wouldn't return for long-acting buprenorphine at 7 days
- Risk of OD and death was greater than risk of early injection
- **We had to change this protocol almost immediately**

WE USE TA GIVE A LITTLE BUT A LITTLE WOULDN'T
DO IT SO THE LITTLE GOT MORE AND MORE.....



GAME CHANGER: MACRODOSING, HERE WE COME!

- MAXIMUM DAILY DOSING: 32 MG BUP/NAL
- RAPID TITRATION WITH MACRODOSING BUP/NAL

Sometimes higher during stabilization

Day 1: COWS>12 + no fentanyl use >24 hrs
Dosing: **24mg then 8 mg q1h prn X1**
Total dose over 1-2 hours= 32mg

** PEOPLE WHO USE FENTANYL **

Within 1-3 hours most patients are comfortable and feeling
no withdrawal symptoms

1. JACOBS P ET AL. *AM J ADDICT* 2015;24:667-75.

2. CARROLL GG ET AL. *PREHOSP EMERG CARE* 2021;25:289-93.


3. HERRING AA ET AL. *JAMA NETW OPEN*. 2021;4:E2117128.


4. <https://cabridge.ca>

5. Mariani JJ et al. *Am J addict*. 2021;1-7

6. Korownyk et al, *Canadian Family Physician*;2018:321-33

UPDATED ORDER SETS

 Timmins and District Hospital L'Hôpital de Timmins et du district		Demographic Label
OPIOID WITHDRAWAL ADMISSION ORDER SET		
<input type="checkbox"/> No Known Drug Allergies <input type="checkbox"/> Allergies: _____ For orders with <input type="checkbox"/> indicate with <input checked="" type="checkbox"/> Changes to be initiated by MD		
Admitting Diagnosis _____ <input checked="" type="checkbox"/> Admit to bed Code Status: <input type="checkbox"/> Full Resuscitation <input type="checkbox"/> CNR <input checked="" type="checkbox"/> MRP <input checked="" type="checkbox"/> See RPMH		
Consult: <input checked="" type="checkbox"/> Social worker <input type="checkbox"/> Dietician <input checked="" type="checkbox"/> AMCT clinician (ALL to be entered via Meditech)		
Opioid Withdrawal Protocol MD to assess indication for buprenorphine/naloxone (Suboxone®); must meet both criteria: <input checked="" type="checkbox"/> Clinical Opiate Withdrawal Scale (COWS) greater than 12 AND (at least one of the following) <input type="checkbox"/> Greater than 12 hours since oral/crushed/smoked/injected immediate release opioids > Heroin/HYDROMorphone/Morphine/Doy/CODONE/Codine OR <input type="checkbox"/> Greater than 12 hours since crushed/smoked/smoked/injected controlled release/long-acting opioids > HYDROMorphone Contin (CR)/Morphine Extended Release (ER) <input type="checkbox"/> Greater than 24 hours since smoked/IV Fentanyl or oral controlled release/long-acting opioids > HYDROMorphone Contin (CR)/Morphine Extended Release (ER) <input type="checkbox"/> OR <input type="checkbox"/> At least 72 hours since last methadone use MD to complete: _____ Time of last opioid intake: _____ (24h) Route: _____ Types of opioid used: _____		
<input checked="" type="checkbox"/> Assess for contraindications to receive Buprenorphine/Naloxone (Suboxone®): • Hypersensitivity/allergies, unable to provide informed consent, altered level of consciousness, currently taking methadone, severe or acute liver disease, alcohol or benzodiazepine intoxication/dependence, shock states/hypotension, severe head injury, acute intra-abdominal conditions		
Assessments and Monitoring <input checked="" type="checkbox"/> Vital signs including SpO ₂ : At baseline, with every COWS assessment during induction of Buprenorphine/Naloxone (Suboxone®) then daily and PRN, or as per MD. <input checked="" type="checkbox"/> Notify MD if COWS increases (to assess for precipitated withdrawal) <input checked="" type="checkbox"/> Discontinue COWS after second dose and use SOWS q1-2h pm while awake for subsequent dosing <input checked="" type="checkbox"/> Notify MD to reassess patient when total daily dose of Buprenorphine/Naloxone (Suboxone®) 32mg/8mg is given <input checked="" type="checkbox"/> HOLD all medication and notify MD if drowsy or vital unstable: Unstable vitals: BP less than 90/60 HR greater than 100 or less than 60 RR less than 12 SpO ₂ less than 92%		
Physician Signature: _____ Physician Name: _____ (Print) Date: _____ Time: _____		

 Timmins and District Hospital L'Hôpital de Timmins et du district		Demographic Label
OPIOID WITHDRAWAL ADMISSION ORDER SET		
Nutrition <input type="checkbox"/> Regular diet <input checked="" type="checkbox"/> Double portions: _____ <input type="checkbox"/> Diabetic <input type="checkbox"/> Food sensitivities: _____ <input type="checkbox"/> Local/day		
Activity <input checked="" type="checkbox"/> Activity as tolerated <input type="checkbox"/> Other: _____		
Peer Support <input checked="" type="checkbox"/> Refer to Peer Support Worker (when appropriate). Available between 1400-2200 at (705) 365-6613		
Lab Investigation <input type="checkbox"/> CBC, Cr, Glucose, Lysis, LFTs <input type="checkbox"/> HEP B, C and HIV <input type="checkbox"/> HEP C RNA Viral Load <input type="checkbox"/> Overdose Pack <input type="checkbox"/> Broad Spectrum Urine drug screen <input checked="" type="checkbox"/> Beta-human Chorionic Gonadotropin (urine [HCG]) for all admitted female patients		
Pharmacological Management DAY ONE: INITIAL DOSE: IF COWS > 12: ***IF PATIENT'S DRUG OF CHOICE IS FENTANYL*** <input type="checkbox"/> Buprenorphine/Naloxone (Suboxone®) 24mg/6mg sublingual and reassess in ONE hour <input type="checkbox"/> Done in ER ***ALL OTHER OPiates*** <input type="checkbox"/> Buprenorphine/Naloxone (Suboxone®) sublingual <input type="checkbox"/> 3mg/2mg OR <input type="checkbox"/> 16mg/4mg and reassess in ONE hour. <input type="checkbox"/> Done in ER ***IF ELDERLY (OVER 65YO) OR RISK OF RESPIRATORY DEPRESSION*** <input type="checkbox"/> Buprenorphine/Naloxone (Suboxone®) 2mg/0.5mg sublingual and reassess in ONE hour. <input type="checkbox"/> Done in ER *Notify MD/MP if 1 hour after initial dose of Buprenorphine/Naloxone (Suboxone®) the COWS score has worsened as this may indicate precipitated withdrawal*		
Physician Signature: _____ Physician Name: _____ (Print) Date: _____ Time: _____		

CLINICAL OBSERVATIONS SUPPORT MACRODOSING

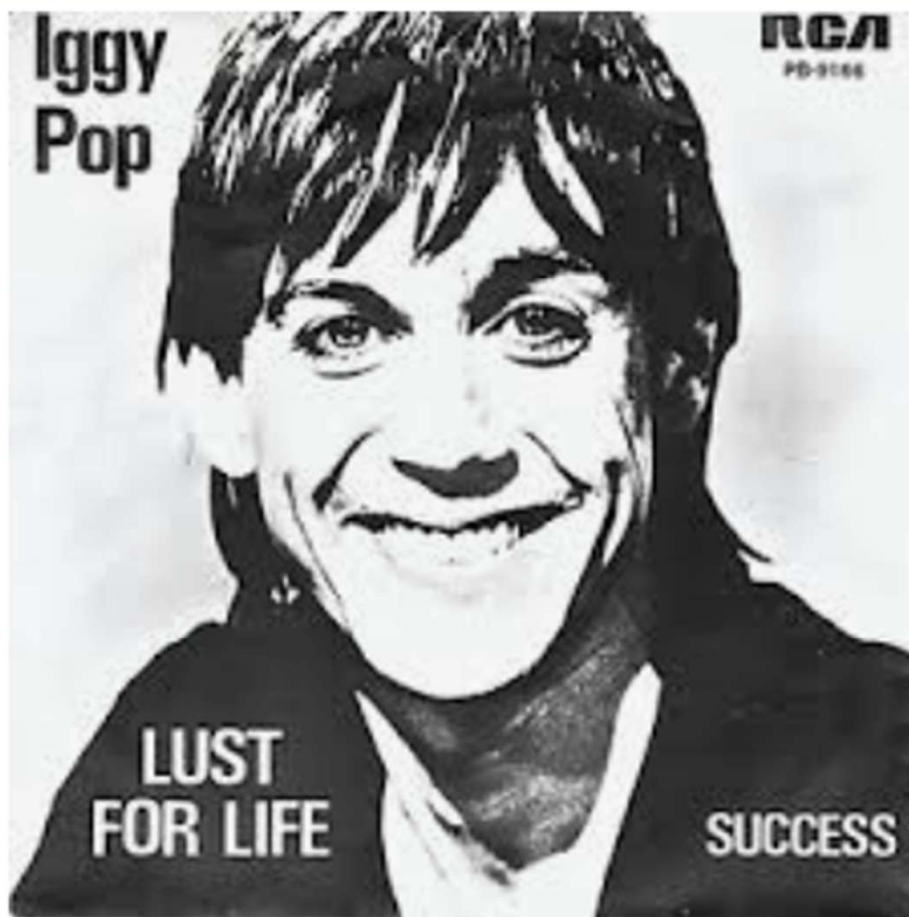
- WE OBSERVED NO AES AFTER TREATING OVER 180 PEOPLE USING THIS PROTOCOL
- **WE HAVE NEVER GIVEN TOO MUCH SUBLINGUAL BUPRENORPHINE-NALOXONE, BUT WE HAVE GIVEN TOO LITTLE**
THIS MAY RESULT IN THE PATIENT LEAVING

Urgency of this crisis supports practiced-based evidence
AND REMEMBER:
Medicine makes evidence

Macro dosing can potentially circumvent
precipitated withdrawal

**Iggy
Pop**

RCA
PD-9166



**LUST
FOR LIFE**

SUCCESS

EVIDENCE FOR MACRODOSING

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

JAMA Network Open. 2021;4(7):e2117128.

High Dose BUP/NAL (28-32 mg) is safe, well tolerated and may impart substantial OD protection & is effective in blunting the euphoric & reinforcing effects of any opioids used in the high-risk window following ED discharge

Therapeutic dose of BUP/NAL was achieved in < 3 hrs of ED stay & low acuity treatment areas

EVIDENCE FOR MACRODOSING

Single high-dose buprenorphine for opioid craving during withdrawal

Jamshid Ahmadi^{1*}, Mina Sefidfard Jahromi¹, Dara Ghahremani² and Edythe D. London^{2,3,4}

Ahmadi et al. *Trials* (2018) 19:675

Single Doses of BUP/NAL up to 96 mg were safe and did not cause respiratory depression & adequately treat cravings and withdrawals

EVIDENCE FOR MACRODOSING

Am J Addict. 2015 October ; 24(7): 667–675. doi:10.1111/ajad.12288.

Treatment Outcomes in Opioid Dependent Patients With Different Buprenorphine/Naloxone Induction Dosing Patterns and Trajectories

Petra Jacobs, MD¹, Alfonso Ang, PhD², Maureen P. Hillhouse, PhD², Andrew J. Saxon, MD³, Suzanne Nielsen, PhD⁴, Paul G. Wakim, PhD⁵, Barbara E. Mai, PhD⁶, Larissa J. Mooney, MD², Jennifer S. Potter, PhD⁷, and Jack D. Blaine, MD¹

Higher doses (16&32 mg) with
quicker titration
-less drop out rates at 7 days
-No major AEs

Rapid Heroin Detoxification Using a Single High Dose of Buprenorphine

Ilan Kutz & Victor Reznik

To cite this article: Ilan Kutz & Victor Reznik (2001) Rapid Heroin Detoxification Using a Single High Dose of Buprenorphine, *Journal of Psychoactive Drugs*, 33:2, 191-193, DOI: [10.1080/02791072.2001.10400484](https://doi.org/10.1080/02791072.2001.10400484)

32 mg induction dose
All Abstinent at 7days
No major AEs

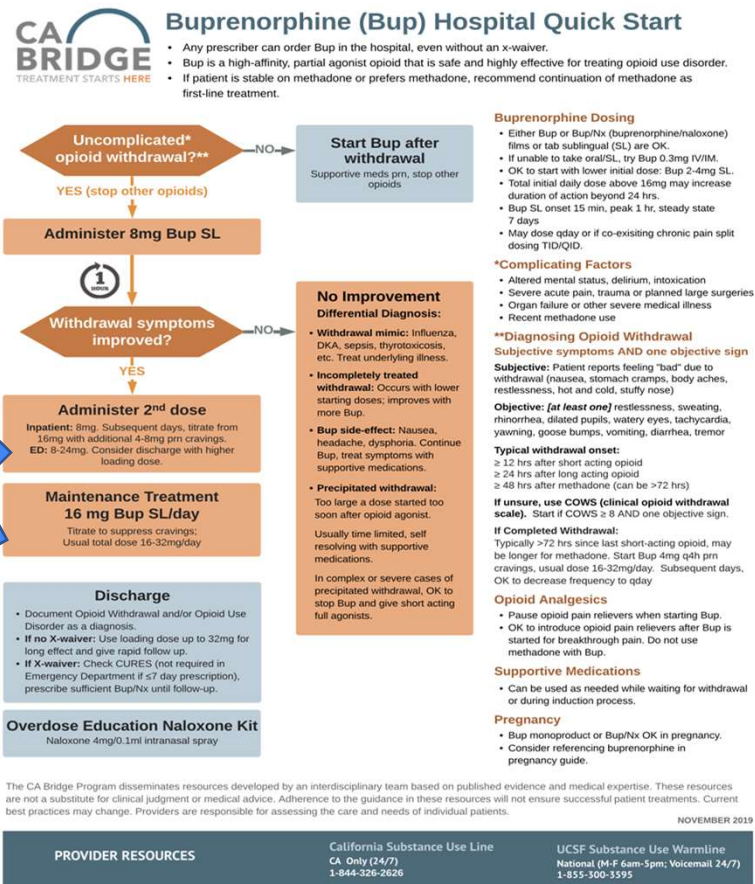
EVIDENCE OF MACRODOSING

BUPRENORPHINE FIELD INITIATION OF ReSCUE TREATMENT BY EMERGENCY MEDICAL SERVICES (BUPE FIRST EMS): A CASE SERIES

Gerard G. Carroll, MD FAAEM EMT-P, Deena D. Wasserman, MD FAWM, Aman A. Shah, MD, Matthew S. Salzman, MD, Kaitlan E. Baston, MD MSc DFASAM, Rick A. Rohrbach, BSN CFRN CCRN-K MICP, Iris L. Jones, MA LPC, LCADC, Rachel Haroz, MD, FAACT

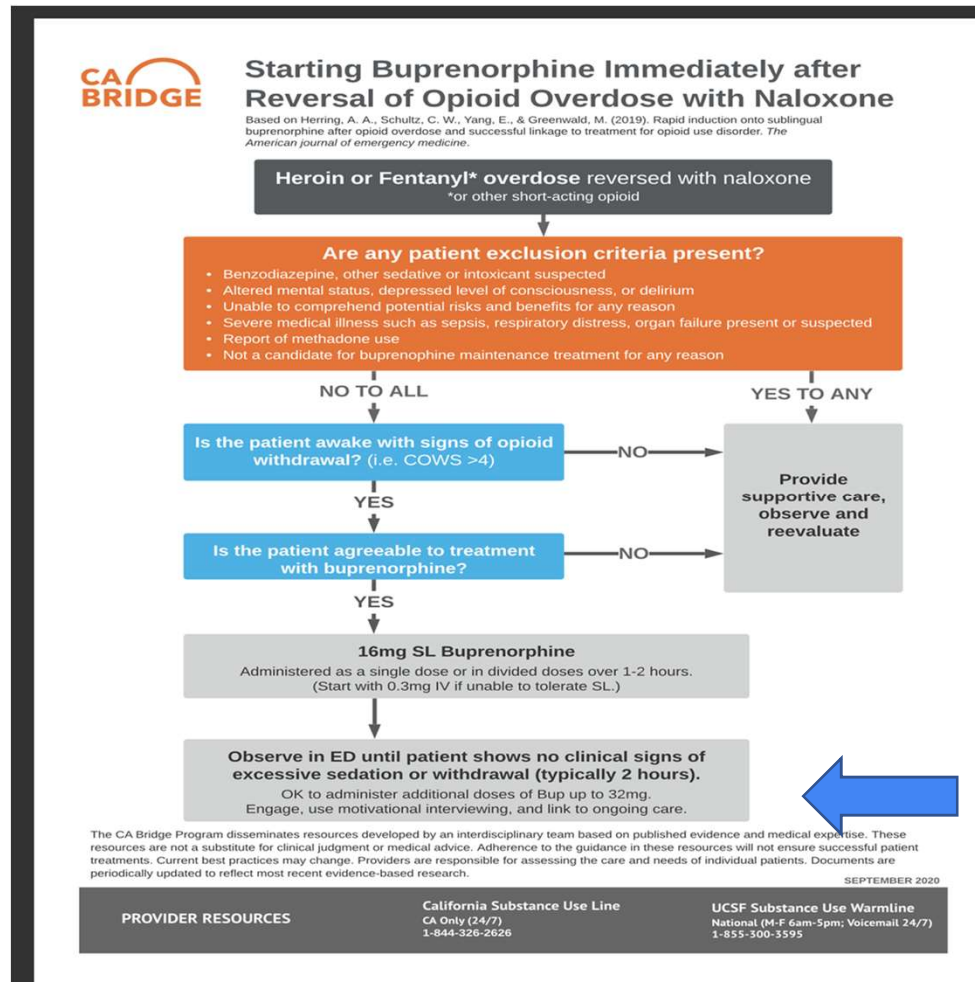
Prehospital Emergency Care March/April 2021 Volume 25, Number 2

PROTOCOLS FOR MACRODOSING



8-24 mg
May need higher
loading dose 32
mg

PROTOCOLS FOR MACRODOSING



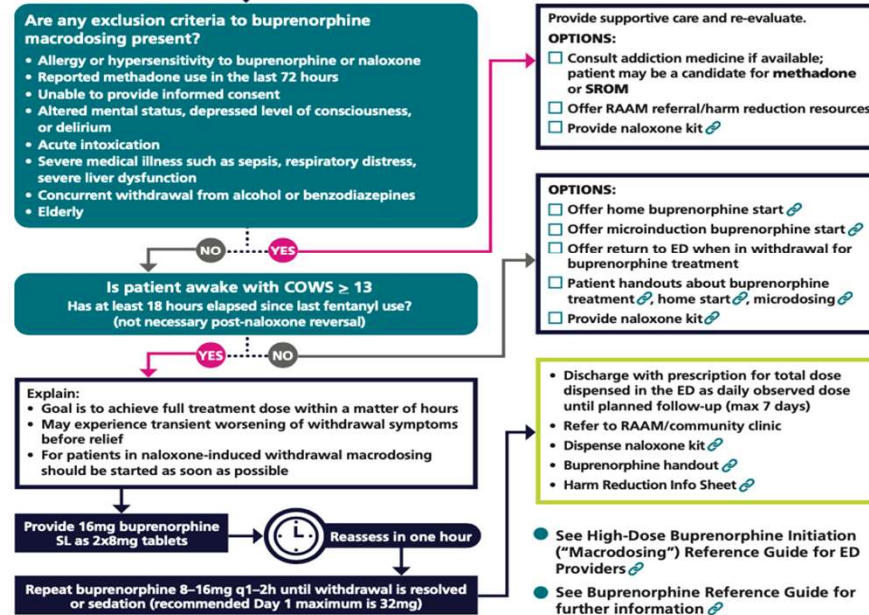
Buprenorphine Macro dosing Initiation

Macro dosing is an alternative approach to initiating buprenorphine for patients who do not meet traditional criteria and for whom delays in treatment pose significant risk. Macro dosing should be reserved for people with high opioid tolerance. Higher initial and total Day 1 doses are off-label but have been shown to be effective in achieving therapeutic levels of buprenorphine.¹

Contact ED substance use navigator/hospital to home coordinator if available.

Indications:

- Patients in withdrawal from fentanyl use, or
- Patients who have had full naloxone reversal of an opioid overdose (i.e., naloxone-induced withdrawal)



¹ <https://cabridge.org/resource/starting-buprenorphine-immediately-after-reversal-of-opioid-overdose-with-naloxone/>

EARLY DEPO-BUP CONSIDERATIONS

WHY CAN'T WE GIVE DEPO-BUP EARLY-DAY 1-3?

Why do I have to wait 7 days for my injection
(Patient)



WHAT IS THE DIFFERENCE BETWEEN

- 8 MG FOR 1-3 DAYS VS 7 DAYS?
- 7 DAYS X 8 MG VS 2 DAYS X 32 MG

EVIDENCE FOR EARLY DEPO-BUP ADMINISTRATION

ClinicalTrials.gov

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Trial record **1 of 393** for: Sublocade | (

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An Open-Label Pilot Study of Sublocade as Treatment for Opiate Use Disorder

EVIDENCE FOR EARLY DEPO-BUP ADMINISTRATION

Open-label trial of a single-day induction onto buprenorphine extended-release injection for users of heroin and fentanyl

John J. Mariani MD^{1,2}  | Amy L. Mahony LMHC¹ | Samuel C. Podell BS³ |
Daniel J. Brooks LCSW¹ | Christina Brezing MD^{1,2} | Sean X. Luo MD, PhD^{1,2} |
Nasir H. Naqvi MD, PhD^{1,2} | Frances R. Levin MD^{1,2} 

EVIDENCE FOR EARLY DEPO-BUP ADMINISTRATION

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Trial record **4 of 148** for: sublocade | Recruiting, Not yet recruiting Studies

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Buprenorphine Extended-Release Subcutaneous Injection (RBP-6000) in High-risk Users

EVIDENCE FOR EARLY DEPO-BUP ADMINISTRATION

Initiating Monthly Buprenorphine Injection After Single Dose of Sublingual Buprenorphine

Katharina Wiest¹ | Stephanie Stafford² | Sunita Shinde³ | Amy Heath¹ | Robert Dobbins² | Howard Hassman¹ | 1. Pacific Vascular Specialists, Portland, OR | 2. Indivior, Inc., Richmond, VA | 3. Hassman Research Institute LLC, Marlton, NJ

Aims

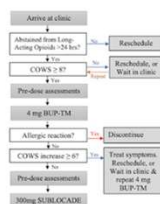
Buprenorphine extended-release injection (SUBLOCADE) is indicated for treatment of moderate/severe opioid use disorder (OUD) in patients who have initiated treatment with transbuprenorphine (BUP-TM), followed by dose adjustment for a minimum of 7 days.¹ In the current medical climate, there is great interest in initiating a depot formulation as rapidly as possible, increasing the likelihood of patient adherence to treatment from the outset, and reducing the need to provide take-home transbuprenorphine (TM) buprenorphine for outpatient use.^{2,3} We evaluated withdrawal symptoms, safety and tolerability of initiating SUBLOCADE one hour after administering a single dose of 4 mg BUP-TM.

Methods

Study Design

This open-label, post-approval study was registered as NCT03993392. Qualitative and quantitative urine drug screens, self-reported drug use, and the clinical opiate withdrawal scale (COWS) were completed before buprenorphine administration. If COWS score was ≥8, staff administered 4 mg BUP-TM. If the participant did not exhibit hypersensitivity, symptoms of precipitated withdrawal (PW), or sedation within 1h, 300 mg of SUBLOCADE was administered and clinical assessments were completed inpatient for 48 hours and outpatient up to 28 days post-injection. Rescue medications and supplemental BUP-TM were permitted to treat withdrawal and recommended psychosocial counseling was provided to all participants. Endpoints were: 1) COWS score increase of ≥6 and 2) independent adjudication of PW.

Figure 1 Schematic Diagram Depicting Rapid Induction Procedure



BUP-TM: buprenorphine, COWS: Clinical Opiate Withdrawal Scale, TM: transbuprenorphine

Supported by funding from Indivior, Inc.

Participants

- ≥18 years of age
- Documented history of moderate or severe OUD as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)
- Seeking buprenorphine-assisted treatment for OUD
- Abstained from short-acting opioids for at least 6 hours and long-acting opioids for 24 hours before arriving at the clinic on the morning of Day 1

Table 1 Demographic and Opioid Use Disorder Characteristics at Screening of Enrolled Participants

Parameter	Transbuprenorphine Enrolled Population (N=26)	SUBLOCADE 300 mg Safety Analysis Set (N=24)
Age (years)	41.4 (±14.0)	42.2 (±13.4)
Sex		
Male	14 (53.8%)	12 (50.0%)
Female	12 (46.2%)	12 (50.0%)
Race		
African American	11 (42.3%)	9 (37.5%)
White	11 (50.0%)	13 (54.2%)
Other	17 (7.7%)	2 (8.3%)
Ethnicity		
Not Hispanic or Latino	24 (92.3%)	22 (91.7%)
Not Reported	2 (7.7%)	2 (8.3%)
BMI (kg/m ²)	22.6 (±3.9)	22.6 (±4.0)
Opioid Use		
Opioids - Lifetime Use (years)	15.8 (±15.1)	15.8 (±15.1)
Opioids - Last 30 days (days)	28.9 (±1.6)	28.9 (±1.6)
Opioids - Intravenous Route	6 (23.1%)	6 (25.0%)
Day 1 Drug Screen		
Opioids	5 (20.0%)	5 (20.8%)
Morphine	5 (20.0%)	5 (20.8%)
Methadone	1 (4.2%)	1 (4.2%)
Fentanyl	17 (65.4%)	17 (70.8%)
Oxycodone	3 (11.5%)	3 (12.5%)

Values are mean (SD) or number of participants (N).

Results

- 26 participants received BUP-TM, 24 proceeded to SUBLOCADE injection (Table 1), and 20 completed the study.
- After SUBLOCADE injection, mean±SD COWS scores decreased from a pre-SUBLOCADE baseline of 12.6±4.1 to 6.9±4.1 at 6h and to 4.2±3.2 at 24h (Figure 2). 15 participants (62.5%) had maximum COWS score pre-injection.
- 2 participants had a COWS score increase of ≥6 from the pre-injection value (events occurred at 1h and 2h post-injection). No participants had severe withdrawal and one participant had moderately severe withdrawal (maximum COWS score=27 at 2h post-injection). (Table 2)
- By independent adjudication, 2/24 participants experienced PW. There was concordance between the protocol definition and adjudication assessment of precipitated withdrawal for 25 (97%) of the participants post BUP-TM and 22 (92%) of the participants post SUBLOCADE.
- The mean opioid craving score fell by 24.4 points at 12 hours post-SUBLOCADE and continued to decrease through completion of the study.

Figure 2 Mean (SD) Clinical Opiate Withdrawal Scale (COWS) Scores Before and Following Administration of SUBLOCADE

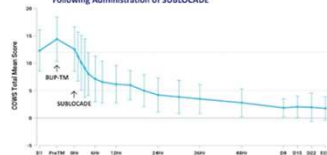
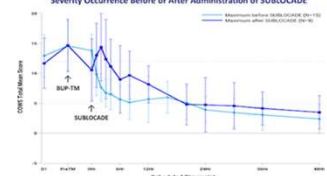


Table 2 COWS Scores by Severity and Timing of Maximum Severity Occurrence and Increase of ≥6 (Number of participants [N])

	Participants Receiving SUBLOCADE (N=24)	
	Maximum Severity	Increase of ≥6
Pre-SUBLOCADE	15 (62.5%)	1 (4.2%)
1 hour post-SUBLOCADE	4	0
2 hour post-SUBLOCADE	5 (20.8%)	1 (4.2%)
6 hour post-SUBLOCADE	1	1
12 hour post-SUBLOCADE	2	0
24 hour post-SUBLOCADE	2	0
48 hour post-SUBLOCADE	2	0
72 hour post-SUBLOCADE	1	0
96 hour post-SUBLOCADE	1	0
120 hour post-SUBLOCADE	1	0
144 hour post-SUBLOCADE	1	0
168 hour post-SUBLOCADE	1	0
192 hour post-SUBLOCADE	1	0
216 hour post-SUBLOCADE	1	0
240 hour post-SUBLOCADE	1	0
264 hour post-SUBLOCADE	1	0
288 hour post-SUBLOCADE	1	0
312 hour post-SUBLOCADE	1	0
336 hour post-SUBLOCADE	1	0
360 hour post-SUBLOCADE	1	0

Figure 3 Mean (SD) Clinical Opiate Withdrawal Scale (COWS) Scores by Maximum Severity Occurrence Before or After Administration of SUBLOCADE



Safety Results

Table 3 Summary of Treatment-Emergent Adverse Events (TEAEs)

Parameter	Participants Receiving SUBLOCADE (N=24)	TEAEs within 48h
Any TEAE	20 (83.3%)	19 (79.2%)
Treatment Related TEAEs	5 (20.8%)	4 (16.7%)
Serious TEAEs	0 (0.0%)	0 (0.0%)
Treatment Related Serious TEAEs	0 (0.0%)	0 (0.0%)
Severe TEAEs	5 (20.8%)	5 (20.8%)
Injection site reaction TEAE	3 (12.5%)	1 (4.2%)
TEAE resulting in study treatment withdrawal or interruption	0 (0.0%)	0 (0.0%)
TEAE resulting in death	0 (0.0%)	0 (0.0%)

- Irritability, anxiety, nausea, and pain were the most common treatment emergent adverse events (TEAEs).
- Most TEAEs were moderate or mild in intensity. Five participants reported a total of 8 severe TEAEs (irritability [n=4], pain [n=2], chills [n=1] and vomiting [n=1]), which all occurred within 48 hours of SUBLOCADE administration.
- Two participants received 4 mg BUP-TM after SUBLOCADE injection and 15 received other rescue medications.
- Rescue medications included ondansetron for nausea/vomiting [10 (41.7%), clonidine for anxiety/irritability [10 (41.7%)], buprenorphine for pain/body aches [9 (37.5%)], and trazodone for insomnia [5 (20.8%)].
- Potential limitations of this study include the small number of participants and the heterogeneous group of opioid-tolerant patients that might not fully represent the real-world population of patients with OUD.

Conclusions

- Initiating SUBLOCADE 300 mg following a single 4 mg dose of BUP-TM indicated a safety profile similar to that observed with SUBLOCADE induction per current labeling.¹
- After SUBLOCADE injection, withdrawal symptoms and opioid craving scores improved within 12h. Improvements were sustained for 4 weeks.

References

- SUBLOCADE United States Prescribing Information, February 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/2018010000000.pdf accessed October 30, 2020.
 - Dorsey A, Leshgry B, Mattern D, et al. Challenges in maintaining treatment services for people who use drugs during the COVID-19 pandemic. *Am J Public Health*. 2020;110:1726.
 - Farrington A, Barilachini A, Clark N, et al. COVID-19 and Substance Use Disorders: Recommendations for a Comprehensive Health System Response. An International Society of Addiction Medicine Practice and Policy Interest Group Position Paper. *Basic Clin Neurosci*. 2020;11:133.
- PRESENTED VIRTUALLY AT THE ANNUAL MEETING OF THE COLLEGE ON PROBLEMS OF DRUG DEPENDENCE, 23 JUNE 2021 Virtual Poster Q&A Session 10: Opioids/Opioids

SUBLOCADE OFFERS PROTECTION

Real-World Evidence for the Optimal Management of Opioid Use Disorder (OUD) During COVID-19 Pandemic for Patients Receiving Opioid Agonist Treatment (OAT)

Kenneth Lee¹ | Christopher Fraser² | Tazmin Merali³ | Marie-Christine Mormont⁴ | Brian Conway⁵

¹London MAM Clinic, London, ON, Canada | ²Coal Aid Community Health Centre, Victoria, BC, Canada | ³Strong Intelligence Inc, Toronto, ON, Canada | ⁴Trident Inc, Montreal, QC, Canada | ⁵Vancouver Infectious Diseases Center and Simon Fraser University, Vancouver, BC, Canada

background

COVID-19 pandemic declared by WHO as of March 11, 2020

- Less direct interactions/follow-up between patients and their health care provider
- Significant adverse effect on care to vulnerable populations
- Disruptions of usual OAT patterns of care and increase use of illicit synthetic opioids
- Increased opioid-use related deaths reported in Canada in COVID world
- Long-acting OAT may be particularly beneficial in this setting, to maintain therapeutic engagement and reduce opioid-related harms

Primary Objectives:

- To describe the real-world use and patient characteristics of patients treated with each OAT modality
- To quantify the proportion of patients who experienced fatal or non-fatal overdose events whilst on methadone, buprenorphine-containing sublingual tablets, and buprenorphine extended-release injection

Methods

- An open-label, multi-cohort, retrospective observational study
- Patients started on Opioid Agonist Treatment (OAT) as of March 11, 2020*, or thereafter

Inclusion criteria:

- Age ≥ 18 years
- Diagnosis of moderate to severe opioid use disorder
- Started OAT treatment on March 11, 2020, or thereafter, but ≥ 6 months before data collection occurs
- Not pregnant or actively planning for pregnancy at start of treatment

7 treating physicians (BC, ON):

- All assigns to cohort on intent to treat (ITT) basis at start of treatment
- Follow-up period: 6 months from the start of drug treatment, or until occurrence of a fatal event, whichever comes first
- One-time data collection, using a standardized data collection form after 6 months on OAT
- Urine Drug Screens (UDS) collected at follow-up appointments

140 OUD cases across three cohorts, 6 months' follow-up:

- Buprenorphine extended-release injection: 41 (29%)
- Buprenorphine-containing S/L tablets: 51 (36%)
- Methadone: 48 (34%)

Other study investigators

Dr Raj Mehta, Sunny Health Centres | Dr Laila Prasad, Hamilton, Ontario
Dr Jennifer Johnson, Hamilton, Ontario | Dr Brenda Haffin, London, Ontario

*List of randomly selected physicians by county in BC

Patient Cohort Description

	Buprenorphine Extended-release Injection	Buprenorphine-Containing S/L Tablets	Methadone	Total
Number of Patients	41	51	48	140
Age Range (Median)	19 – 65 (38)	19 – 61 (38)	22 – 65 (39)	
Gender:				
Male	26 (63%)	34 (67%)	29 (60%)	89 (64%)
Female	15 (37%)	17 (33%)	19 (40%)	51 (36%)
Stable Housing	38 (93%)	33 (65%)	24 (50%)	95 (68%)
Employment:				
Employed	12 (29%)	22 (43%)	8 (17%)	42 (30%)
Unemployed	12 (29%)	21 (41%)	21 (43%)	54 (39%)
Disability	9 (22%)	6 (12%)	15 (31%)	30 (21%)
Student	1 (2%)	1 (2%)	1 (2%)	3 (2%)
Other	2 (5%)	1 (2%)	1 (2%)	4 (3%)
Receiving Concomitant Psychosocial Support	12 (29%)	8 (16%)	30 (63%)	50 (36%)

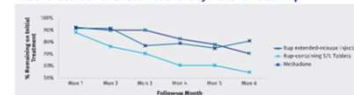
Risk Factors & Concomitant Medical Conditions

	Buprenorphine Extended-release Injection	Buprenorphine-Containing S/L Tablets	Methadone	Total
Number of Patients	41	51	48	140
Opioid Abuse History:				
< 5 years	9 (22%)	19 (37%)	5 (10%)	33 (24%)
5 – 10 years	13 (32%)	11 (22%)	11 (23%)	35 (25%)
> 10 years	19 (46%)	21 (41%)	32 (67%)	72 (51%)
History of Injectable Opioid / Illicit Drug Use	22 (54%)	31 (61%)	42 (88%)	95 (68%)
History of Patient Reported / Illicit Drug Use	12 (29%)	16 (31%)	16 (33%)	44 (31%)
Prior OAT Treatment	39 (95%)	33 (65%)	43 (90%)	115 (82%)
Concomitant Medical Conditions:				
HIV	1 (2%)	1 (2%)	7 (15%)	9 (6%)
HCV	7 (17%)	13 (26%)	28 (58%)	48 (34%)
Mental Health Disorder	16 (39%)	16 (31%)	24 (50%)	56 (40%)
Alcohol Use Disorder	9 (22%)	7 (14%)	7 (15%)	23 (16%)
Non-Opioid Substance Use Disorder	16 (39%)	21 (41%)	32 (67%)	69 (49%)
Chronic Pain	12 (29%)	6 (12%)	12 (25%)	30 (21%)

Patient Treatment & Retention

	Buprenorphine Extended-release Injection	Buprenorphine-Containing S/L Tablets	Methadone	Total
Number of Patients	41	51	48	140
Dose Range	100 – 300 mg	2 – 36 mg	15 – 280 mg	-
Achievement: Patients with < 4 out of 6 months of documented retention	36 (88%)	34 (67%)	35 (73%)	105 (75%)
Retention: Patients maintained on same treatment at month 6	29 (71%)	28 (55%)	39 (81%)	96 (69%)

Patient Retention on Initial Treatment by Month of Follow-up



Patient Outcomes – Timing of Non-Fatal Overdose Events

	Buprenorphine Extended-release Injection	Buprenorphine-Containing S/L Tablets	Methadone	Total
Number of Patients	41	51	48	140
Patient Reported Non-Fatal Overdose Events	1	8	15	24
Patients with >1 Event	1 (2%)	6 (12%)	9 (19%)	16 (11%)
Total Events	1	8	15	24

Overdose Event Incidence in the Subgroup of Patients with Prior History of Reported Opioid Use



Patient Outcomes on Treatment Over 6-Month Follow-up

	Buprenorphine Extended-release Injection	Buprenorphine-Containing S/L Tablets	Methadone	Total
Number of Patients	41	51	48	140
Concerned Substance Abuse:				
Self-Reported Opioid/Illicit Drug Use	24 (59%)	33 (65%)	45 (94%)	102 (73%)
Urine Positive for Fentanyl	11 (27%)	15 (29%)	25 (52%)	51 (36%)
Urine Positive for Non-Fentanyl Substance	22 (54%)	32 (63%)	38 (79%)	92 (66%)
Urine Positive for Illicit Substance	21 (51%)	34 (67%)	39 (81%)	94 (67%)
Urine Positive for Any Substance	22 (54%)	34 (67%)	39 (81%)	95 (68%)
Patient Status at 6 Months:				
Alive	35 (85%)	32 (63%)	39 (81%)	106 (76%)
Lost to Follow-up	6 (15%)	19 (37%)	9 (19%)	34 (24%)
Deceased	-	-	-	-

Conclusions

In this observational cohort, use of buprenorphine extended-release injection is associated with a reduction in documented drug-related overdoses as compared with the use of other standard OAT modalities, especially with the use of methadone.

Some potential patient selection bias was noted for the buprenorphine extended-release injection group:

- Less prior history of injectable opioid/illicit drug use
- More stable housing
- Unmeasured selection bias for selection of buprenorphine extended-release injection as a treatment modality

Differences in outcomes were noted between the 3 groups, and between methadone and S/L buprenorphine in terms of adherence, retention in treatment, and illicit drug use during treatment. Buprenorphine extended-release injections may present a unique option in terms of maintenance of engagement in care and reduction of drug-related harms.

These observations warrant confirmation in a validation cohort.

Disclosures

Researcher: Kenneth Lee, Christopher Fraser, Tazmin Merali, Marie-Christine Mormont, Brian Conway

Medical Writer: Tazmin Merali, Marie-Christine Mormont, Brian Conway

Medical Writer: Tazmin Merali, Marie-Christine Mormont, Brian Conway

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GAME CHANGER: EARLY DEPOT-BUP HERE WE COME!

- MAXIMUM DAILY DOSING: 32 MG

BUP/NAL

Sometimes higher during stabilization

Day 1: COWS>12 + no fentanyl use >24 hrs
Dosing: **24mg then 8 mg q1h prn X1**
Total dose over 1-2 hours= 32mg

- RAPID TITRATION WITH MACRODOSING
BUP/NAL
- EARLY DEPO-BUPRENORPHINE

24-72 hours after first sublingual buprenorphine-naloxone dose

**** PEOPLE WHO USE FENTANYL ****

Within 1-2 days → patients receive depot-bup
no withdrawal symptoms

1. JACOBS P ET AL. AM J ADDICT 2015;24:667-75.
2. CARROLL GG ET AL. PREHOSP EMERG CARE 2021;25:289-93.
3. ERRING AA ET AL. JAMA NETW OPEN. 2021;4:E2117128.

4. <https://cabridge.ca>

5. Mariani JJ et al. Am J addict.2021;1-7

6. Korownyk et al, Canadian Family Physician;2018:321-33

Updates from TADH



2021 ACUTE WITHDRAWAL MANAGEMENT BEDS TIMMINS AND DISTRICT HOSPITAL

	Number of Admissions	Avg Occupancy	Avg LOS	Alcohol Use Disorder	Opiate Use Disorder	Polysubstance Use Disorder	Suboxone Starts	Sublocade
Dec-20	7	36%	2.3	3	4		4	1
Jan-21	11	50%	3.5	4	7		7	4
Feb-21	13	82%	3.6	3	10		10	6
Mar-21	13	79%	3.8	2	11		11	10
Apr-21	14	79%	3	3	11		10	6
May 1-22, 2021	13	65%	2.6	3	10		10	9
Jun-21	14	73%	2.9	1	13		11	11
Jul-21	13	42%	2.7	0	13		9	7
Aug-21	10	55%	3.1	1	8	1	8	7
Sep-21	16	82%	2.7	5	11		11	11
Oct-21	13	63%	3.1	2	10	1	10	7
Nov-21	16	62%	3	7	9		9	4
Dec-21	5	40%	5	0	4	0	4	4

TOTAL : 148
AUD:27 (18%)
OUD:121 (82%)

AVERAGE LOS
3.1

BUV/NLX START
FOR OUD
114/121(94%)

DEPO-BUP
START
87/114 (76%)

2021 DEPO-BUP AT TADH

DECEMBER 7TH, 2020 – DECEMBER 31ST, 2021

TOTAL:

122 doses given

LOCATION:

87 doses : WMS beds

35 doses : Medical floor, Surgical floor, MHU

MARCH-JULY 2022

TOTAL: 121

OD: 77 (64%)
AD: 44 (36%)
LOS: 3.4 days

BUP STARTS:
60
78% OF OD
ADMISSIONS

DEPOT-BUP:
52
68% OF OD
ADMISSION
87% OF BUP START



COMMUNICATION STRATEGIES

- Listen to the patient
- Understand their language
- Understand where they are along the treatment continuum
- Show compassion and patience
- Discuss a variety of treatment options available with supporting pros and cons
- Involve the person in treatment decisions (they may change their mind many many many times)

CASE PRESENTATIONS

34 yo female presenting to ER last used IV fentanyl 6 hrs ago asking for help with her opioid use (also uses IV Crystal Meth). Uses 0.5-1 g IV fentanyl x 5 yrs

25 yo male presenting to ER fully reversed with naloxone in severe withdrawals unsure if he wants help for his opioid use but wants to feel better immediately. Smokes fentanyl and crack x 2 years approximately 1-1.5 grams per day.

40 to female in withdrawals and last used fentanyl 22 hours ago asking for help with her opioid use. Uses “a few points per day” of fentanyl, IV and smoked x 5 years. Use speed, cocaine, CM also IV and smoked.

REFLECTION ON PAST AND PRESENT SUCCESSES

What did we do before? We were letting these patients down.
-RN ICU and physicians

We haven't seen J.S. in a long time in emerg.
-RN ER & physician



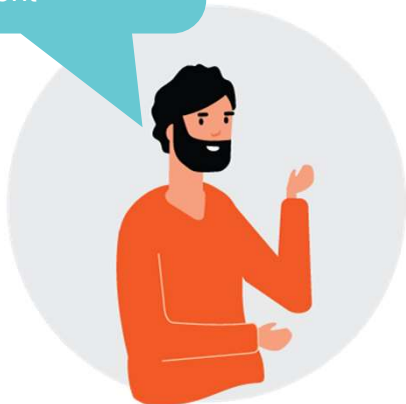
We no longer send people home if our beds are "full"
RN ER & physician

This is AMAZING, the change we are making for these patients.
-RN ICU

REFLECTION ON PAST AND PRESENT SUCCESSES

I have never felt
this good...

-Patient



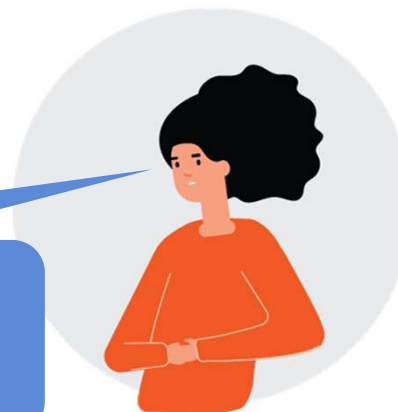
I was using 1 g of fentanyl a day
48 hours ago and now I have no
cravings and no withdrawals...
I thought it would be impossible.

-Patient



My friend was here 2 months ago and is still
not using drugs... I need to get on “the
needle”

-Patient



3

TIMMINS AND DISTRICT HOSPITAL

TRIAGE:13/10/21-1923-SMIKA04

COMPLAINT:Alcohol/Drug Withdrawal

DETAIL:pt here for "suboxone injection" - pt states he used fentanyl x 1 hr ago - denies injecting - pt states he is feeling like he is in withdrawal

T:36.1 Ty P:79 R:18 BP:126/80 SaO2:95 % RA WT:

3

TIMMINS AND DISTRICT HOSPITAL

TRIAGE:01/11/21-2040-WELSH04

COMPLAINT:Prescription/Medication Request

DETAIL:Pt here to get rx for sublocate injection... states is going to be traveling out of town... Been over a month since last injection. states only smoked weed yesterday.

T:36.3 Ty P:124 R:18 BP:129/88 SaO2:98 % RA WT:

k

TAKE HOME MESSAGES

LISTEN TO THE PATIENTS

DON'T BE AFRAID TO PUSH LARGER "MACRODOSES" OF SL BUP/NLX FOR INDUCTION AND PW

BUP/NLX NEEDS TO BE STANDARD OF CARE IN ER OF OUD

CONSIDER GIVING EARLY DEPOT BUPRENORPHINE WITHIN 24 HRS OF INDUCTION

THINK OUTSIDE THE BOX AND BE FLEXIBLE

REDUCE STIGMA & BARRIERS ASSOCIATED WITH ADDICTIONS IN YOUR HEALTH CARE SETTING

TAKE HOME MESSAGES

TREAT THEM AND STREET THEM CAN NO LONGER OCCUR

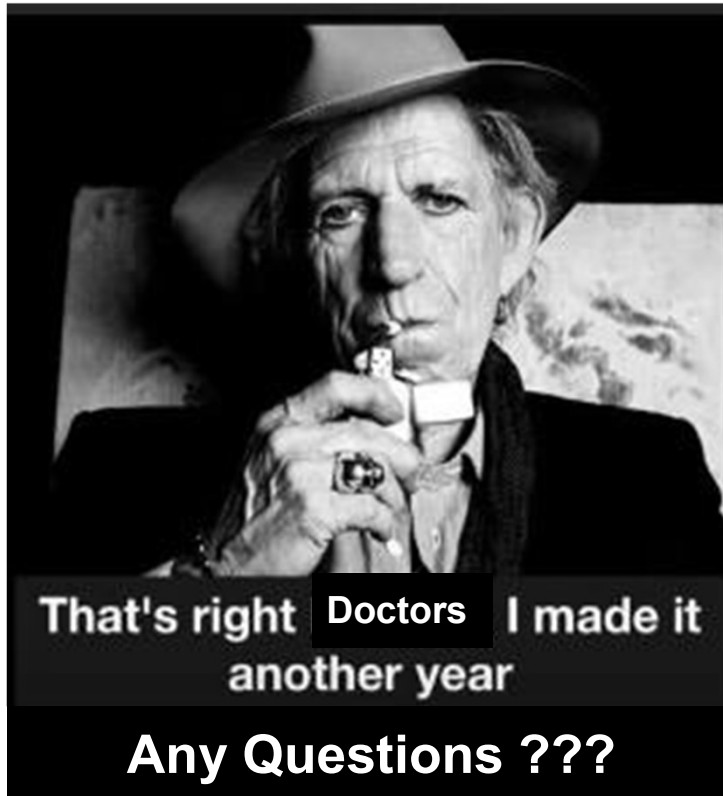
PATIENTS CAN'T REMAIN ON TREATMENT IF THEY ARE NOT STARTED ON TREATMENT

DON'T SETTLE FOR "WE CAN'T DO IT" ... THE QUESTION SHOULD BE "HOW CAN WE DO IT"

IT'S NOT A PATIENT PROBLEM... IT'S A SYSTEM PROBLEM



AND.....HAVE NO REGRETS



That's right Doctors I made it
another year

Any Questions ???



THANK YOU !!

- Julie Samson : jsamson5@me.com
- Louisa Marion-Bellemare:
lm Marionbellemare@nosm.ca