BREAKING BARRIERS FOR OUD USING MACRODOSING & EARLY DEPOT BUPRENORPHINE

DR. LOUISA MARION-BELLEMARE
AND
DR. JULIE SAMSON

JANUARY 24TH, 2022

DISCLOSURES

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- Indivior Advisory Board Rapid Buprenorphine Initiation Sept/2021
- Speaker Honorarium: Indivior October/21

SPONSORS/GRANTS

- NONE but open to suggestions !!

RESEARCH EXPERIENCE

- NONE but we are working on it!!!

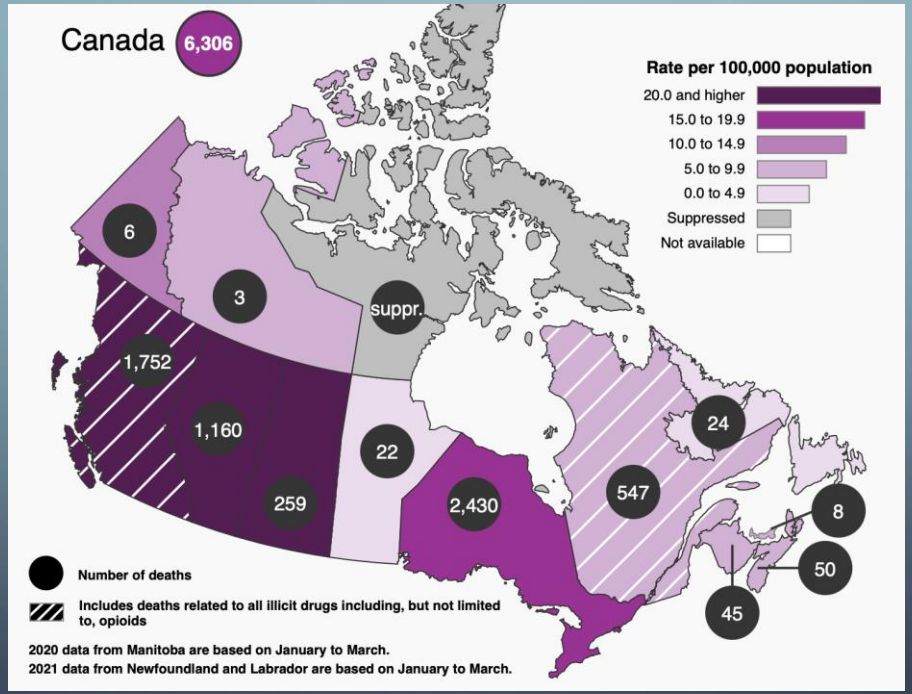
MITIGATING POTENTIAL BIAS

Content reports on clinical experience and as such includes off-label uses

LEARNING OBJECTIVES

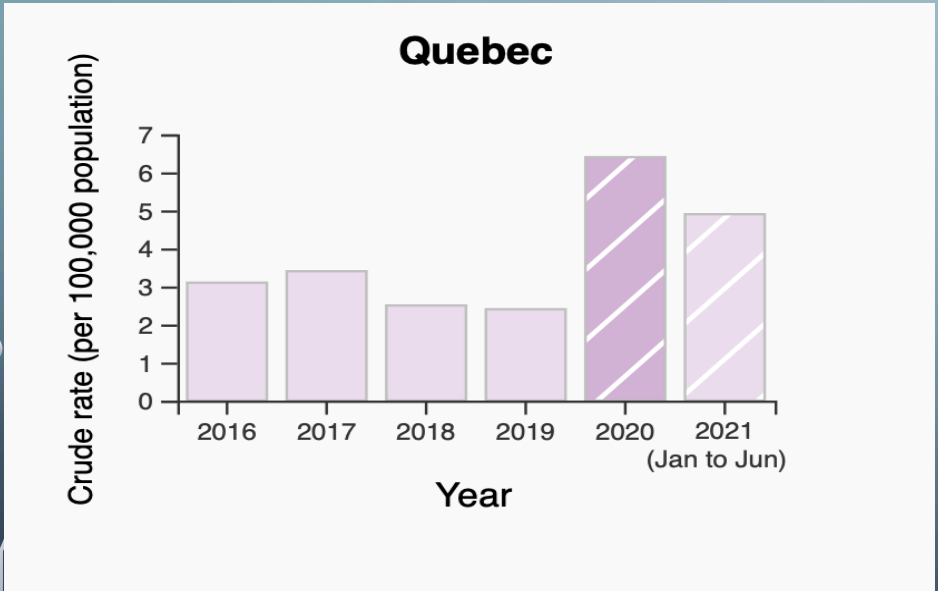
- Discuss “macrodosing” options for starting oral buprenorphine/naloxone
- Discuss early depot-buprenorphine administration
- Share case studies and success stories with flexible treatment based on practice based evidence

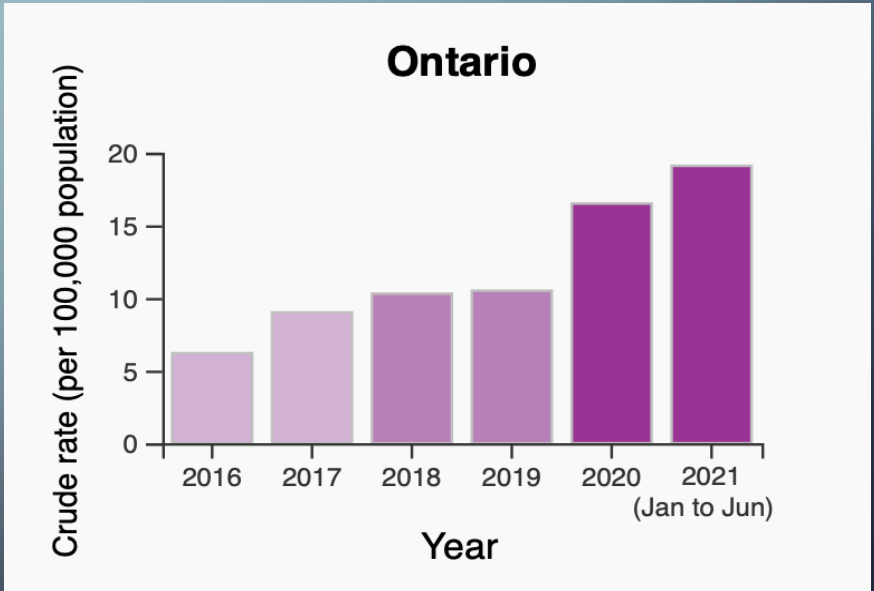
OPIOID RELATED DEATHS IN CANADA 2020



https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/maps

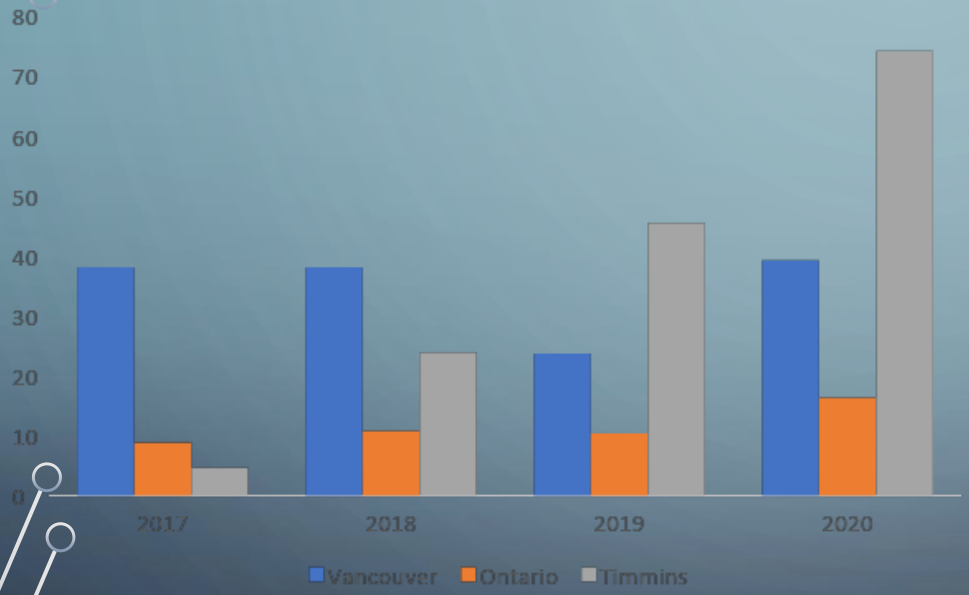
OPIOID RELATED DEATH RATES (PER 100,000 POPULATION)





https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/maps

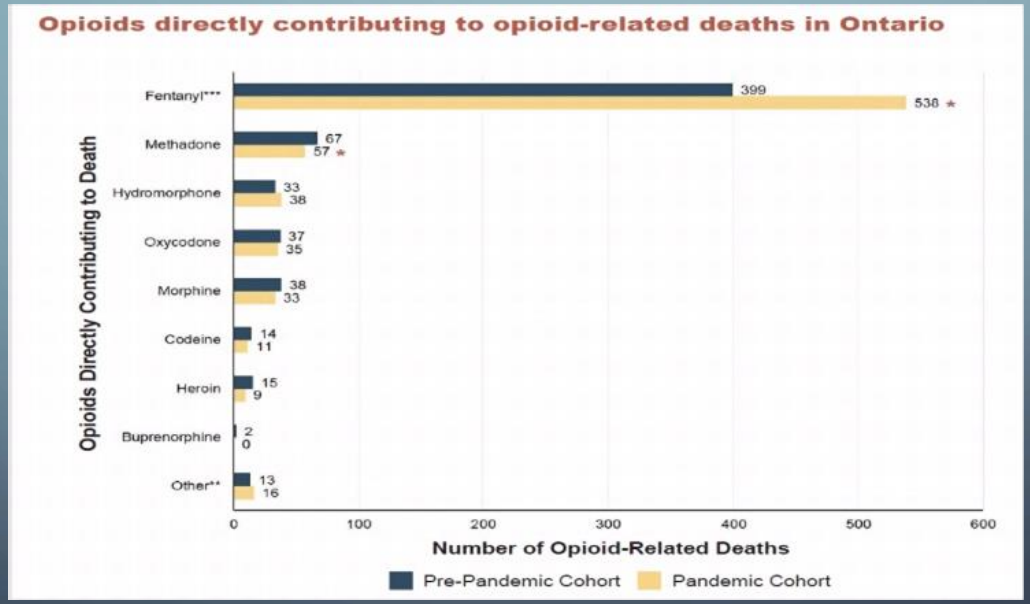
LOCAL CRISIS



Rates of opioid-related mortality in Ontario, Timmins and Vancouver 2017 to 2020

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

ONTARIO OPIOID RELATED DEATHS 2020



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

“The Status Quo is Contributing to Deaths”

What’s going on in our city? It has never been this bad.
-ER RN

We need to be part of the solution, not part of the problem. There must be something we can do to help these patients.
-L.M.B. and J.S., ER physicians

EMS is coming in with J.S. again, his third OD this week. He was in respiratory arrest and now breathing after Narcan… you would think that would make him want to stop.
-ER physician

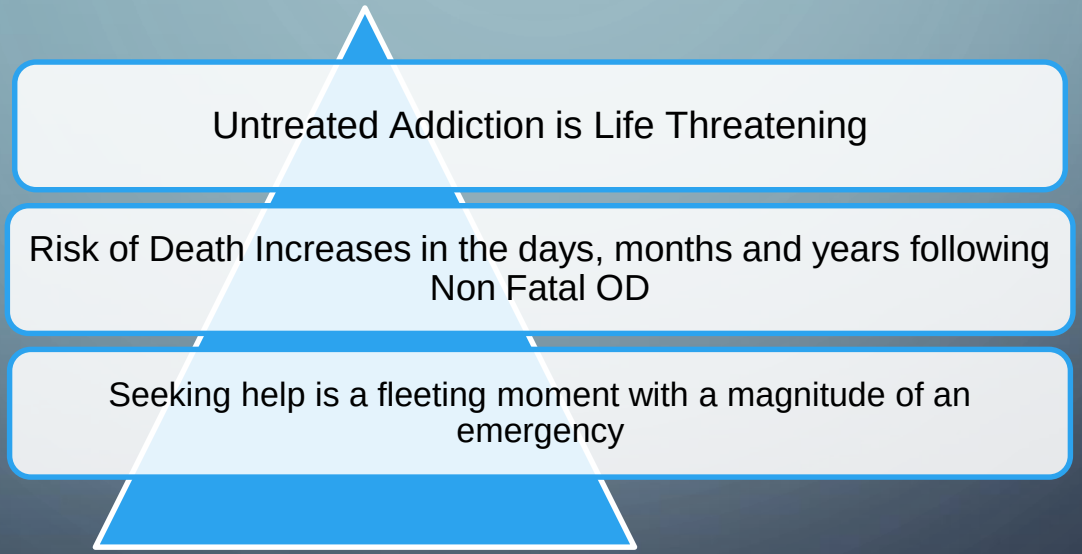
DR. LOUISA MARION-BELLEMARE AND DR. JULIE SAMSON, 2020

DEFINING SUBSTANCE USE DISORDER/ OPIOID USE DISORDER

- **Treatable Chronic Relapsing Illness**
- **Compulsive Disorder**
- **DSM V Criteria for Diagnosis**

“MEDICALIZATION OF SUD/OUD CAN REDUCE STIGMA AMONGST HEALTHCARE PROVIDERS”

ADDICTION IS AN EMERGENCY



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

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[‖‖‖]

2. Initiate first-line opioid agonist treatment in patients with opioid use disorder

a) Patients who meet criteria for opioid use disorder should be offered buprenorphine/naloxone initiation in the ED. Take-home doses may be dispensed as an alternate approach to buprenorphine/naloxone initiation in the ED.

b) Providers should be familiar with other forms of opioid agonist therapy, such as methadone and sustained release oral morphine.

c) Providers should treat opioid withdrawal early, aggressively, and compassionately to reduce the risk of fatal overdose.

Managing Opioid Withdrawal in the Emergency Department With Buprenorphine

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

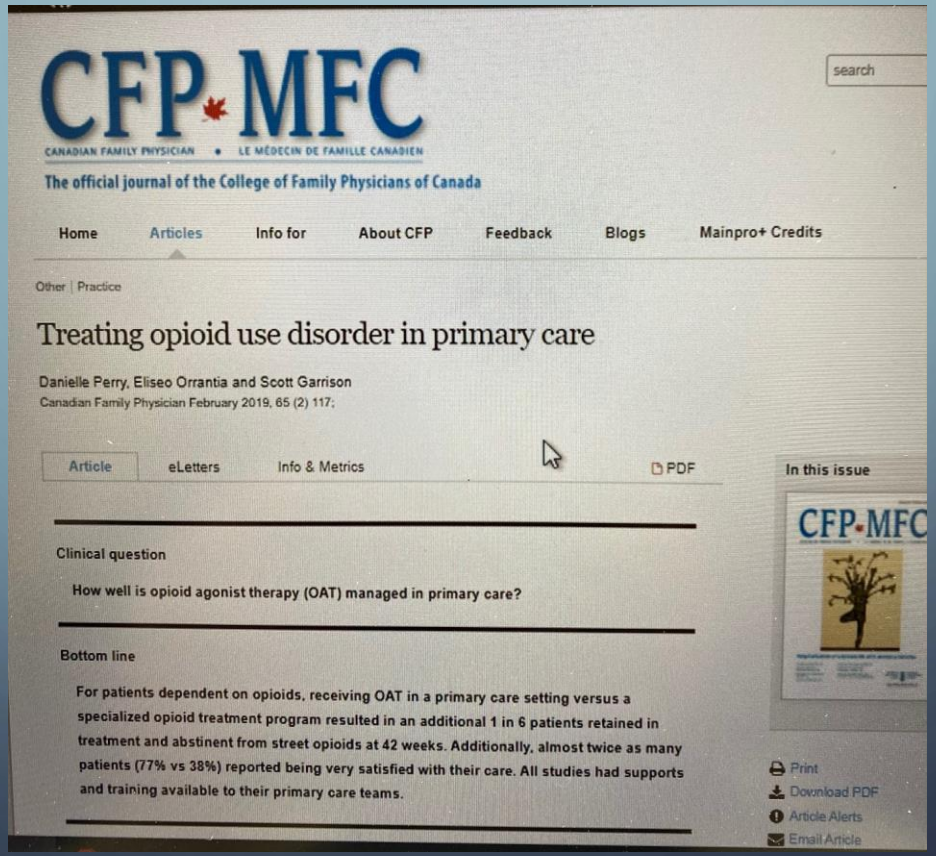
*Corresponding Author. E-mail: lewis.nelson@rutgers.edu, Twitter: @LNelsonMD.

0196-0644/$-see front matter

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

PRACTICE GUIDELINES FOR TREATMENT OF OUD



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 2018

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

HQO Opioid Use Disorder Quality Statements 2018

PRACTICE GUIDELINES FOR TREATMENT OF OUD

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

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)

QUEBEC GUIDELINES

Guide québécois d'amélioration des pratiques sur la prise en charge du trouble lié à l'utilisation des opioïdes (TUO)

http://dependanceitinerance.ca/dependance/

IUD INSTITUT UNIVERSITAIRE SUR LES DÉPENDANCES

Québec

"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/do/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

WHY BUPRENORPHINE/NALOXONE?

Thrombolytics for STEMI

NNT 43

ASA for Acute Ischemic Stroke

NNT 79

Odansetron for Paediatric Gastro

NNT 15

BUP/NAL (>16 mg)

NNT 2

https://www.thennt.com

EVIDENCE FOR OAT IN OUD

- Decrease mortality 70-80%
- Decrease morbidity: HIV, Hep C, Infective endocarditis, cellulitis, abscesses
- Decrease in OD related mortality

Meta-analysis Sordo et al, 2017

- Yearly retention is 74% in treatment
- People in treatment more likely to remain in remission, employed and have stable housing
- Improved quality of life

Social et al, 2018

FORMS OF BUPRENORPHINE/SUBOXONE

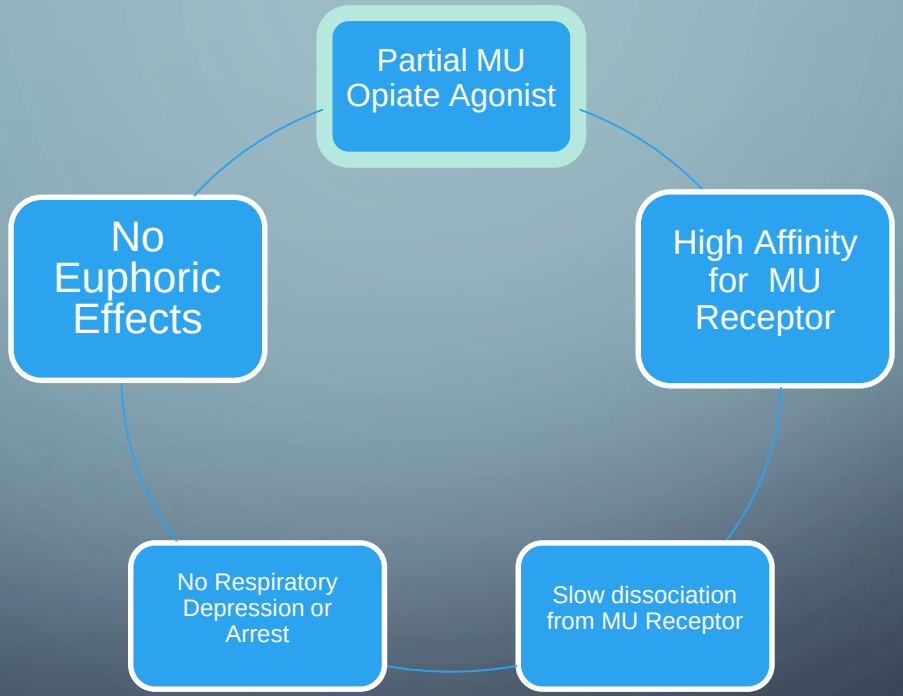
Film

Tablet

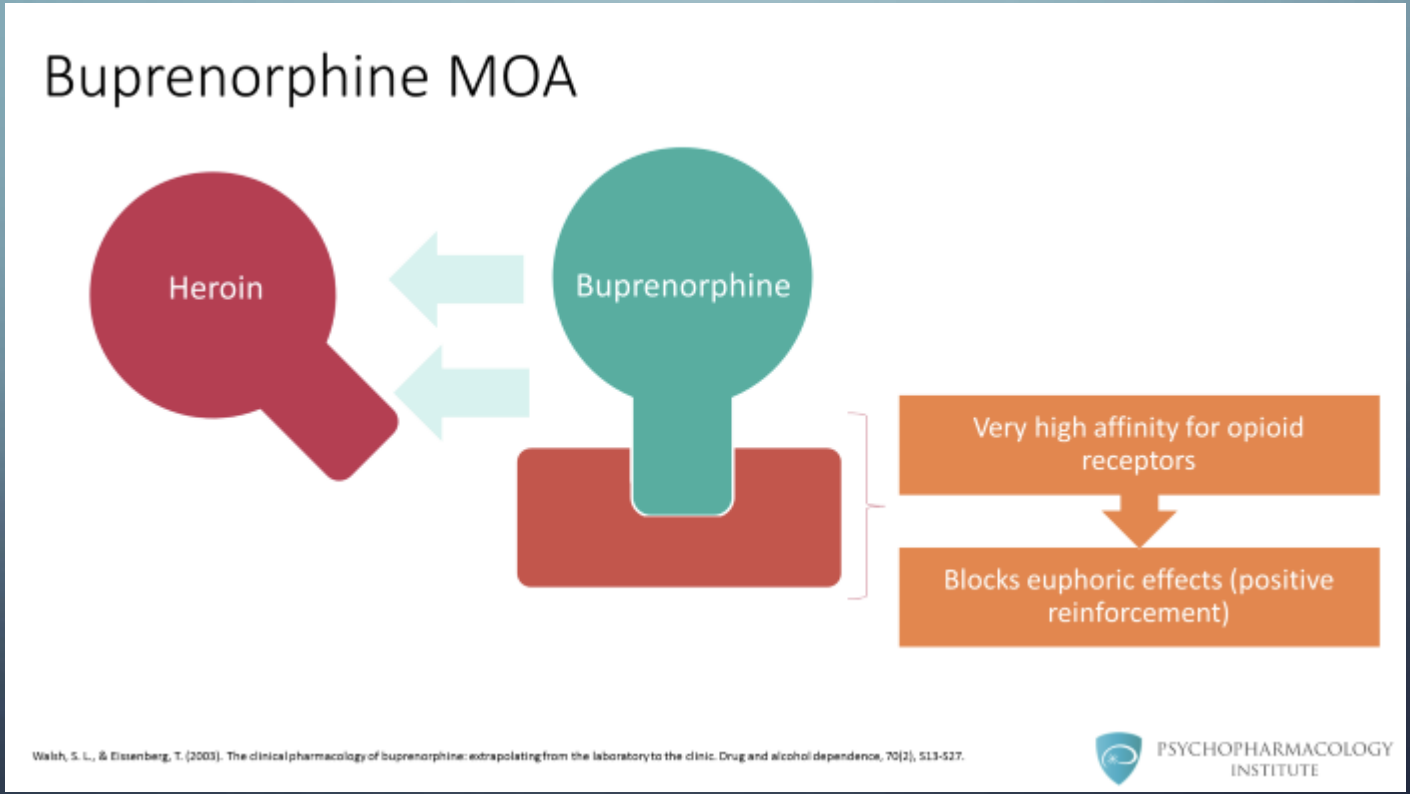
FORMS OF BUPRENORPHINE

Injectable / Depot /Long Acting

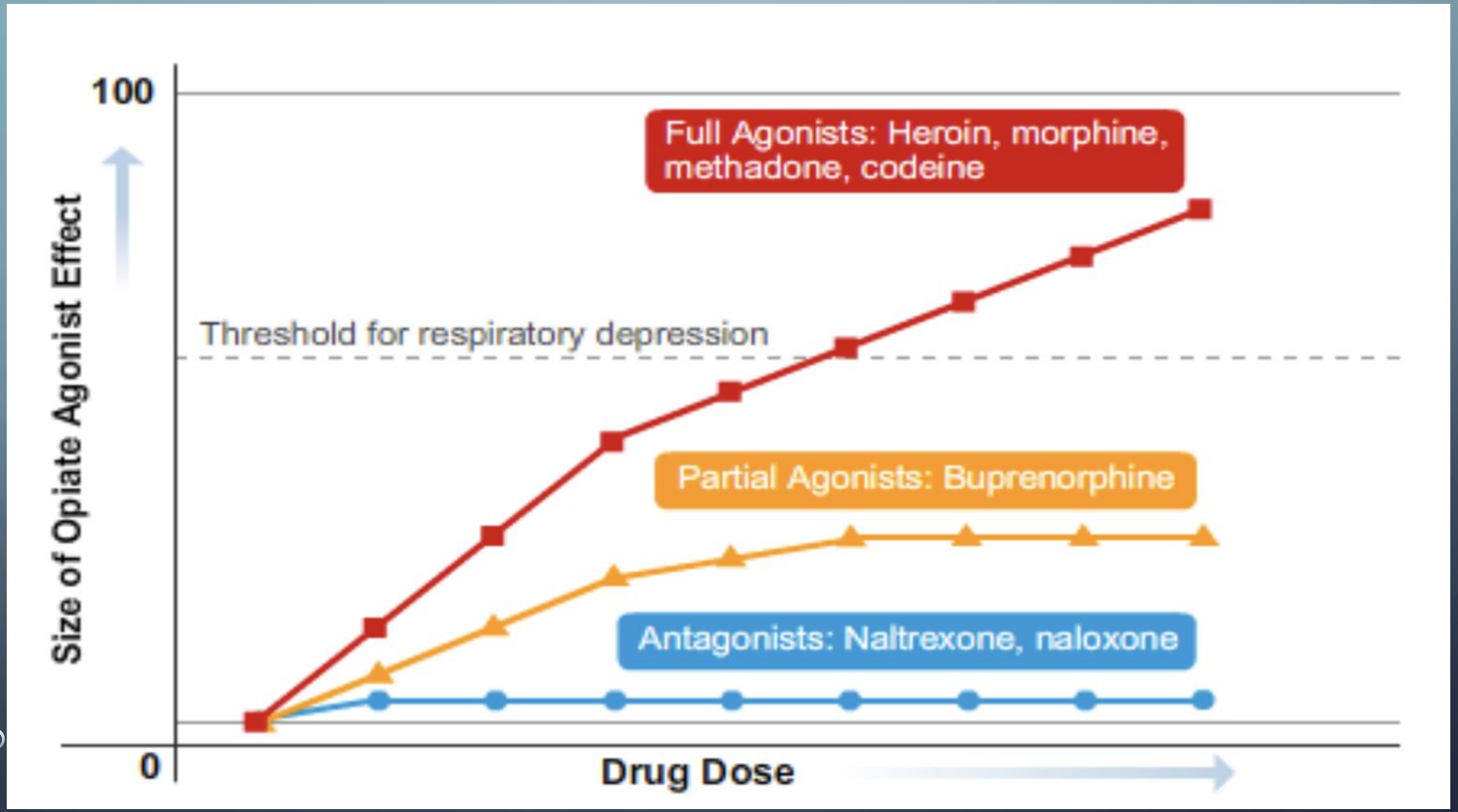
MECHANISM OF ACTION OF BUPRENORPHINE



MECHANISM OF ACTION OF BUPRENORPHINE



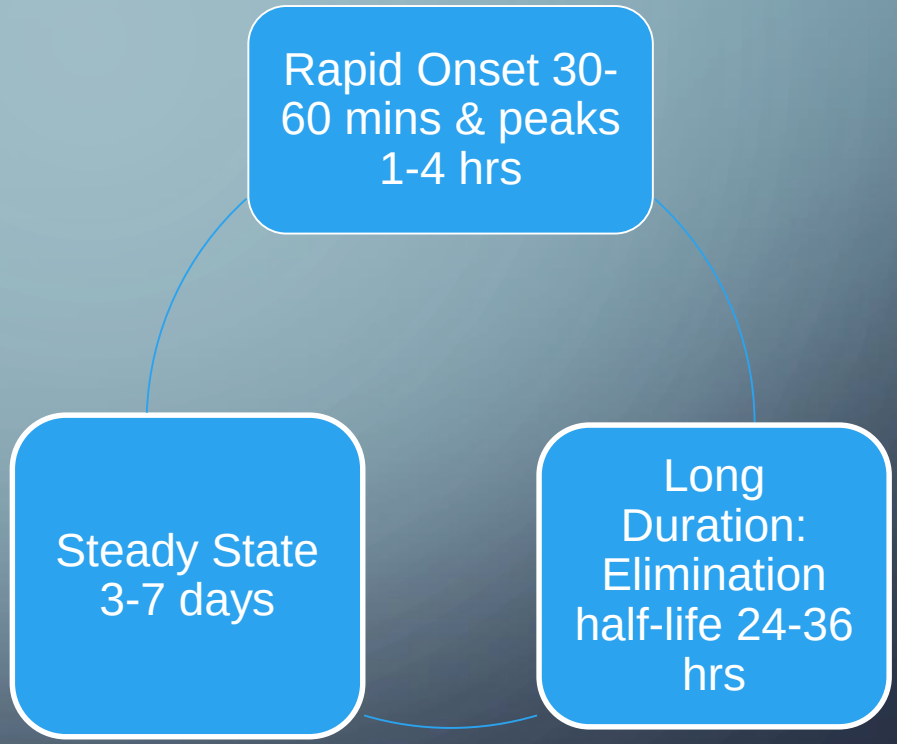
HOW SAFE IS BUPRENORPHINE?



DURATION OF ACTION OF SL BUP/NAL

Why is Naloxone in Bup/Nal?

-Prevents Diversion if Injected as will cause withdrawal
-When taken SL Naloxone has no effect due to first past effect of liver



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

WHAT IS BUP/NAL INDUCED PRECIPITATED WITHDRAWAL?

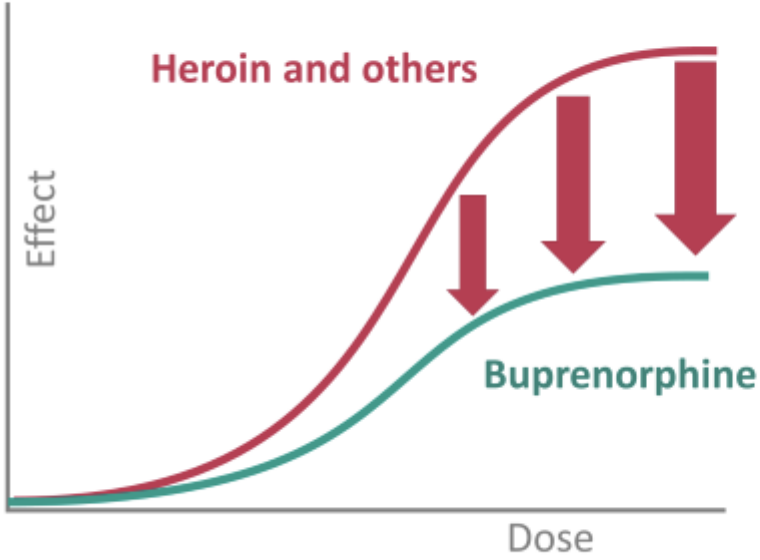
Sudden onset of severe withdrawal symptoms if BUP/NAL is administered too soon after a sufficient dose of full opioid agonist (ie. fentanyl) has been taken

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

Buprenorphine is introduced



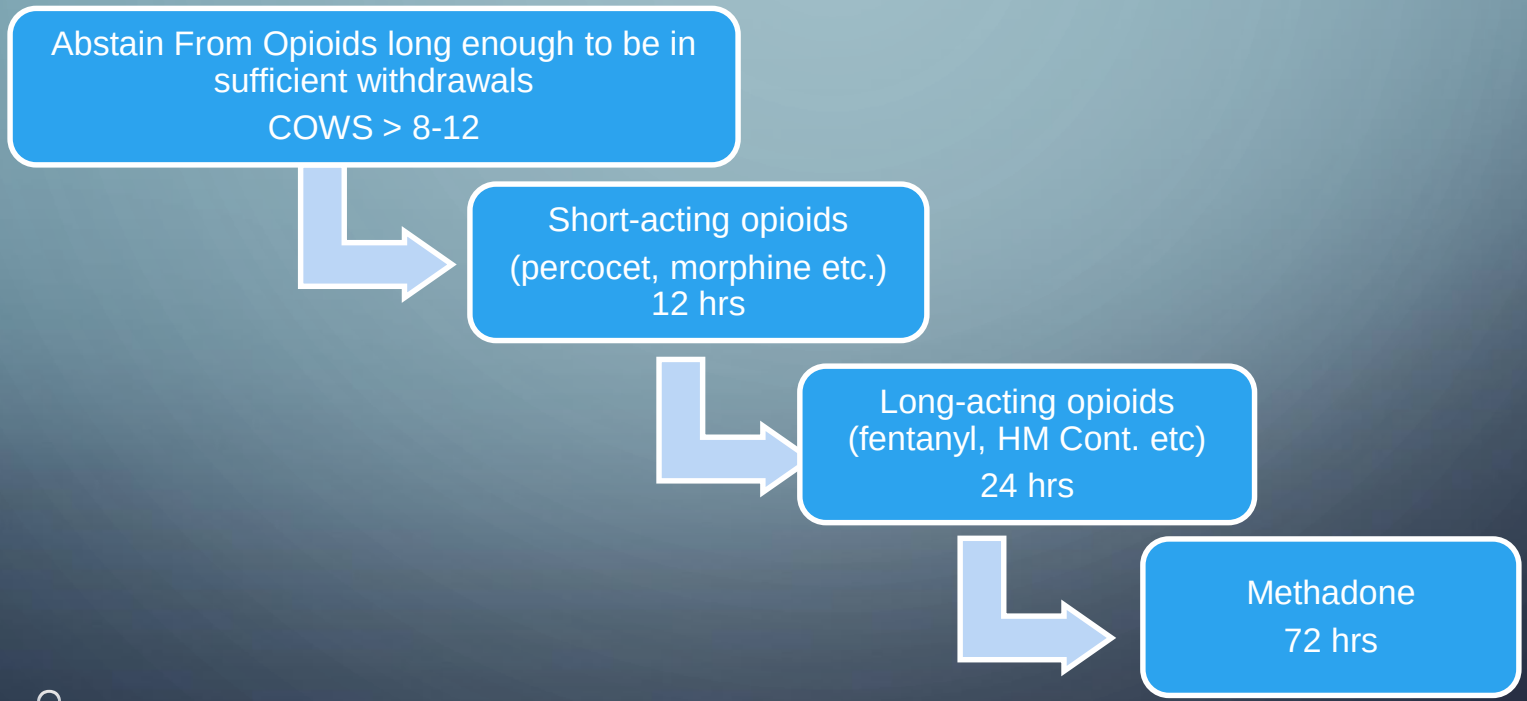
Partial activation

- Experienced as withdrawal
- Antagonist effect

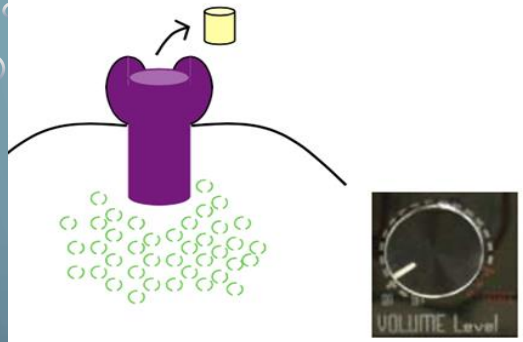
Walsh, S. L., & Eissenberg, T. (2003). The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. Drug and alcohol dependence, 70(2), S13-S27.

PSYCHOPHARMACOLOGY INSTITUTE

PREVENTING PRECIPITATED WITHDRAWAL



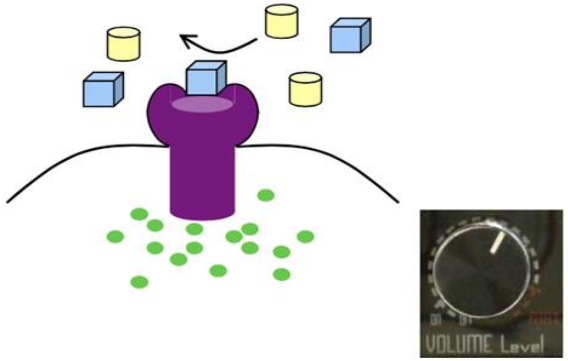
TYPICAL INDUCTION WITH BUP/NAL



Withdrawal

Most receptors unbound

"Volume" on low



Buprenorphine

Binds preferentially to receptors

"Volume" on medium

Induction:

relative to withdrawal, Buprenorphine "turns on" receptors more so patients feel better

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

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 Haldol or Olanzapine

CAbridge.org

LouJu.org

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

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 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

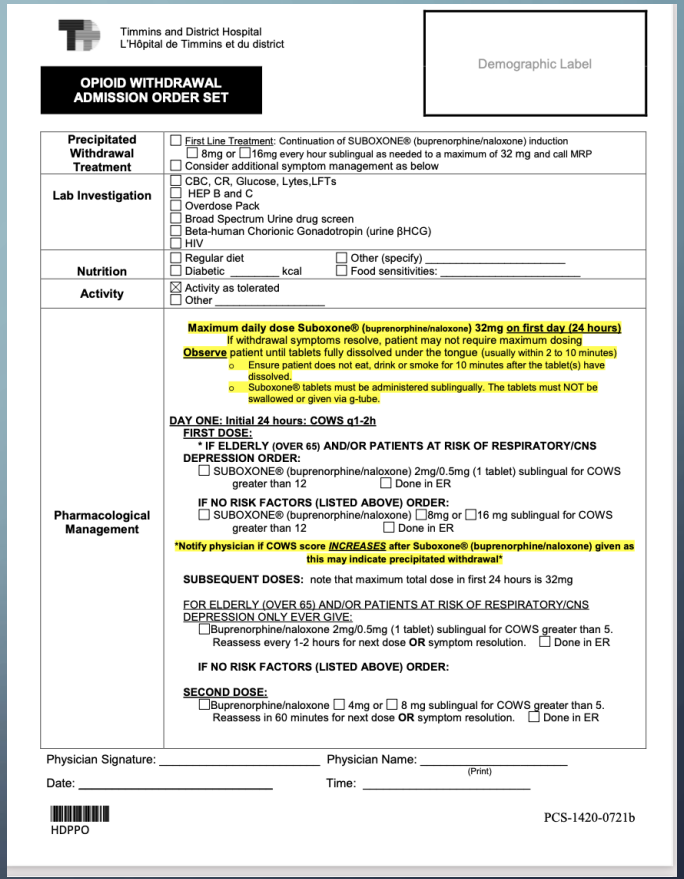
GAME CHANGER: MACRODOSING, HERE WE COME!

- Maximum daily dosing: 32 mg
  - Sometimes higher during stabilization
- Rapid titration with macrodosing
  - Day 1: COWS>12 + no fentanyl use >24 hrs
  - Dosing: 16/8/8 mg q1h
  - Total dose over 3 hours = 32mg
- Early depot-buprenorphine
  - 24-72 hours after first sublingual buprenorphine-naloxone dose (can you believe it!!!!)

Within 3 hours 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.org
5. Mariani JJ et alAm J Addict. 2021;1-7.

ORDER SETS



Timmins and District Hospital
L'Hôpital de Timmins et du district

Demographic Label

OPIOID WITHDRAWAL ADMISSION ORDER SET

Precipitated Withdrawal Treatment	☐ First Line Treatment: Continuation of SUBOXONE® (buprenorphine/naloxone) induction ☐ 8mg or ☐16mg every hour sublingual as needed to a maximum of 32 mg and call MRP ☐ Consider additional symptom management as below
Lab Investigation	☐ CBC, CR, Glucose, Lytes,LFTs ☐ HEP B and C ☐ Overdose Pack ☐ Broad Spectrum Urine drug screen ☐ Beta-human Chorionic Gonadotropin (urine βHCG) ☐ HIV
Nutrition	☐ Regular diet ☐ Other (specify) _____ ☐ Diabetic _____ kcal ☐ Food sensitivities: _____
Activity	☒ Activity as tolerated ☐ Other _____
Pharmacological Management	**Maximum daily dose Suboxone® (buprenorphine/naloxone) 32mg on first day (24 hours)** If withdrawal symptoms resolve, patient may not require maximum dosing **Observe** patient until tablets fully dissolved under the tongue (usually within 2 to 10 minutes) o Ensure patient does not eat, drink or smoke for 10 minutes after the tablet(s) have dissolved. o Suboxone® tablets must be administered sublingually. The tablets must NOT be swallowed or given via g-tube. **DAY ONE: Initial 24 hours: COWS q1-2h** **FIRST DOSE:** *** IF ELDERLY (OVER 65) AND/OR PATIENTS AT RISK OF RESPIRATORY/CNS DEPRESSION ORDER:** ☐ SUBOXONE® (buprenorphine/naloxone) 2mg/0.5mg (1 tablet) sublingual for COWS greater than 12 ☐ Done in ER **IF NO RISK FACTORS (LISTED ABOVE) ORDER:** ☐ SUBOXONE® (buprenorphine/naloxone) ☐8mg or ☐16 mg sublingual for COWS greater than 12 ☐ Done in ER ***Notify physician if COWS score *INCREASES* after Suboxone® (buprenorphine/naloxone) given as this may indicate precipitated withdrawal*** **SUBSEQUENT DOSES:** note that maximum total dose in first 24 hours is 32mg FOR ELDERLY (OVER 65) AND/OR PATIENTS AT RISK OF RESPIRATORY/CNS DEPRESSION ONLY EVER GIVE: ☐Buprenorphine/naloxone 2mg/0.5mg (1 tablet) sublingual for COWS greater than 5. Reassess every 1-2 hours for next dose **OR** symptom resolution. ☐ Done in ER **IF NO RISK FACTORS (LISTED ABOVE) ORDER:** **SECOND DOSE:** ☐Buprenorphine/naloxone ☐ 4mg or ☐ 8 mg sublingual for COWS greater than 5. Reassess in 60 minutes for next dose **OR** symptom resolution. ☐ Done in ER

Physician Signature: _____ Physician Name: _____ (Print)

Date: _____ Time: _____

HDPPO

PCS-1420-0721b

CLINICAL OBSERVATIONS SUPPORT MACRODOSING

- We observed no AEs after treating over 100 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

Macrodosing can potentially circumvent precipitated withdrawal

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

High Dose BUP/NAL 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 prior to engagement and follow up

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

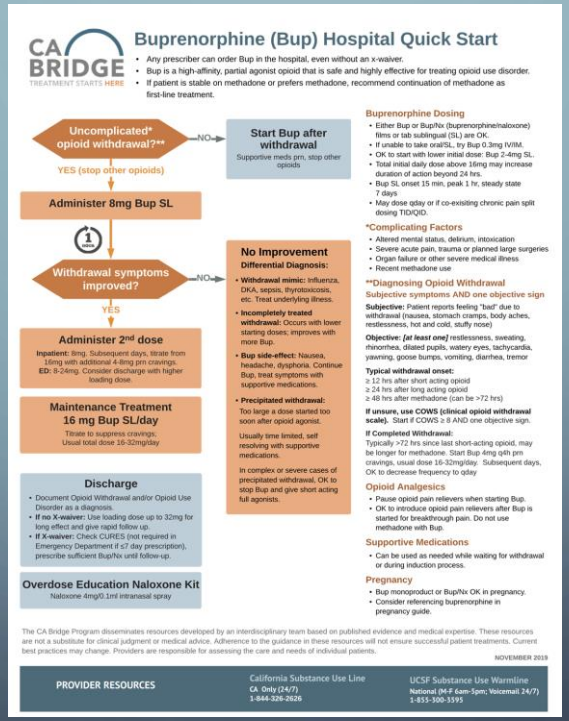
Jamshid Ahmadi[1*], Mina Sefidfard Jahromi[1], Dara Ghahremani[2] and Edythe D. London[2,3,4]

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

Shiraz University, Iran

PROTOCOLS FOR MACRODOSING

8-24 mg
May need higher loading dose 32 mg



CA BRIDGE
TREATMENT STARTS HERE

Buprenorphine (Bup) Hospital Quick Start

- Any prescriber can order Bup in the hospital, even without an x-waiver.
- Bup is a high-affinity, partial agonist opioid that is safe and highly effective for treating opioid use disorder.
- If patient is stable on methadone or prefers methadone, recommend continuation of methadone as first-line treatment.

Uncomplicated* opioid withdrawal?** — NO → **Start Bup after withdrawal**
Supportive meds prn; stop other opioids

YES (stop other opioids)

Administer 8mg Bup SL

1 DOSE

Withdrawal symptoms improved? — NO →

No Improvement
Differential Diagnosis:
- **Withdrawal mimic:** Influenza, DKA, sepsis, thyrotoxicosis, etc. Treat underlying illness.
- **Incompletely treated withdrawal:** Occurs with lower starting doses; improves with more Bup.
- **Bup side-effect:** Nausea, headache, dysphoria. Continue Bup, treat symptoms with supportive medications.
- **Precipitated withdrawal:** Too large a dose started too soon after opioid agonist.

Usually time limited, self resolving with supportive medications.

In complex or severe cases of precipitated withdrawal, OK to stop Bup and give short acting full agonists.

YES

Administer 2nd dose
Inpatient: 8mg. Subsequent days, titrate from 16mg with additional 4-8mg prn cravings.
ED: 8-24mg. Consider discharge with higher loading dose.

Maintenance Treatment 16 mg Bup SL/day
Titrate to suppress cravings.
Usual total dose 16-32mg/day

Discharge
- Document Opioid Withdrawal and/or Opioid Use Disorder as a diagnosis.
- **If no X-waiver:** Use loading dose up to 32mg for long effect and give rapid follow up.
- **If X-waiver:** Check CURES (not required in Emergency Department if ≤7 day prescription), prescribe sufficient Bup/Nx until follow-up.

Overdose Education Naloxone Kit
Naloxone 4mg/0.1ml intranasal spray

Buprenorphine Dosing
- Either Bup or Bup/Nx (buprenorphine/naloxone) films or tab sublingual (SL) are OK.
- If unable to take oral/SL, try Bup 0.3mg IV/IM.
- OK to start with lower initial dose: Bup 2-4mg SL.
- Total initial daily dose above 16mg may increase duration of action beyond 24 hrs.
- Bup SL onset 15 min, peak 1 hr, steady state 7 days
- May dose qday or if co-exisiting chronic pain split dosing TID/QID.

*Complicating Factors
- Altered mental status, delirium, intoxication
- Severe acute pain, trauma or planned large surgeries
- Organ failure or other severe medical illness
- Recent methadone use

**Diagnosing Opioid Withdrawal
Subjective symptoms AND one objective sign

Subjective: Patient reports feeling "bad" due to withdrawal (nausea, stomach cramps, body aches, restlessness, hot and cold, stuffy nose)

Objective: *[at least one]* restlessness, sweating, rhinorrhea, dilated pupils, watery eyes, tachycardia, yawning, goose bumps, vomiting, diarrhea, tremor

Typical withdrawal onset:
≥ 12 hrs after short acting opioid
≥ 24 hrs after long acting opioid
≥ 48 hrs after methadone (can be >72 hrs)

If unsure, use COWS (clinical opioid withdrawal scale). Start if COWS ≥ 8 AND one objective sign.

If Completed Withdrawal:
Typically >72 hrs since last short-acting opioid, may be longer for methadone. Start Bup 4mg q4h prn cravings, usual dose 16-32mg/day. Subsequent days, OK to decrease frequency to qday

Opioid Analgesics
- Pause opioid pain relievers when starting Bup.
- OK to introduce opioid pain relievers after Bup is started for breakthrough pain. Do not use methadone with Bup.

Supportive Medications
- Can be used as needed while waiting for withdrawal or during induction process.

Pregnancy
- Bup monoproduct or Bup/Nx OK in pregnancy.
- Consider referencing buprenorphine in pregnancy guide.

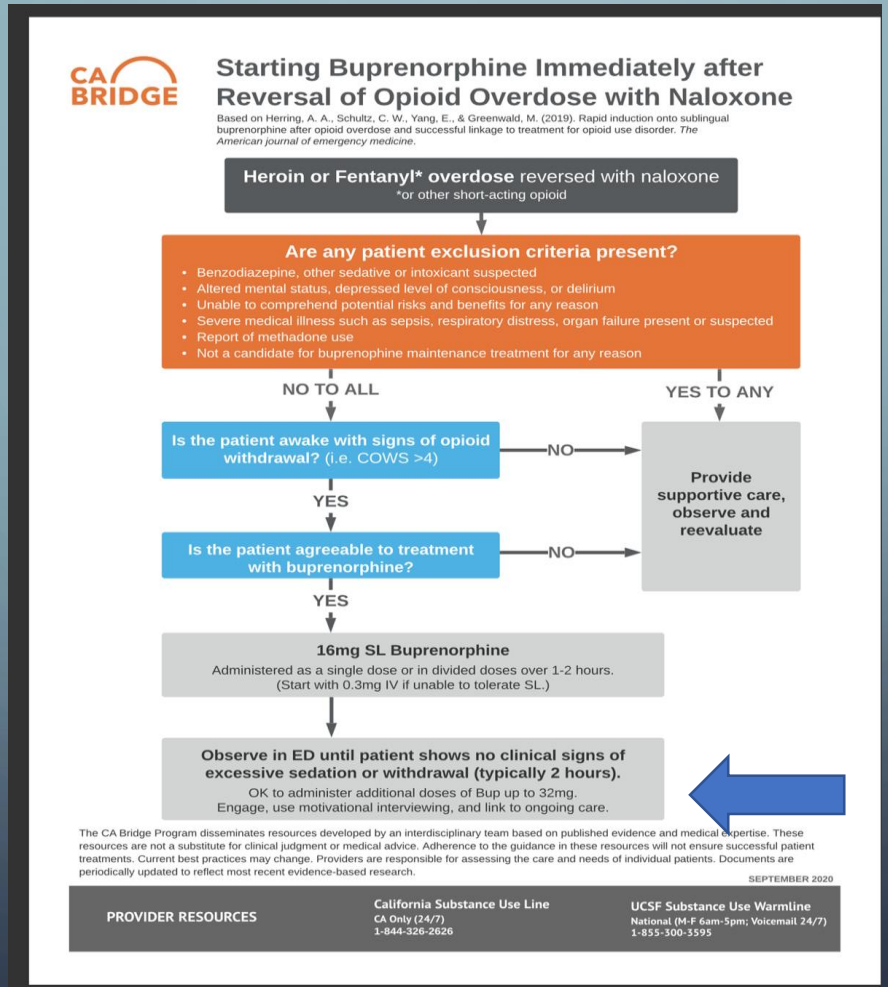
NOVEMBER 2019

PROVIDER RESOURCES

California Substance Use Line
CA Only (24/7)
1-844-326-2626

UCSF Substance Use Warmline
National (M-F 6am-5pm; Voicemail 24/7)
1-855-300-3595

PROTOCOLS FOR MACRODOSING



CA BRIDGE

Starting Buprenorphine Immediately after Reversal of Opioid Overdose with Naloxone

Based on Herring, A. A., Schultz, C. W., Yang, E., & Greenwald, M. (2019). Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder. *The American journal of emergency medicine*.

Heroin or Fentanyl* overdose reversed with naloxone
*or other short-acting opioid

Are any patient exclusion criteria present?

- Benzodiazepine, other sedative or intoxicant suspected
- Altered mental status, depressed level of consciousness, or delirium
- Unable to comprehend potential risks and benefits for any reason
- Severe medical illness such as sepsis, respiratory distress, organ failure present or suspected
- Report of methadone use
- Not a candidate for buprenophine maintenance treatment for any reason

NO TO ALL

YES TO ANY

Is the patient awake with signs of opioid withdrawal? (i.e. COWS >4)

NO

YES

Is the patient agreeable to treatment with buprenorphine?

NO

YES

Provide supportive care, observe and reevaluate

16mg SL Buprenorphine
Administered as a single dose or in divided doses over 1-2 hours.
(Start with 0.3mg IV if unable to tolerate SL.)

Observe in ED until patient shows no clinical signs of excessive sedation or withdrawal (typically 2 hours).
OK to administer additional doses of Bup up to 32mg.
Engage, use motivational interviewing, and link to ongoing care.

The CA Bridge Program disseminates resources developed by an interdisciplinary team based on published evidence and medical expertise. These resources are not a substitute for clinical judgment or medical advice. Adherence to the guidance in these resources will not ensure successful patient treatments. Current best practices may change. Providers are responsible for assessing the care and needs of individual patients. Documents are periodically updated to reflect most recent evidence-based research.

SEPTEMBER 2020

PROVIDER RESOURCES

California Substance Use Line
CA Only (24/7)
1-844-326-2626

UCSF Substance Use Warmline
National (M-F 6am-5pm; Voicemail 24/7)
1-855-300-3595

Up to 32 mg

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?

EVIDENCE FOR EARLY DEPO-BUP ADMINISTRATION

Initiating Monthly Buprenorphine Injection After Single Dose of Sublingual Buprenorphine

Katharina Wiest[1] | Stephanie Strafford[2] | Sunita Shinde[2] | Amy Heath[2] | Robert Dobbins[2] | Howard Hassman[3] | 1. Pacific Vascular Specialists, Portland, OR | 2. Indivior, Inc., Richmond, VA 3. Hassman Research Institute LLC, Marlton, NJ

Aims

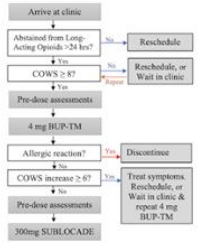
Buprenorphine extended-release injection (SUBLOCADE) is indicated for treatment of moderate/severe opioid use disorder (OUD) in patients who have initiated treatment with transmucosal buprenorphine (BUP-TM), followed by dose adjustment for a minimum of 7 days.[1] In the current medical climate, there 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 transmucosal (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 counselling 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=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; TM=transmucosal

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	Transmucosal Buprenorphine Enrolled Population (N=26)	SUBLOCADE 300 mg Safety Analysis Set (N=24)
Age (Years)	41.4±14.05	40.0±13.45
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	13 (50.0%)	13 (54.2%)
Other	2 (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/m²)	22.61±3.954	22.60±4.058
Opioid Use		
Opioids – Lifetime Use (years)	15.80±15.114	13.88±13.542
Opioids – Last 30 days (days)	28.96±3.693	28.88±3.837
Opioids – Intravenous Route	7 (26.9%)	6 (25.0%)
Day 1 Drug Screen		
Opioids		5 (20.8%)
Morphine		5 (20.8%)
Methadone		1 (4.2%)
Fentanyl		17 (70.8%)
Oxycodone		3 (12.5%)

Values are mean±SD or Number of participants (%)

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

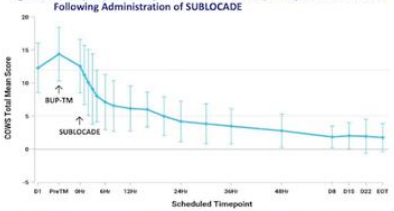
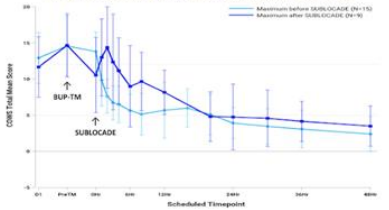


Table 2 COWS Scores by Severity and Timing of Maximum Severity Occurrence and Increase of ≥6 [Number of participants (%)]

	Participants Receiving SUBLOCADE (N=24)	
	Maximum Severity	Increase of ≥6
Pre-SUBLOCADE	15 (62.5%)	1 (4.2%)
Mild	6	0
Moderate	9	1
1 hour post-SUBLOCADE	2 (8.3%)	1 (4.2%)
Mild	1	1
Moderate	1	0
2 hour post-SUBLOCADE	5 (20.8%)	1 (4.2%)
Mild	2	0
Moderate	2	0
Moderately Severe	1	1
3 hour post-SUBLOCADE	2 (8.3%)	
Mild	1	0
Moderate	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)	
	All TEAEs	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%]), ibuprofen for pain/body aches (9 [37.5%]) and trazadone 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

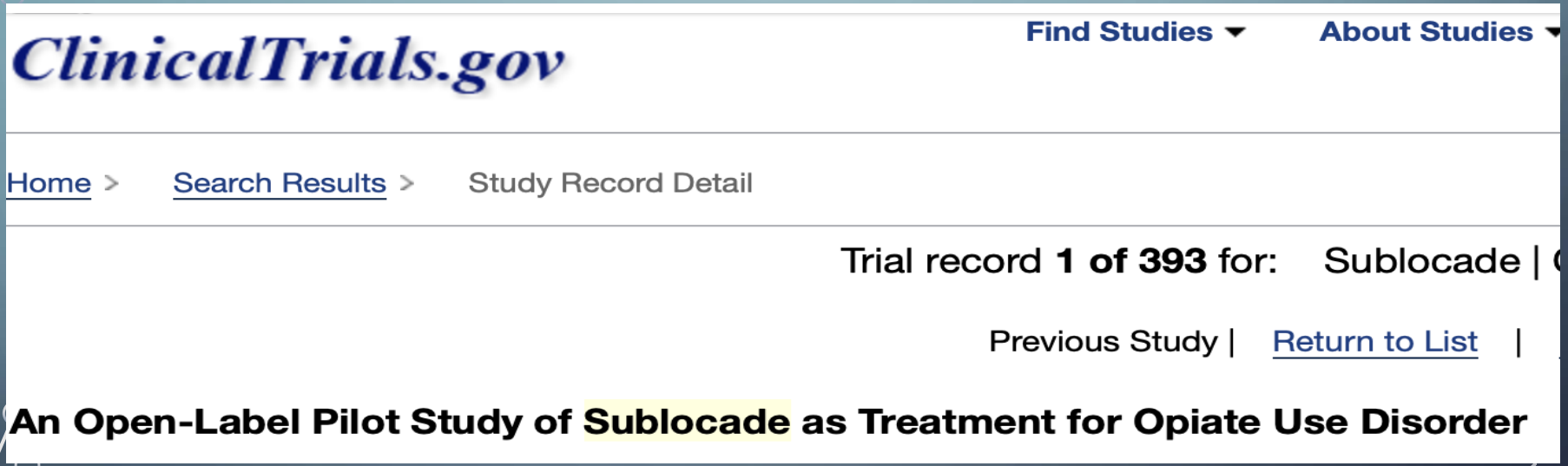
- Initiating SUBLOCADE 300 mg following a single 4 mg dose of BUP-TM indicated a safety profile similar to that observed with SUBLOCADE induction per current labeling.[1]
- After SUBLOCADE injection, withdrawal symptoms and opioid craving scores improved within 12h. Improvements were sustained for 4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

References

1. SUBLOCADE United States Prescribing Information, February 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022410s000lbl.pdf accessed October 30, 2020.
2. Dunlop A, Lokuge B, Masters D, et al. Challenges in maintaining treatment services for people who use drugs during the COVID-19 pandemic. Harm Reduct J. 2020;17:26.
3. Farhoudian A, Baldacchino A, Clark N, et al. COVID-19 and Substance Use Disorders: Recommendations to a Comprehensive Healthcare 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, 28 JUNE 2021 Virtual Poster Q&A Session III: Opiates/Opioids

EVIDENCE FOR EARLY DEPO-BUP ADMINISTRATION



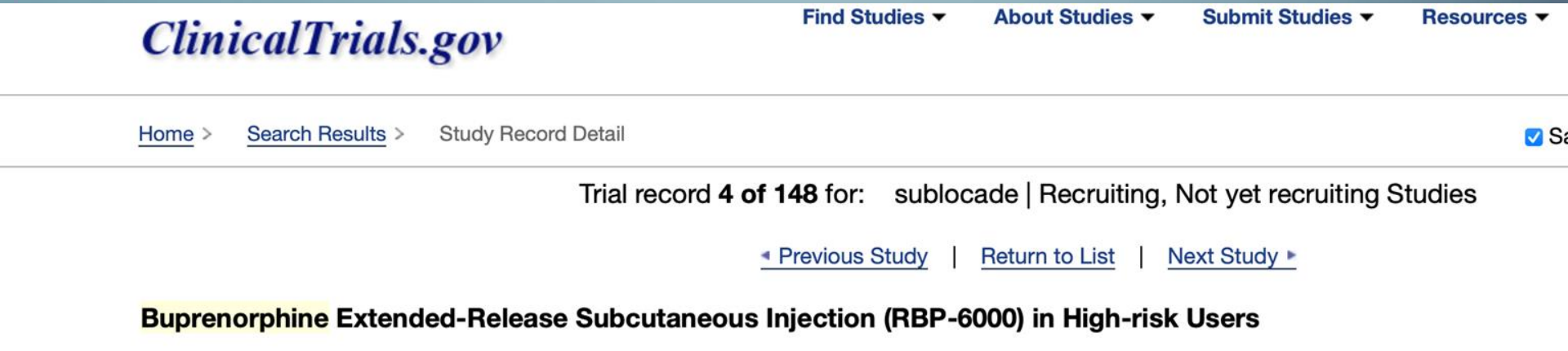
EVIDENCE FOR EARLY DEPO-BUP ADMINISTRATION

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 LMHC[1] | Samuel C. Podell BS[3] | Daniel J. Brooks LCSW[1] | 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

EVIDENCE FOR EARLY DEPO-BUP ADMINISTRATION



SUBLOCADE SEEMS TO 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 Lee[1] | Christopher Fraser[2] | Tazmin Merali[3] | Marie-Christine Mormont[4] | Brian Conway[5]

[1]London RAAM Clinic, London, ON, Canada | [2]Cool Aid Community Health Center, Victoria, BC, Canada | [3]Drug Intelligence Inc, Toronto, ON, Canada | [4]Indivior Inc, Montreal, QC, Canada | [5]Vancouver Infectious Diseases Center and Simon Fraser University, Vancouver, BC, Canada

Background

OVID-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):

- MD assigns to cohort on intend 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%)**
- Analysis based on ITT

Other study investigators Dr Raj Klaire, Surrey, British Columbia | Dr Lori Regenstreif, Hamilton, Ontario | Dr Jaswinder Dhillon, Hamilton, Ontario | Dr Brooke Noftle, London, Ontario

*Start of pandemic-related restrictions in access to MCP

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 – 64 (**39**)	19 – 61 (**38**)	22 – 64 (**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	17 (41%)	22 (43%)	8 (17%)	47 (34%)
Unemployed	12 (29%)	21 (41%)	23 (48%)	56 (40%)
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%)	10 (21%)	30 (21%)

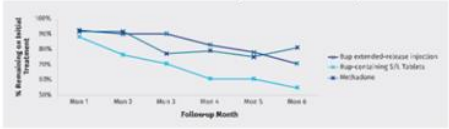
Risk Factors & Concomitant Medical Conditions

	Buprenorphine Extended-Release Injection	Buprenorphine-Containing S/L Tablets	Methadone	Total
Number of Patients	41	51	48	140
Opioid Abuse History:				
< 5 years	9 (24%)	19 (37%)	5 (10%)	33 (24%)
5 – 10 years	13 (32%)	11 (22%)	11 (23%)	55 (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 Overdose Events	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 (25%)	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	13 (32%)	6 (12%)	12 (25%)	31 (22%)

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 – 230 mg	-
Adherence (patients with >5 out of 6 months of documented treatment)	36 (88%)	34 (67%)	35 (73%)	105 (75%)
Retention (patients maintained or same treatment at month 6)	29 (71%)	28 (55%)	39 (81%)	96 (69%)

Patient Retention on Initial Treatment by Month of Follow-up



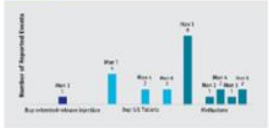
Patient Outcomes – Timing of Non-Fatal Overdose Events

	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 Injectable Opioid Use

Treatment Cohort	Patients with ≥ 1 Event
Buprenorphine injection	1 (5%)
Bup S/L Tablets	6 (19%)
Methadone	9 (21%)

Distribution of Reported Non-Fatal Overdose Events by Month and Treatment Cohort



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
Concurrent Substance Abuse:				
Self-Reported Opioid/Illicit Drug Use	24 (59%)	33 (65%)	45 (94%)	102 (73%)
Urine Positive for Fentanyl	13 (32%)	15 (29%)	35 (73%)	63 (45%)
Urine Positive for Non-Fentanyl Substance	22 (54%)	32 (63%)	38 (79%)	92 (66%)
Urine Positive for Illicit Substance	21 (51%)	34 (67%)	38 (79%)	93 (66%)
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 SL 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

Kenneth Lee
- Honoraria – Indivior, Knight; intends to make therapeutic recommendations for medications that have not received regulatory approval (ie, off-label use of medications)

Christopher Fraser
- Honoraria – Gilead, Indivior, ViiV; Advisory Boards – Gilead, Indivior; Funded Grants, Research or Clinical Trials – AbbVie, Canadian HIV Trials Network, Gilead, Merck, ViiV; intends to make therapeutic recommendations for medications that have not received regulatory approval (ie, off-label use of medications)

Tazmin Merali
- Study management and coordination – Drug Intelligence Inc

Marie-Christine Mormont
- Indivior employee, stock options owner

Brian Conway
- Honoraria – AbbVie, Gilead, Indivior, Merck; Advisory Boards – AbbVie, Gilead, Merck; Funded Grants, Research, or Clinical Trials – AbbVie, Gilead, Indivior, Merck, Roche; intends to make therapeutic recommendations for medications that have not received regulatory approval (ie, off-label use of medications)

CSAM-ISRCR 2021 Scientific Conference October 2021

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

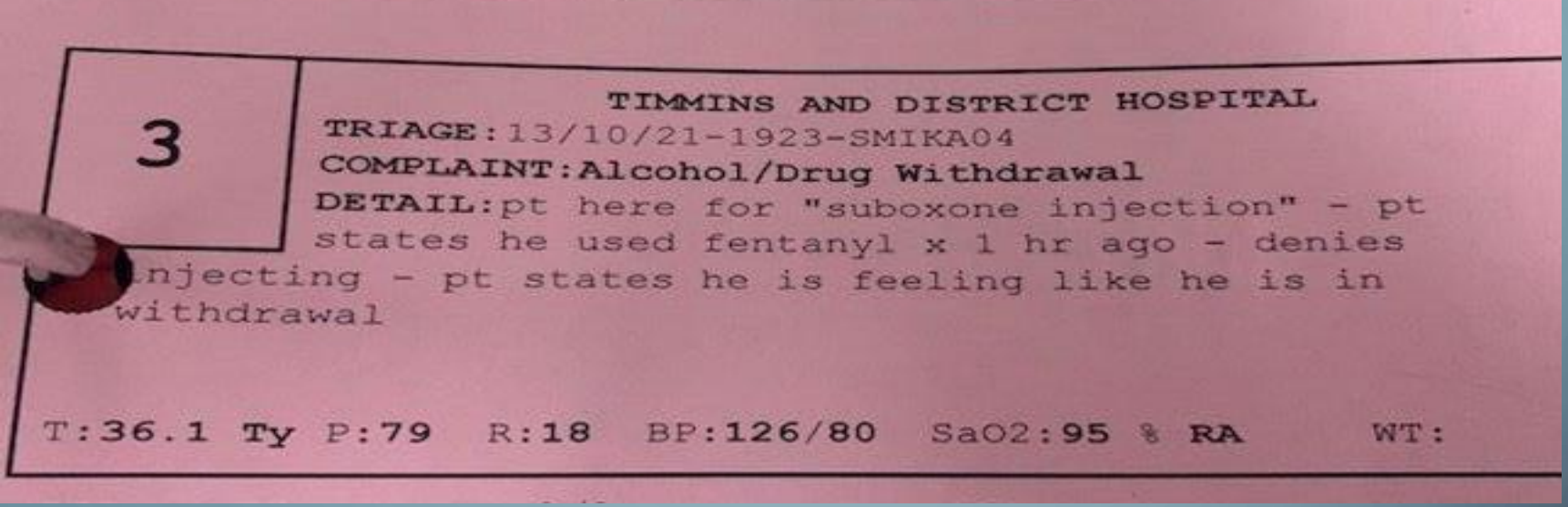
This is AMAZING, the change we are making for these patients.
-RN ICU

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

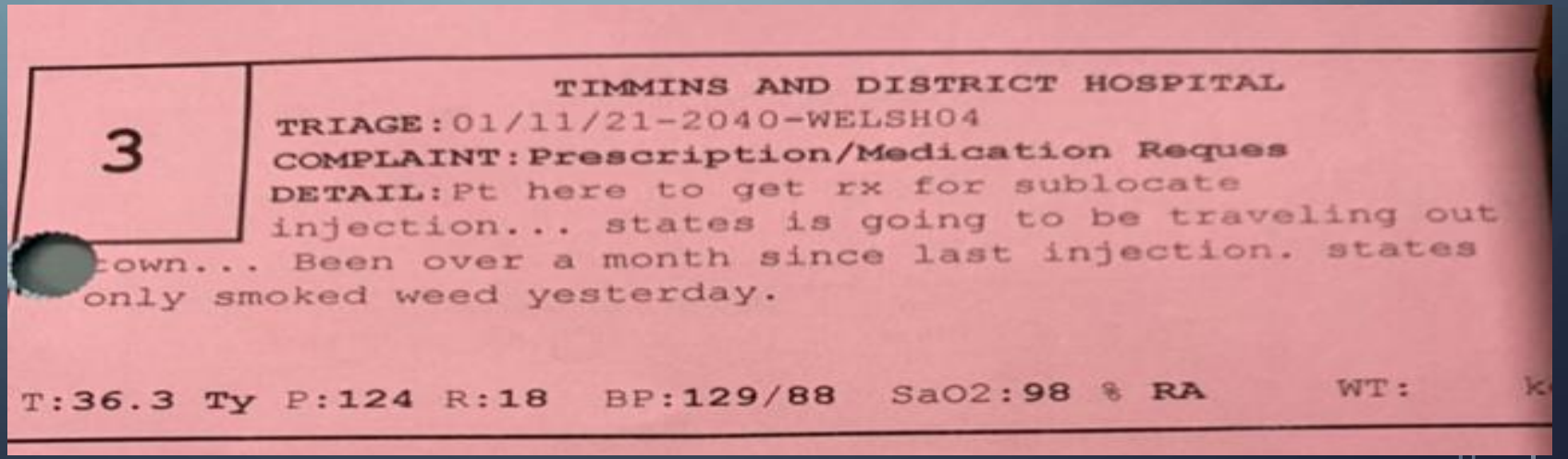


3

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 Reques
DETAIL:Pt here to get rx for sublocate injection... states is going to be traveling out 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:

TAKE HOME MESSAGES

- TREAT THEM AND STREET THEM CAN NO LONGER OCCUR
- 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
- IF TIMMINS IS DOING IT…SO CAN YOU AND SO SHOULD YOU !

TAKE HOME MESSAGES

- Listen to the patients
- Don’t be afraid to push larger “macrodoses” of SL bup/nlx for induction and PW
- 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

Q & A

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