Buprenorphine Initiation after Reversal of Opioid Overdose A New Standard Of Care

Andrew Herring, MD

CA BRIDGE
TREATMENT STARTS HERE

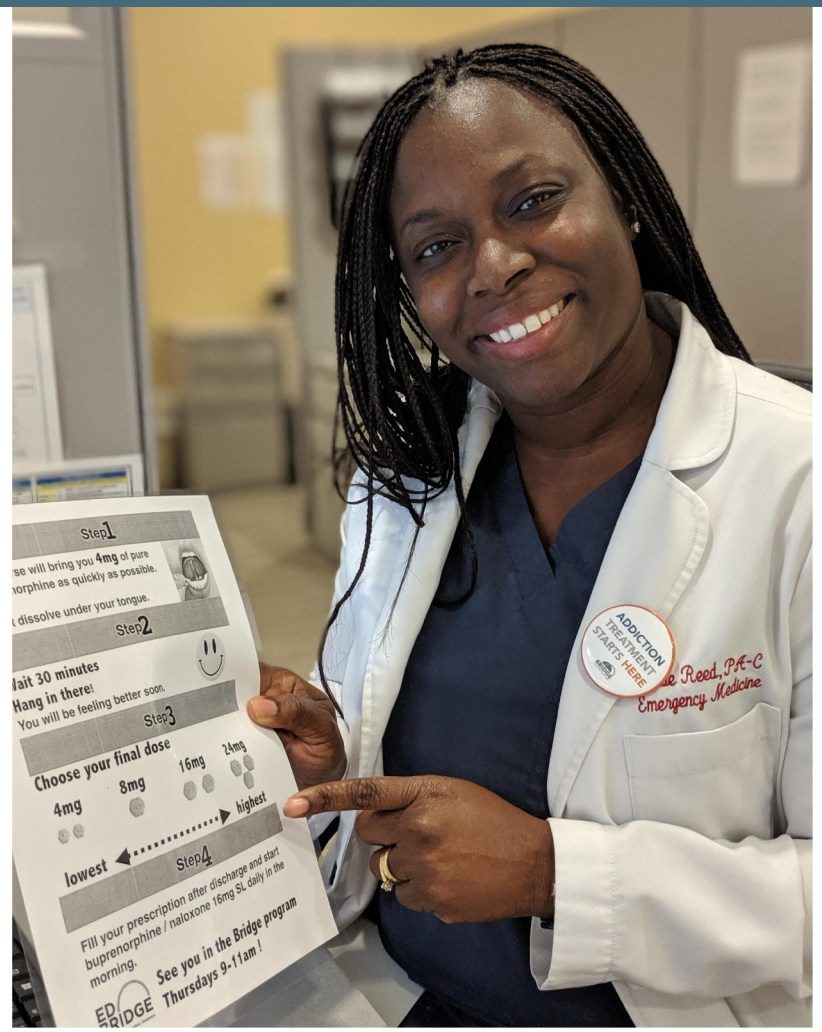
None of the presenters today have any financial disclosures.

Objectives

1. Discuss the pharmacology of buprenorphine relevant to treatment of overdose after naloxone reversal of opioid overdose.

1. Determine appropriate candidates for buprenorphine after naloxone reversal of opioid overdose.

Clinical Toolkit

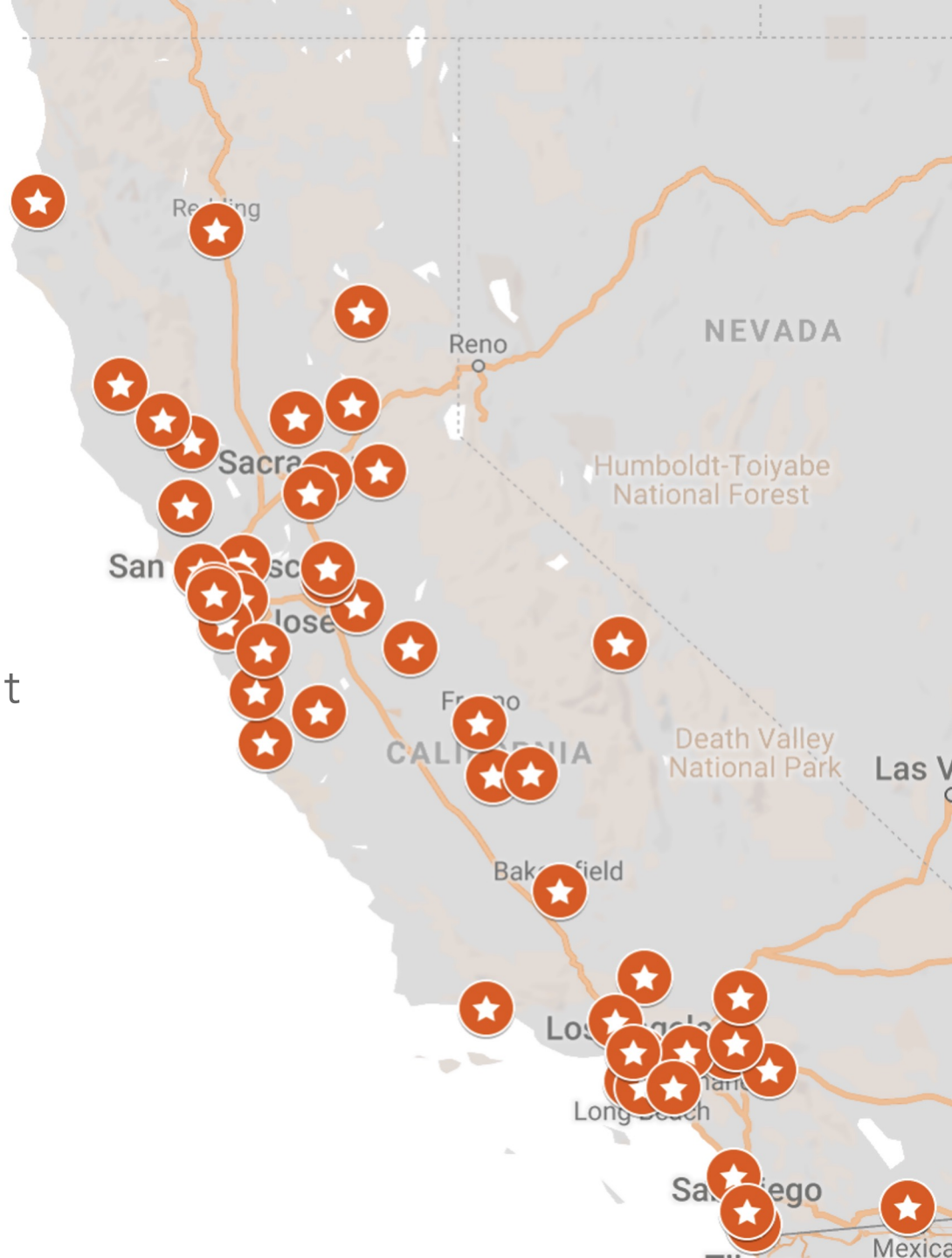


CA BRIDGE

TREATMENT STARTS HERE

Goal: 24-7 access to high quality treatment of substance use disorders (SUD) in all California hospitals by 2025.

Status: 50+ hospitals are currently access points for patients with SUD.



Changing Lives, Changing Health Care

9834

patients identified with OUD

6312

Patients provided with treatment

4486

Patients given a prescription for MAT

3930

Patients linked to follow-up MAT care

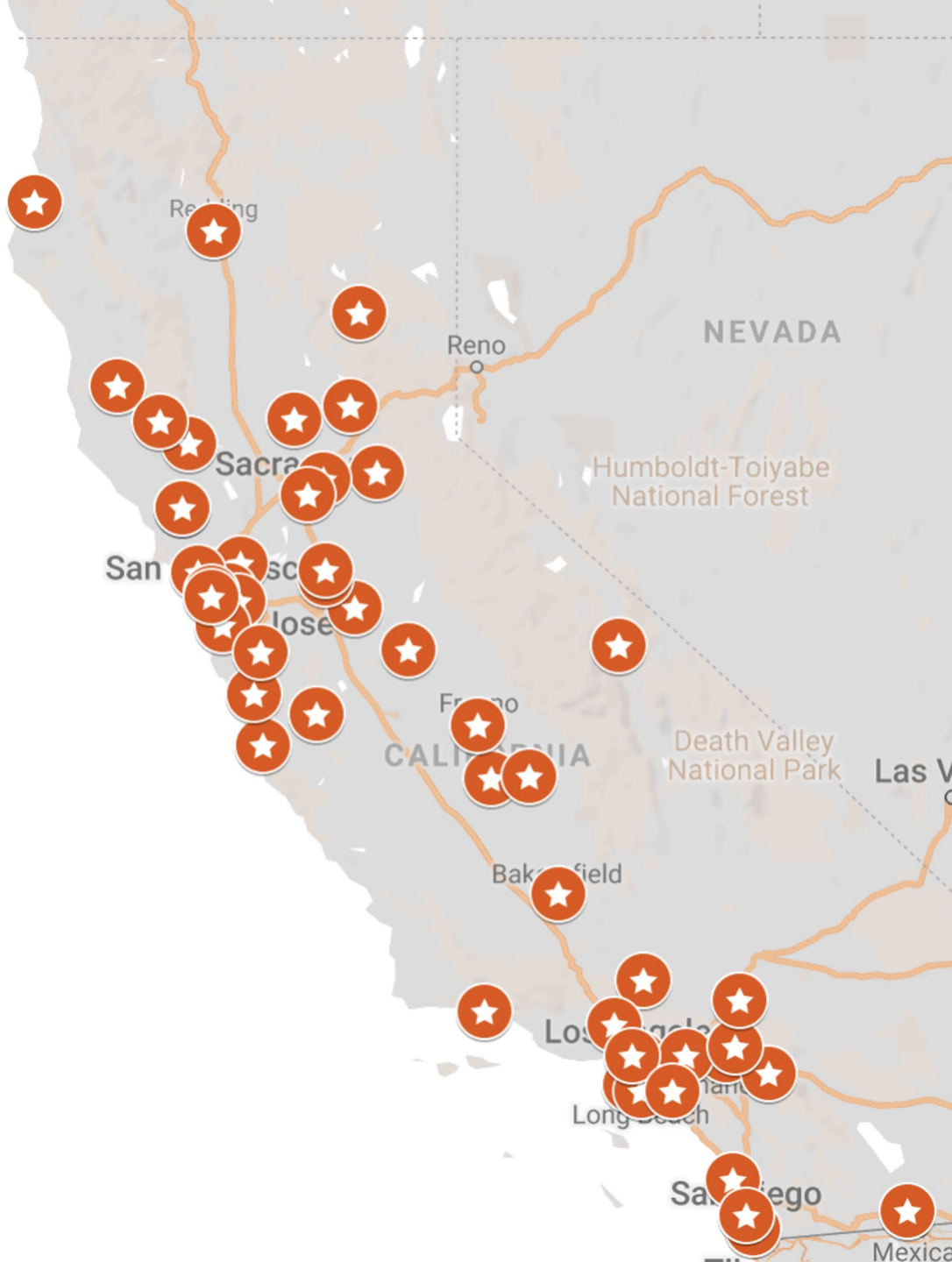
OUD Opioid Use Disorder
MAT Medication for Addiction Treatment

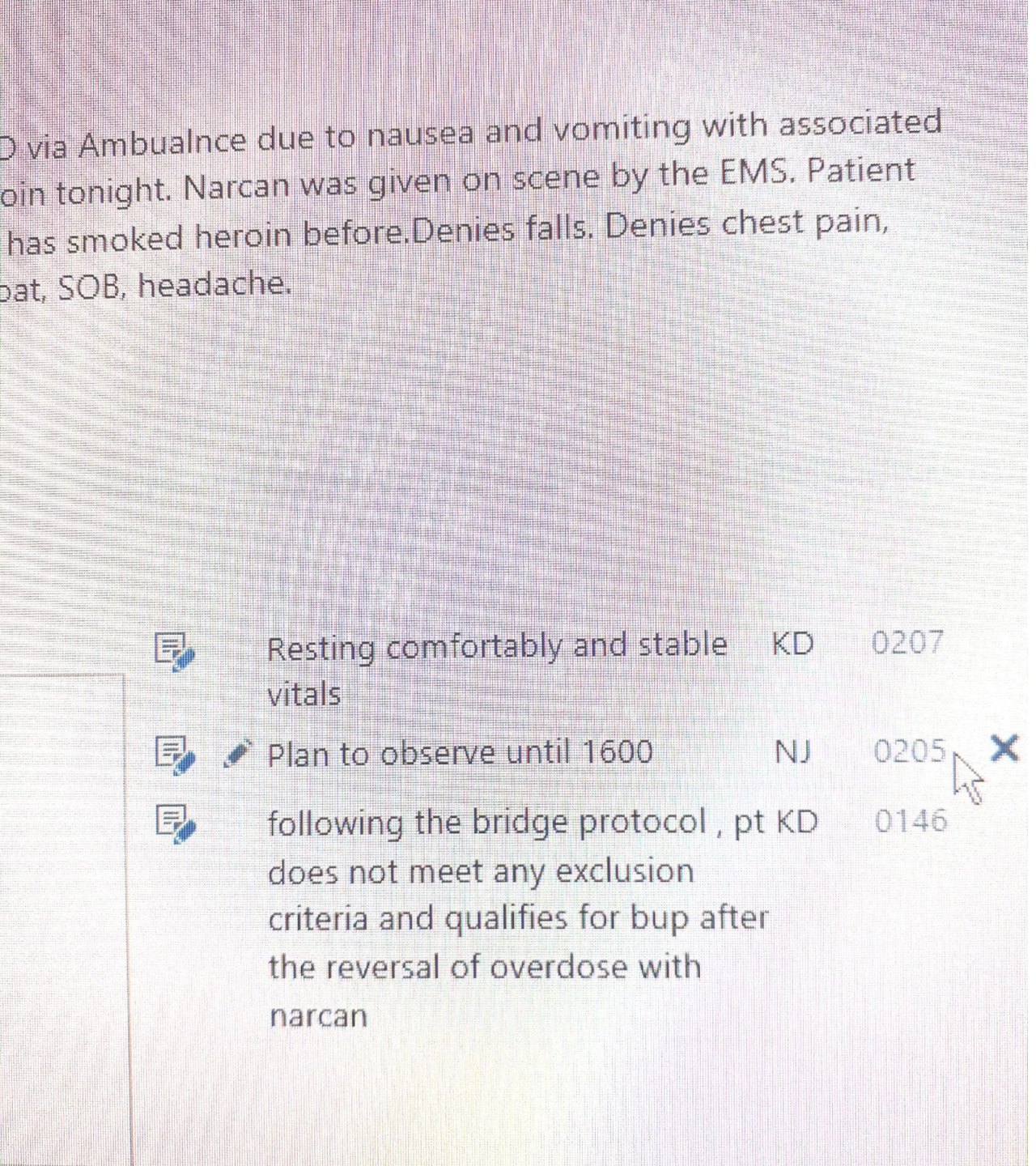
Cumulative totals across all reporting CA Bridge sites (n = 41) as of April 30, 2020

CA BRIDGE

TREATMENT STARTS HERE

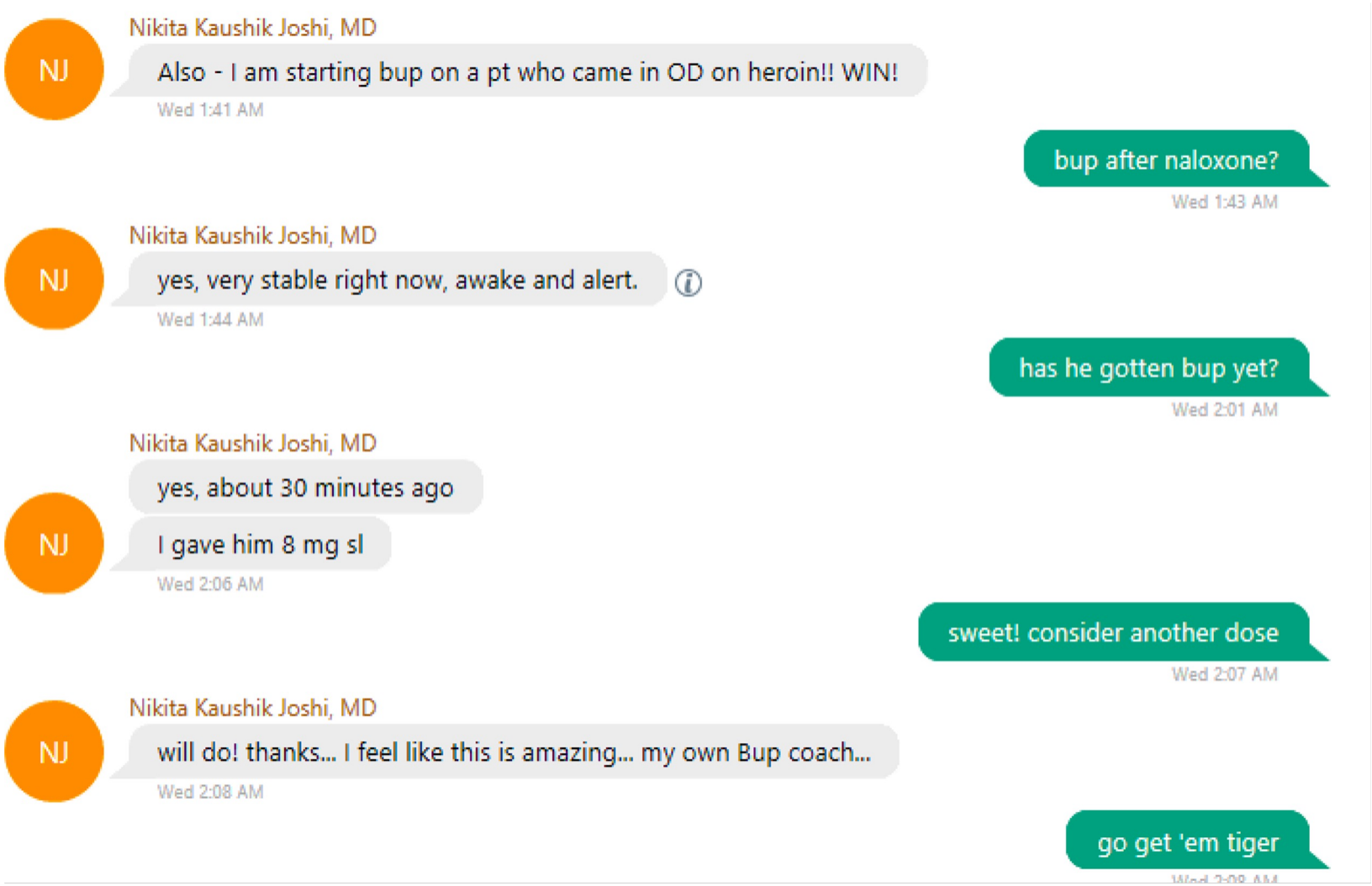
48 of 52 EDs report offering Buprenorphine after Opioid Overdose.

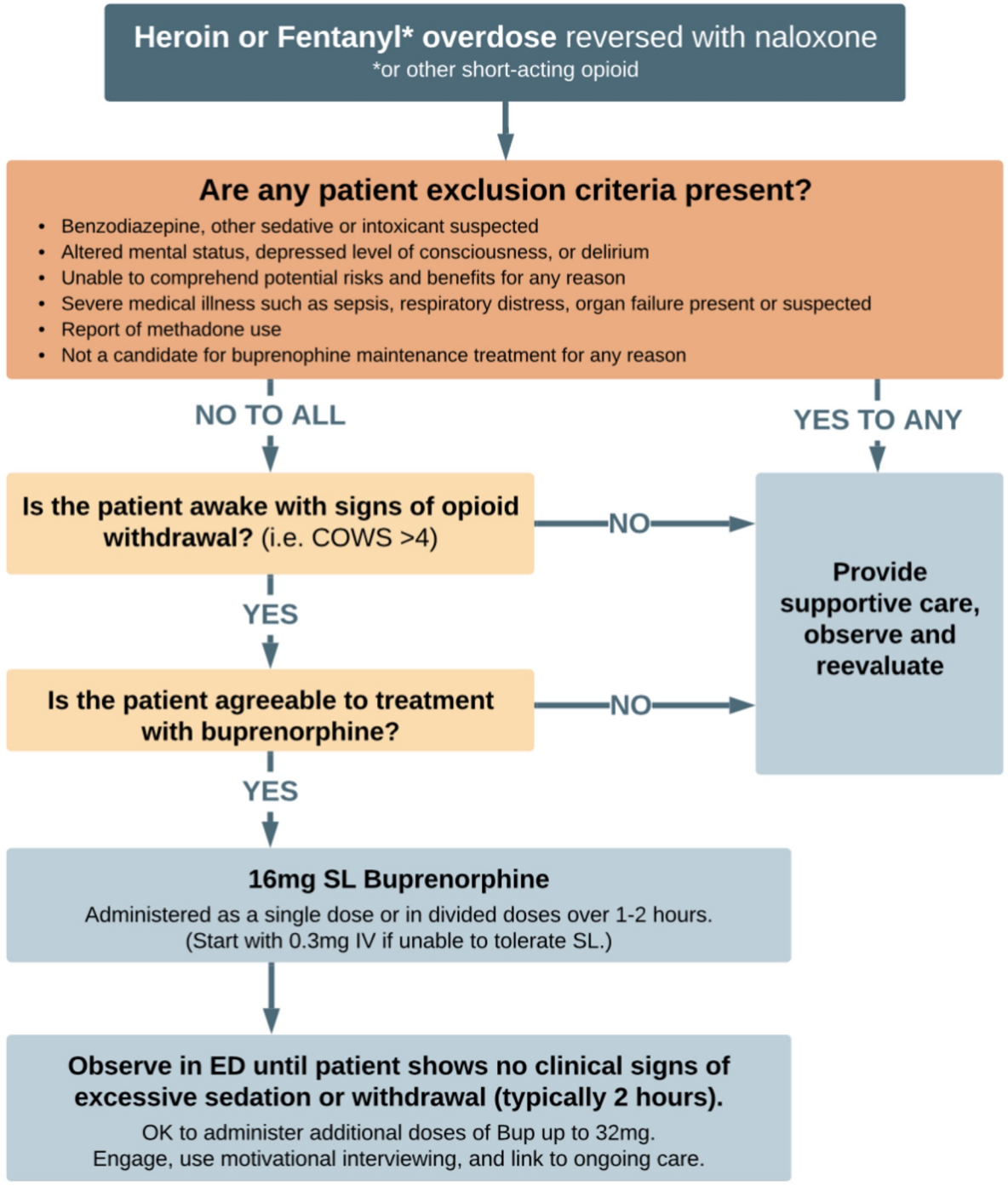




Bup After Overdose

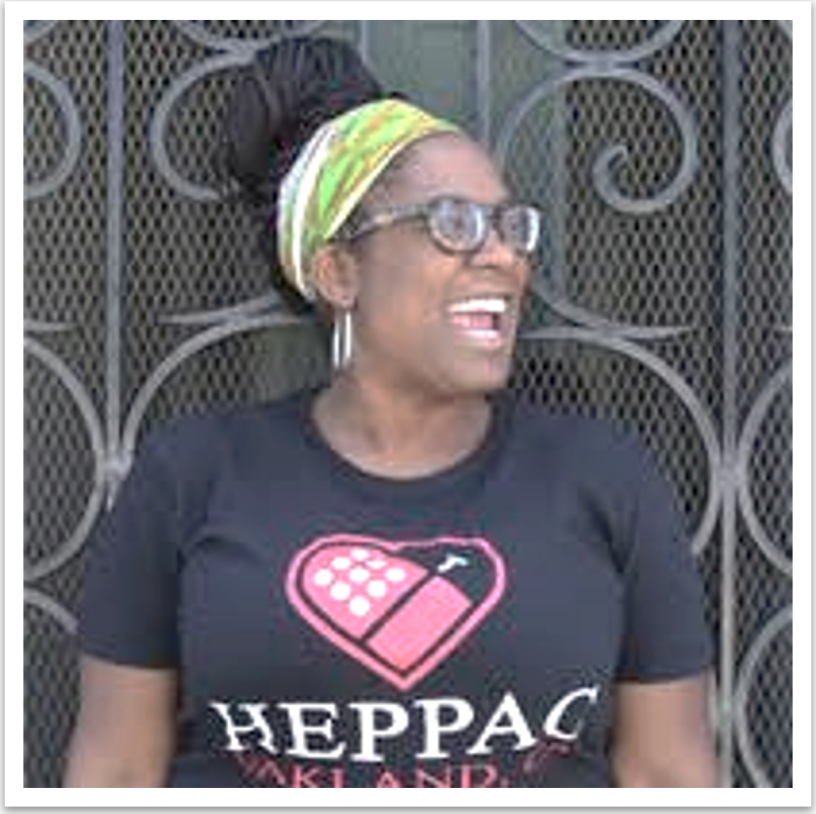
Bup After Overdose





Bup Induction after Overdose

"No Shit Science"



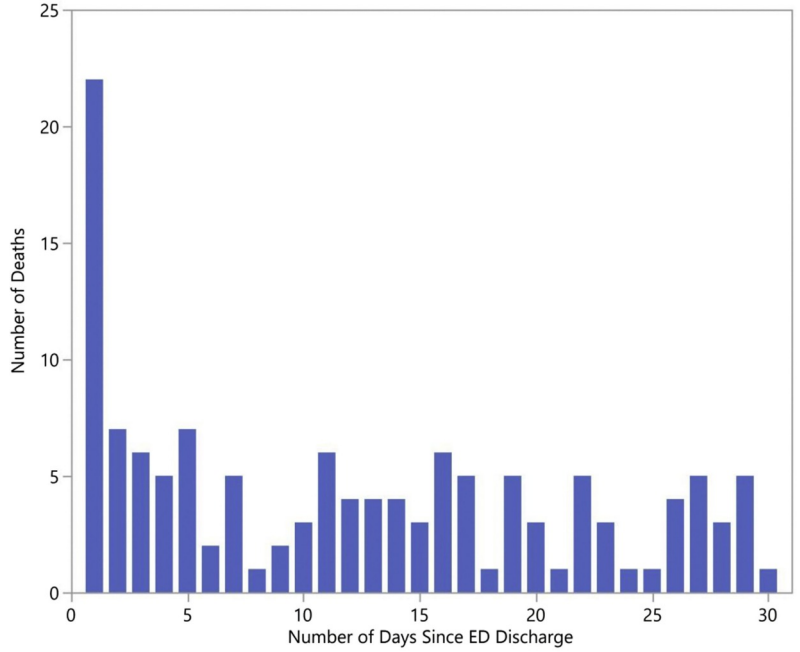
CA Bridge Delivers Addiction Treatments When it Matters Most

One-Year Mortality of Patients After Emergency Department Treatment for Nonfatal Opioid Overdose

Scott G. Weiner, MD, MPH[a,*], Olesya Baker, PhD[a], Dana Bernson, MPH[b], Jeremiah D. Schuur, MD, MHS[c]

- Study of patients treated in Massachusetts EDs for opioid overdose 2011-2015
- Illustrates the short-term increase in mortality risk post-ED discharge
  - Of patients that died, 20% died in the first month
  - Of those that died in the first month, 22% died within the first 2 days

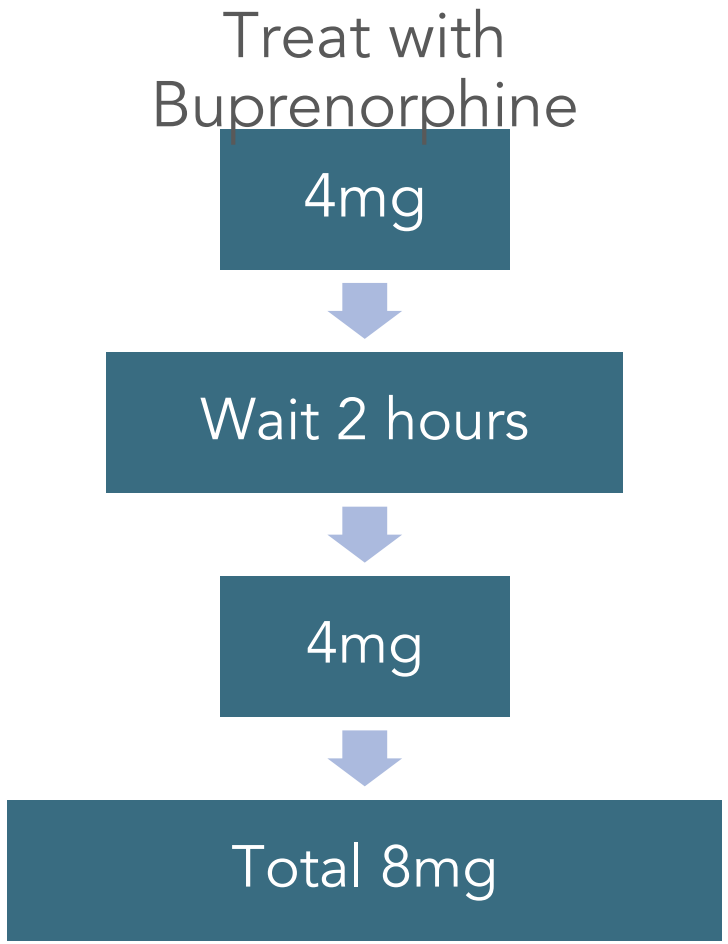
Number of deaths after ED treatment for nonfatal overdose by number of days after discharge in the first month (n=130)



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

Case #1: “By the Book”

- Screen and Diagnose OUD
- Assessment of Withdrawal
- Lab Testing



Screen and Diagnose OUD

DSM-5 Criteria for Diagnosis of Opioid Use Disorder

1. Take more/longer than intended
2. Desire/unsuccessful efforts to quit opioid use
3. A great deal of time taken by activities involved in use
4. Craving, or a strong desire to use opioids
5. Recurrent opioid use resulting in failure to fulfill major role obligations
6. Continued use despite having persistent social problems
7. Important activities are given up because of use.
8. Recurrent opioid use in situations in which it is physically hazardous (e.g. driving)
9. Use despite knowledge of problems
10. Tolerance
11. Withdrawal

Severity

Presence of Symptoms

Mild: 2-3
Moderate: 4-5
Severe: ≥6

At least 2 criteria must be met within a 12 month period

PCSS Providers Clinical Support System

"Why are you asking me these questions?"

"I told you I feel sick"

"Where is the dot phrase"

"I am waiting for psychiatry to call me back"

"We have not been trained on DSM 5"

Assessment of Withdrawal

Clinical Opioid Withdrawal Scale (COWS)

Score:

5-12= Mild

13-24= Moderate

25-36= Moderately Severe

"Why are you asking me these questions?"

↓

"I told you I feel sick"

↓

"Where is the dot phrase"

↓

"I am waiting for psychiatry to call me back"

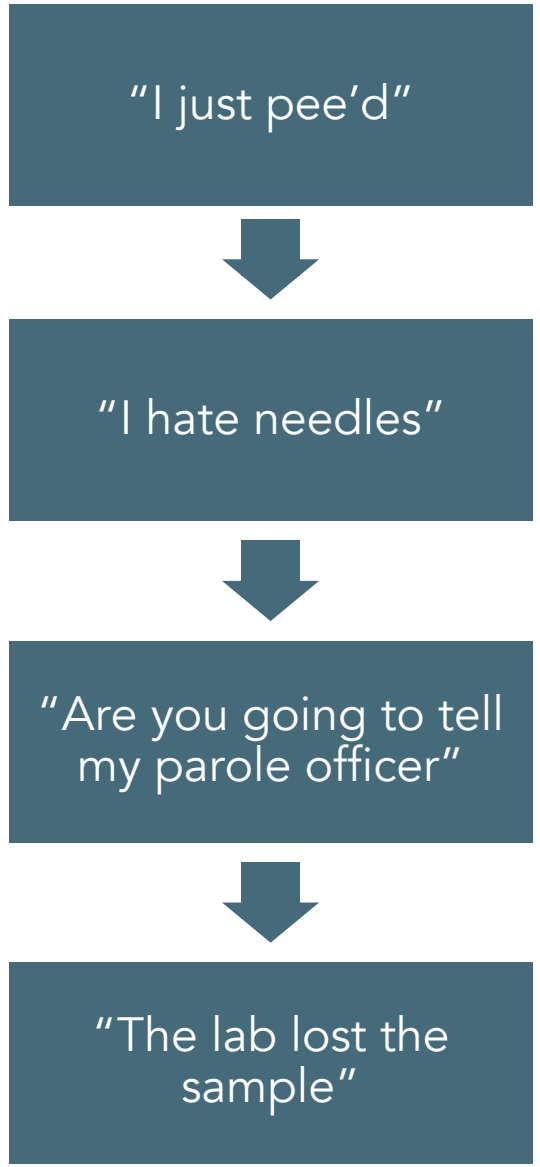
↓

"We have not been trained on COWS"

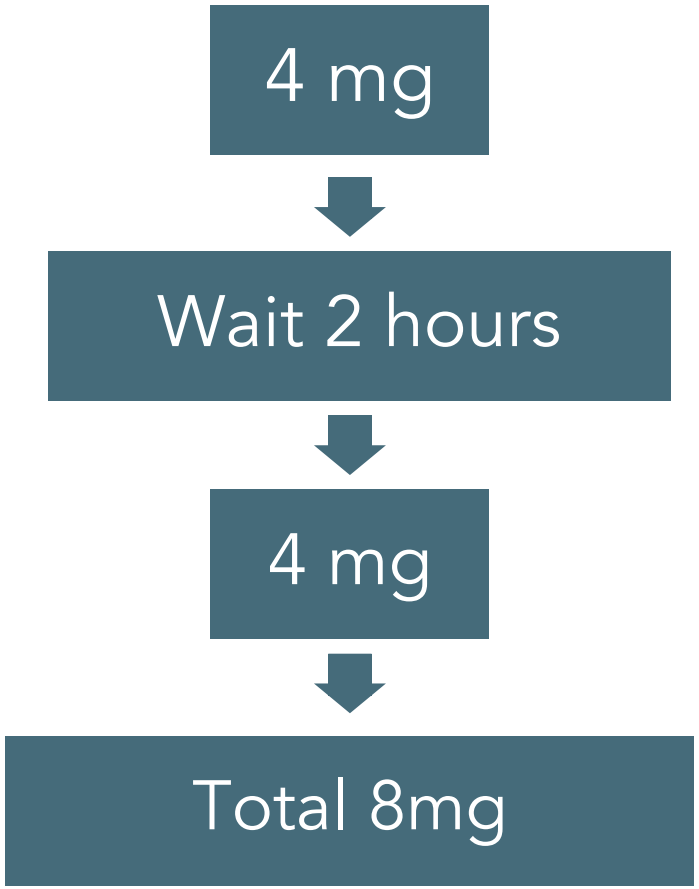
Lab Testing

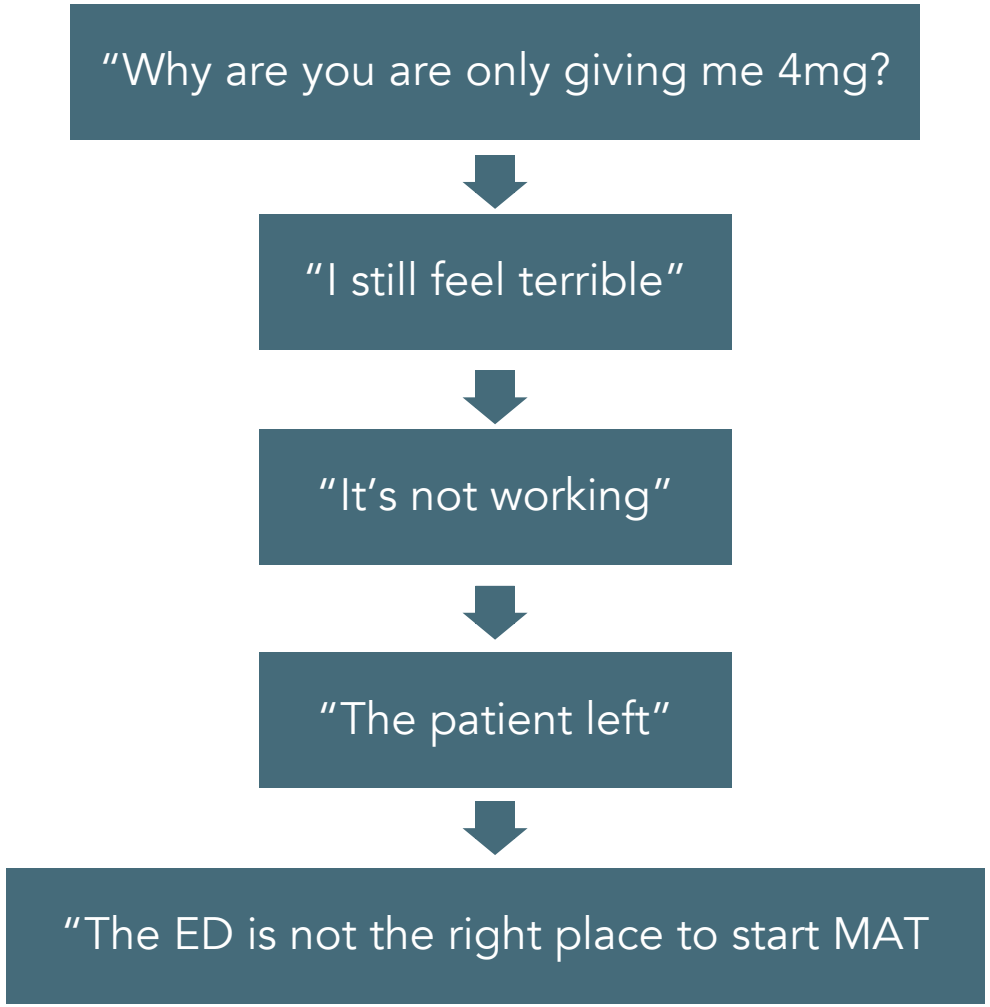
Lab Testing

- Pregnancy testing for women in reproductive years
  - NOT an exclusion but will guide referral process
- Consider urine toxicology testing if
  - Concerns about accuracy of opioid use history
  - Long acting opioid use (i.e. methadone)
  - Note: Fentanyl will not show up in many hospital urine drug screens
- Consider blood testing
  - LFTs if clinical suspicion of liver failure (Buprenorphine contraindicated if LFTs >5 x normal)
  - HIV, Hepatitis B and C if not otherwise available at referral site



Treat with Buprenorphine





M & M Analysis

- Failure of care delivery
- Failure of care coordination
- Overtreatment or low value care
- Pricing failure
- Fraud and abuse
- Administrative complexity

- It didn’t work
- The patient didn’t like it
- It was expensive
- It took to long
- It was complicated

Starting Buprenorphine (Bup),"Subs",Suboxone

Step 1 Wait

0----------6 hours ---------- **12 hours**

Last use

Step 2 Withdrawal (start when you feel sick)

0----------5 ----------10

Feel fine **Very Sick**

Step 3 First Dose

4mg

Light user

8mg

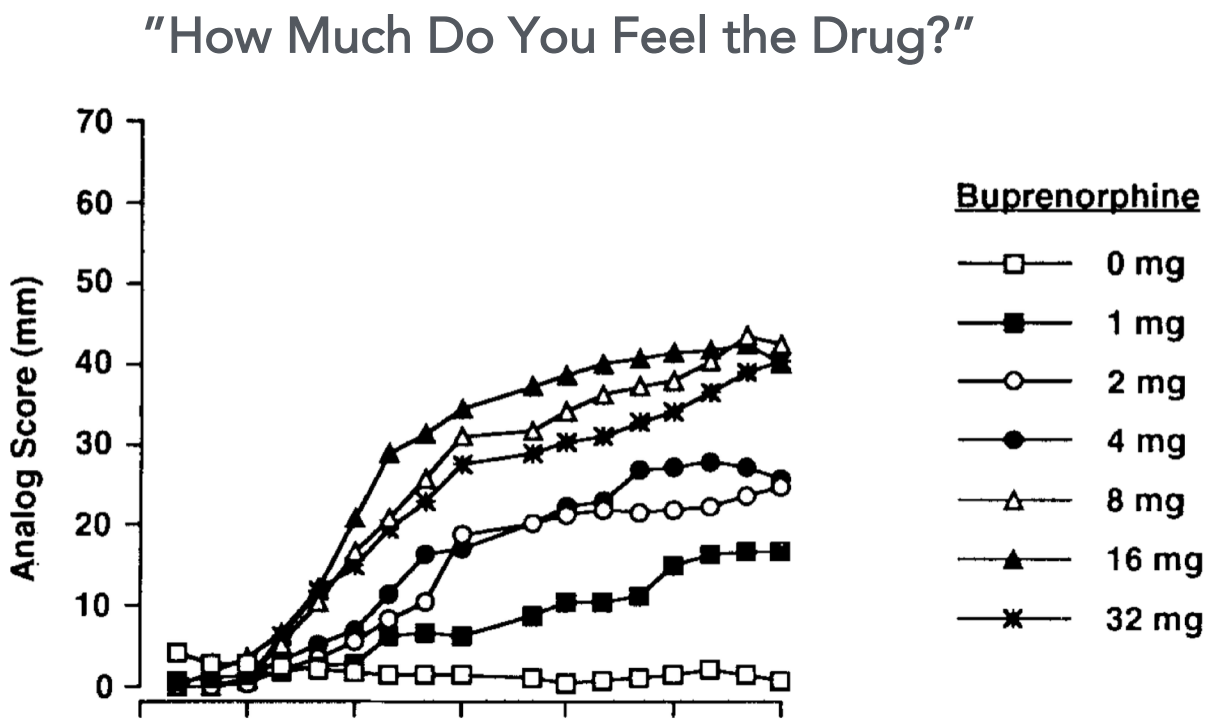
Medium heroin

16mg

Heavy heroin

Ceiling Effect: Sharon Walsh

- 16 healthy non-opioid dependent volunteers



Clinical pharmacology of Buprenorphine: Ceiling effects at high dose

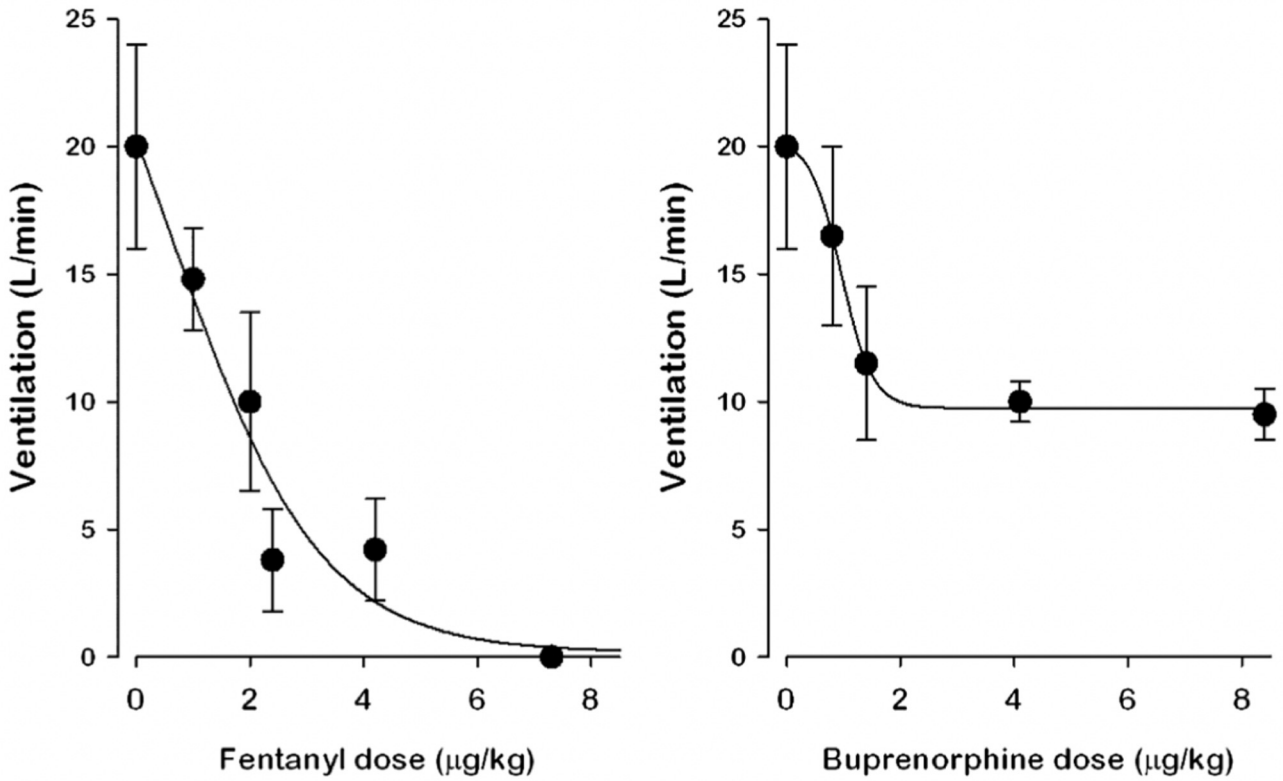
Ceiling Effect

British Journal of Anaesthesia 96 (5): 627–32 (2006)
doi:10.1093/bja/ael051 Advance Access publication March 17, 2006

BJA

Buprenorphine induces ceiling in respiratory depression but not in analgesia

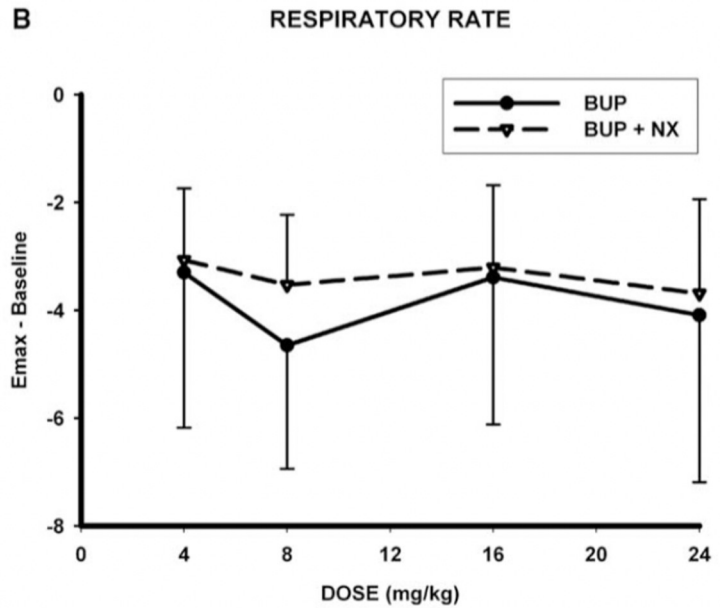
A. Dahan[1]*, A. Yassen[2], R. Romberg[1], E. Sarton[1], L. Teppema[1], E. Olofsen[1] and M. Danhof[2]



Pharmacokinetics and Pharmacodynamics of Multiple Sublingual Buprenorphine Tablets in Dose-Escalation Trials

Domenic A. Ciraulo, MD, Robert J. Hitzemann, PhD, Eugene Somoza, MD, Clifford M. Knapp, PhD, John Rotrosen, MD, Ofra Sarid-Segal, MD, Ann Marie Ciraulo, RN, David J. Greenblatt, MD, and C. Nora Chiang, PhD

38 subjects



Proportionate agonism: Andy Saxon

Withdrawal intensity

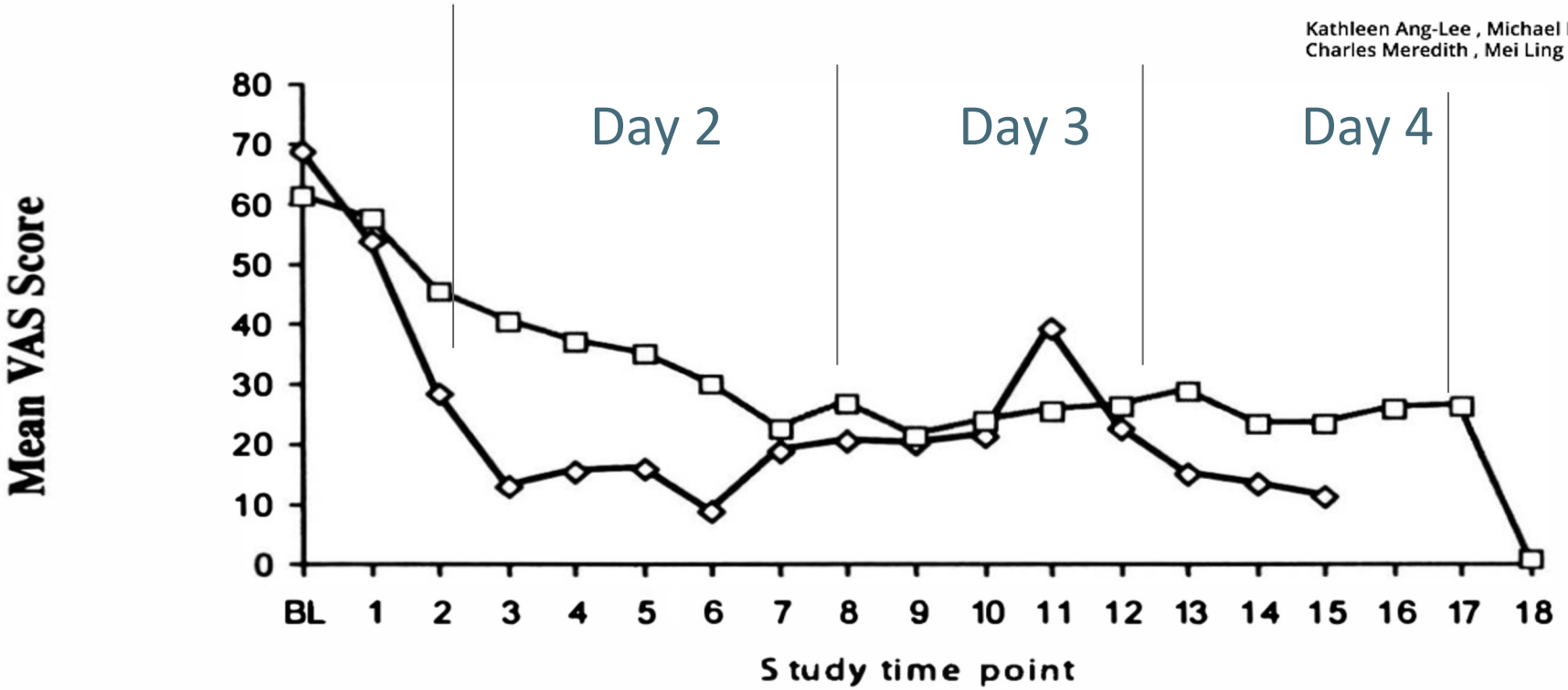
Journal of Psychoactive Drugs

ISSN: 0279-1072 (Print) 2159-9777 (Online) Journal homepage: http://www.tandfonline.com/loi/ujpd20

24mg x 1 vs 8mg daily x 3 days SL BUP

Single Dose of 24 Milligrams of Buprenorphine for Heroin Detoxification: An Open-label Study of Five Inpatients

Kathleen Ang-Lee , Michael R. Oreskovich , Andrew J. Saxon , Craig Jaffe , Charles Meredith , Mei Ling K. Ellis , Carol A. Malte & Patricia C. Knox



High Affinity binding

Mu Opioid Receptor Range of Ki Value	
Buprenorphine	0.21 to 1.5
Fentanyl	0.7 to 1.9
Methadone	0.72 to 5.6
Naloxone	1 to 3 (antagonist effects)
Morphine	1.02 to 4
Codeine	65 to 135

PDSP Ki Database https://pdsp.unc.edu/databases/pdsp.php

Wang D, Sun X, Sadee W. Different effects of opioid antagonists on μ-, δ-, and κ-opioid receptors with and without agonist pretreatment. *J Pharmacol Exp Ther.* 2007;321(2):544-52.

Acta Anaesthesiol Scand 1988: 32: 490–492

Buprenorphine antagonism of ventilatory depression following fentanyl anaesthesia

K. Boysen, S. Hertel, B. Chræmmer-Jørgensen, A. Risbo and N. J. Poulsen

Department of Anaesthesia, University of Copenhagen, Glostrup Hospital, Glostrup, Denmark

0.6 mg bup vs 0.2 mg naloxone

Table 2

Respiratory rate – median (range).

Time: min	Preinduction	0	15	30	60	120
Buprenorphine n = 10	13 (12–14)	0 (0–4)	10 (8–12)	12 (8–16)	11.5 (8–16)	11 (8–12)
Naloxone n = 10	12 (11–15)	0 (0–2)	14.5* (9–20)	14 (10–20)	12 (9–16)	14 (6–16)

Time = min from beginning treatment with either B or N. *$P < 0.05$ between groups.

Zamani et al. Critical Care (2020) 24:44
https://doi.org/10.1186/s13054-020-2740-y

Critical Care

RESEARCH Open Access

Buprenorphine to reverse respiratory depression from methadone overdose in opioid-dependent patients: a prospective randomized trial

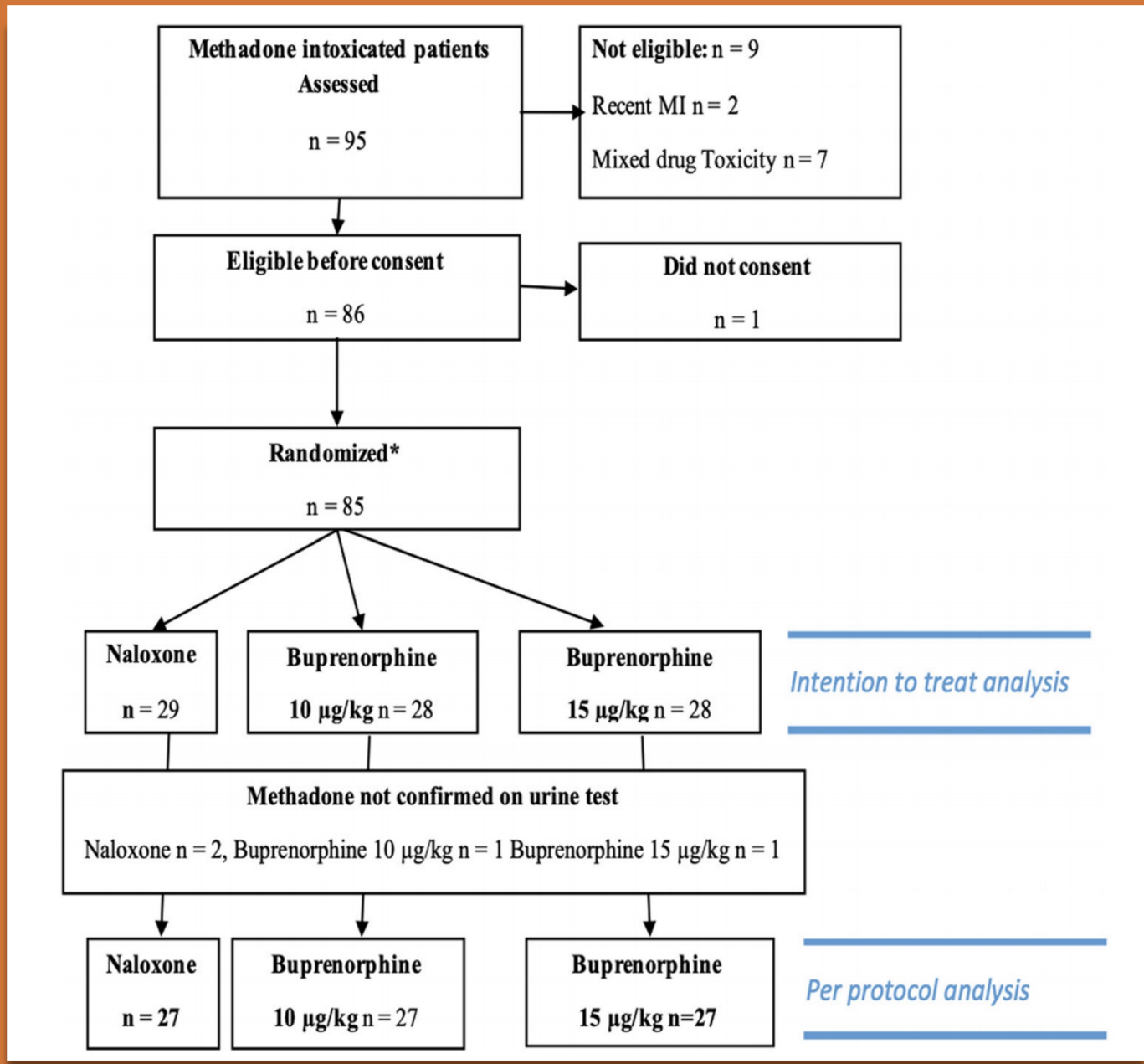
Nasim Zamani[1,2,3], Nicholas A. Buckley[4] and Hossein Hassanian-Moghaddam[1,2*]

Naloxone.

2 mg RR <6; 0.04 mg RR of 6-12

Buprenorphine:

10 µg/kg or 15 µg/kg of IV over 6 and 9 min, respectively.



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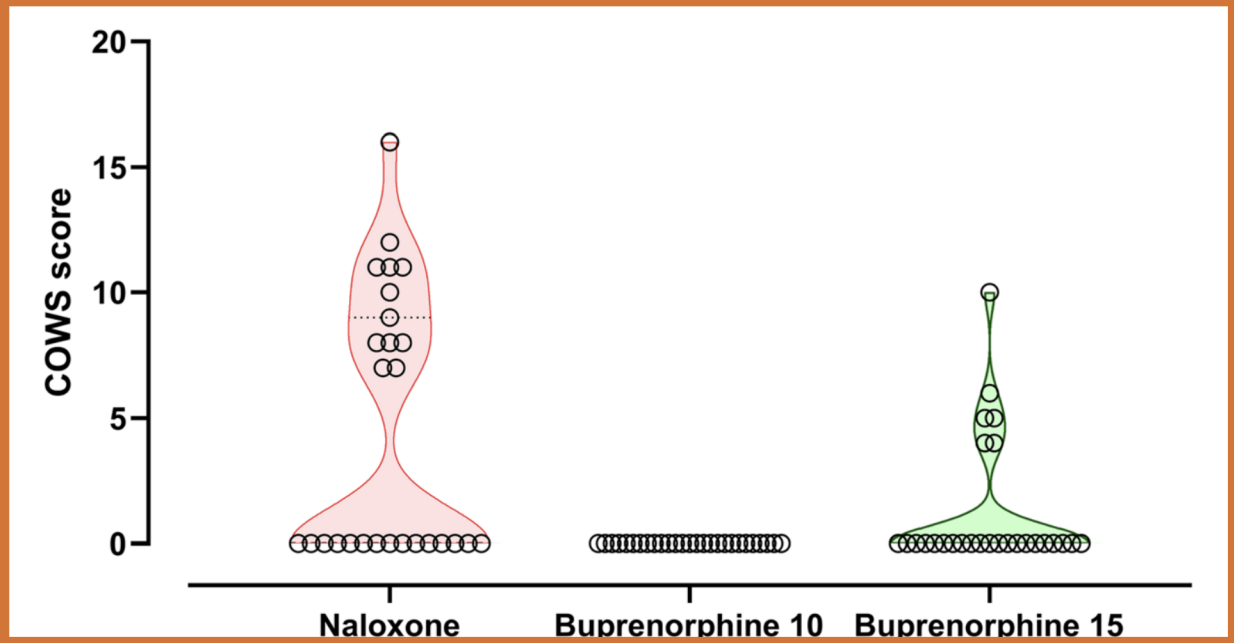


Table 3 Per-protocol comparison of outcomes in three arms of the study ($n = 81$)

Outcome	Naloxone ($n = 27$)	Buprenorphine 10 μg/kg ($n = 27$)	Buprenorphine 15 μg/kg ($n = 27$)
Response to bolus antidote doses	Complete 13 (48%) Partial 13 (48%) No response 1 (4%)	Complete 23 (85%) Relative 3 (11%) No response 1 (4%)	Complete 27 (100%) Partial 0 No response 0
Opioid withdrawal	15 (56%)	0	6 (22%)
Further apnea	6 (22%)	4 (15%)	3 (11%)
Aspiration	1 (4%)	5 (18%)	1 (4%)
Intubation	8 (30%)	4 (15%)	1 (4%)
Continuing sedation	9 (33%)	0	3 (11%)

TOXICOLOGY/CASE REPORT

Elective Naloxone-Induced Opioid Withdrawal for Rapid Initiation of Medication-Assisted Treatment of Opioid Use Disorder

Reid H. Phillips, MD*; Matthew Salzman, MD; Rachel Haroz, MD; Rachel Rafeq, PharmD; Anthony J. Mazzarelli, MD, JD; Alexis Pelletier-Bui, MD

*Corresponding Author. E-mail: phillips-reid@cooperhealth.edu.

Sacred COWS

Drug and Alcohol Dependence 105 (2009) 154–159

Contents lists available at ScienceDirect

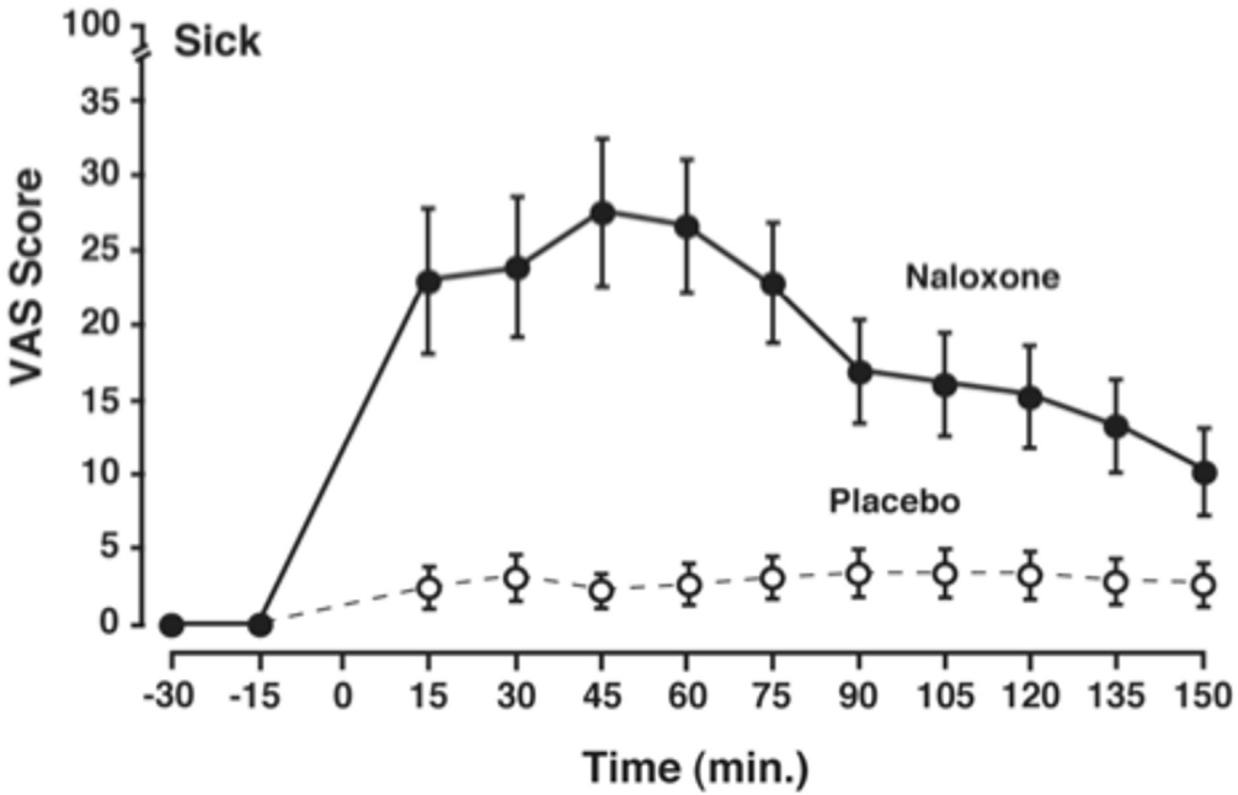
Drug and Alcohol Dependence

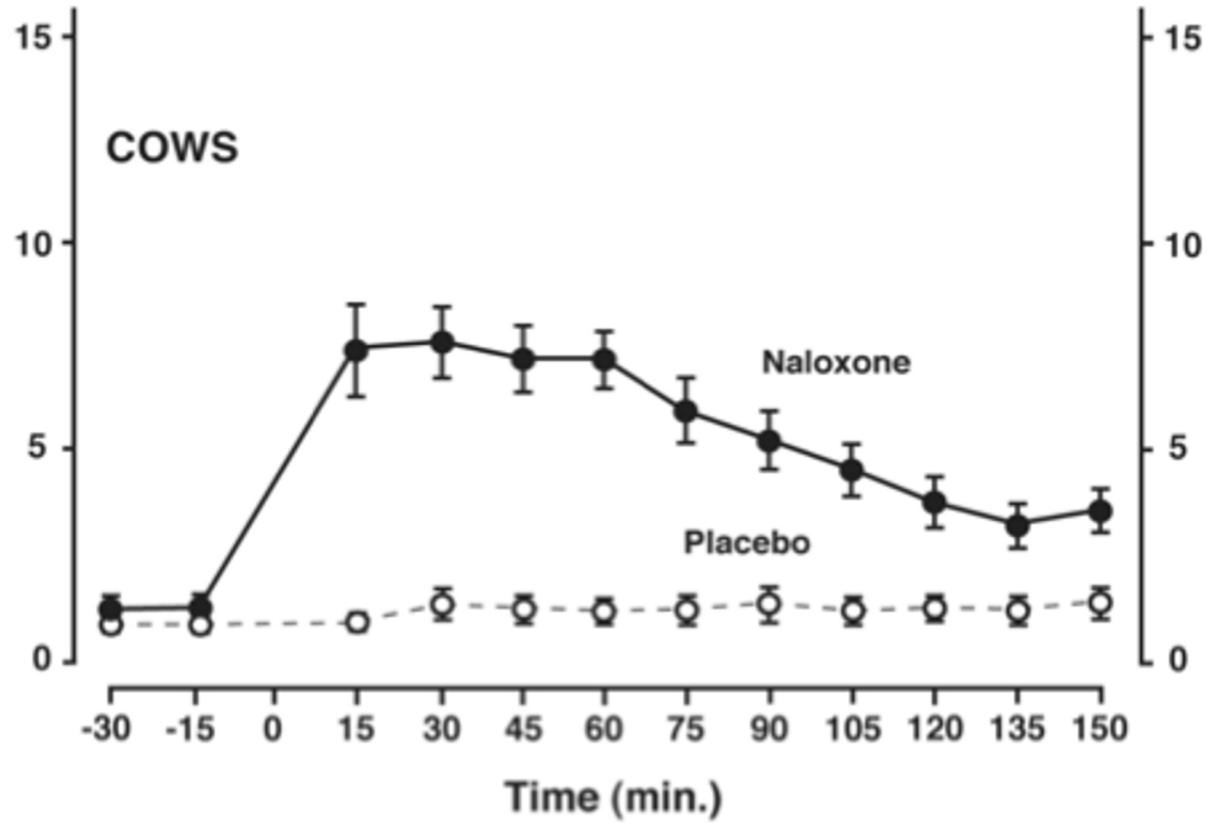
journal homepage: www.elsevier.com/locate/drugalcdep

Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument

D. Andrew Tompkins[a,*], George E. Bigelow[a], Joseph A. Harrison[a], Rolley E. Johnson[a,b], Paul J. Fudala[b], Eric C. Strain[a]

[a] Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Behavioral Pharmacology Research Unit, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA
[b] Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA 23235, USA



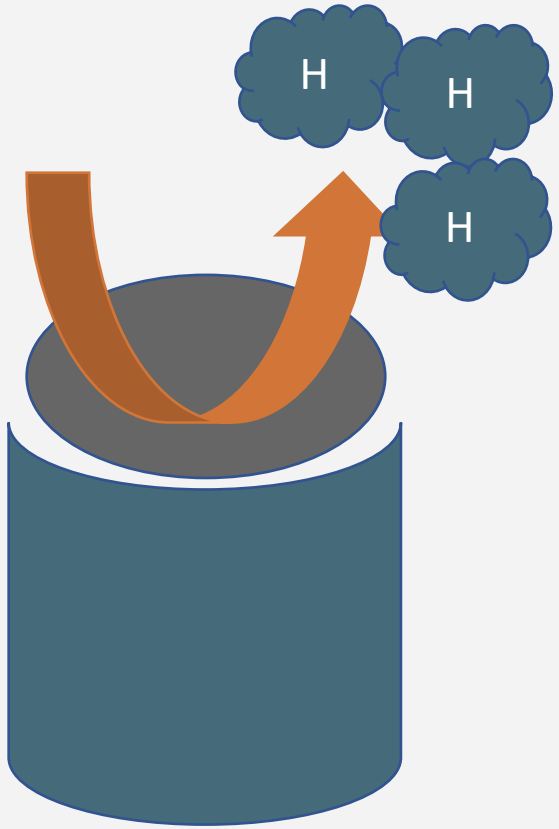


“Single Big Dose”

Discussion "Goldilocks" Dose

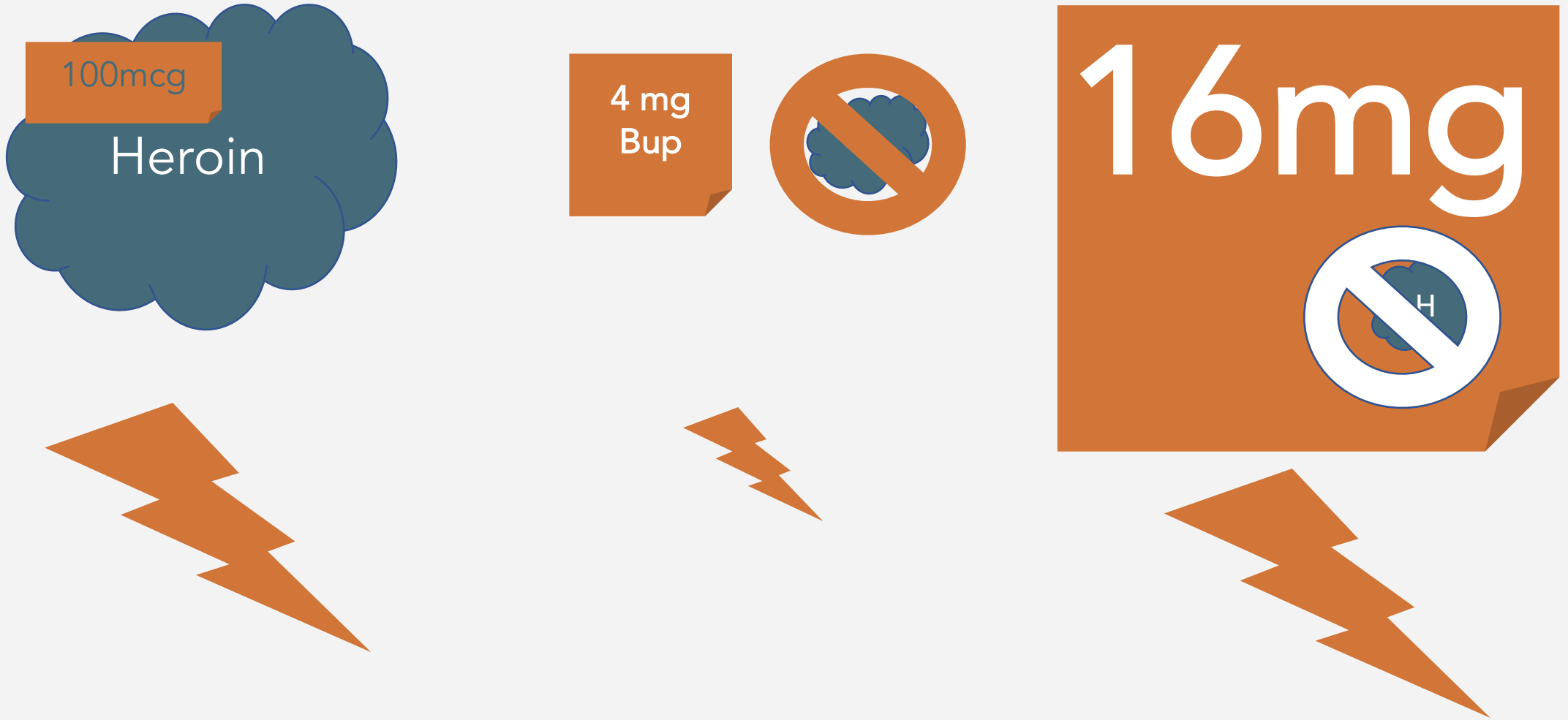
“Do I have to feel sick”: Single Big Dose

Displacement



= Pain

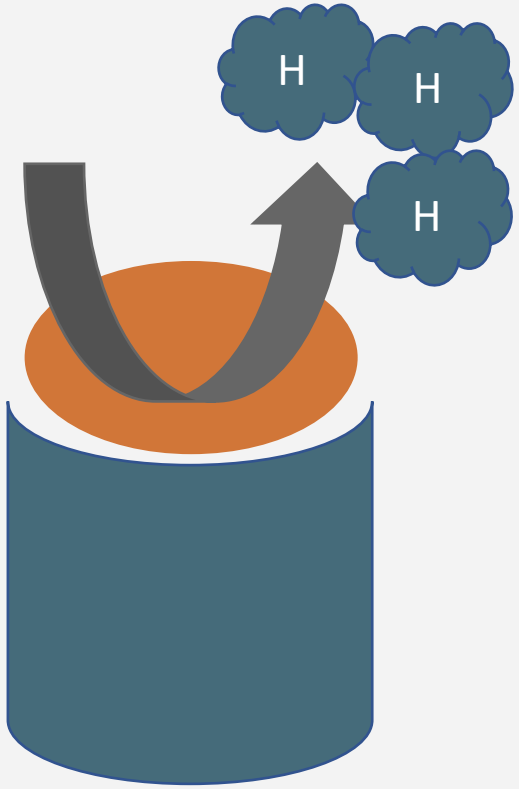
“Do I have to feel sick”: Single Big Dose



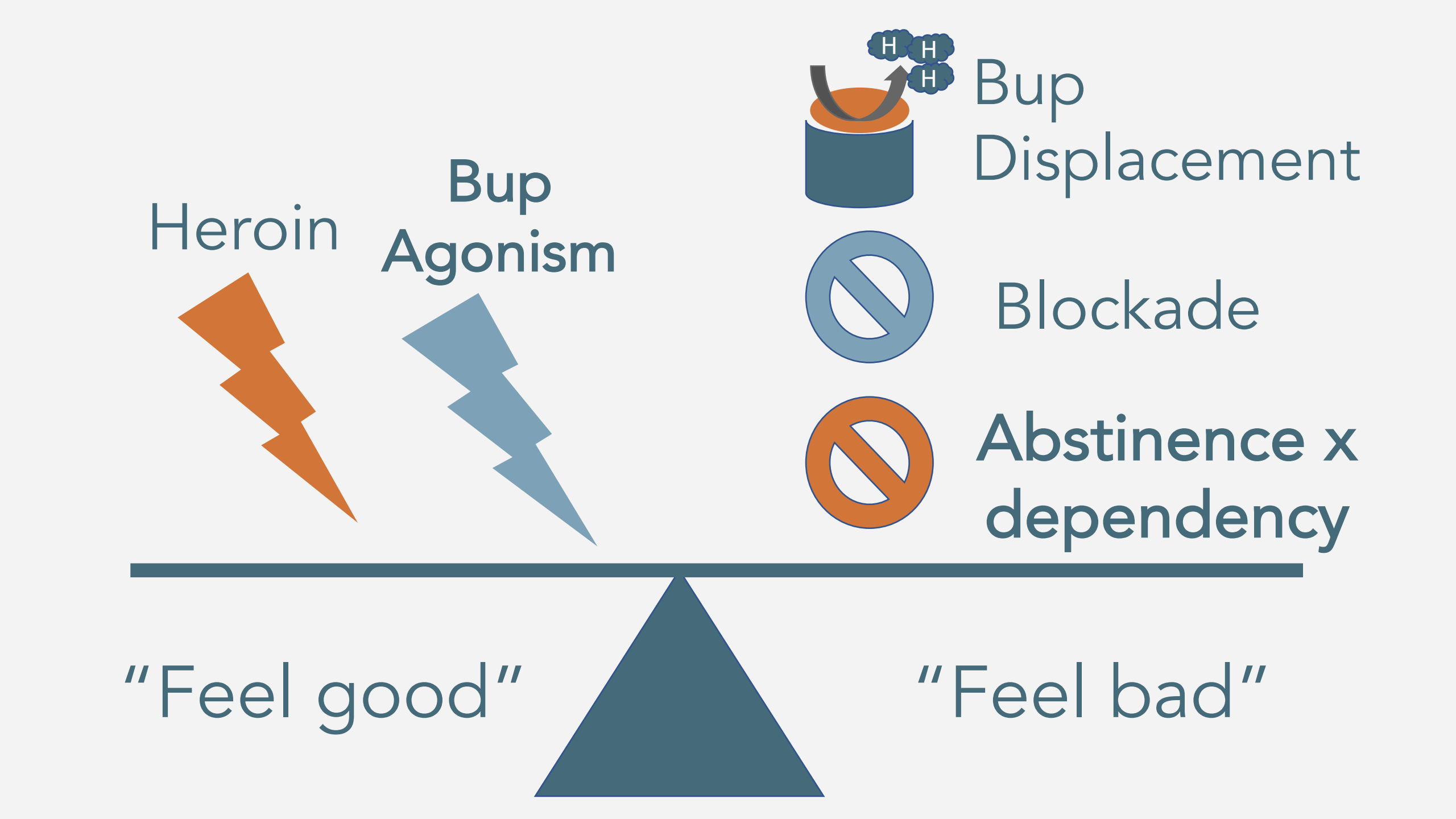
“Do I have to feel sick”: Single Big Dose

Displacement

Agonism

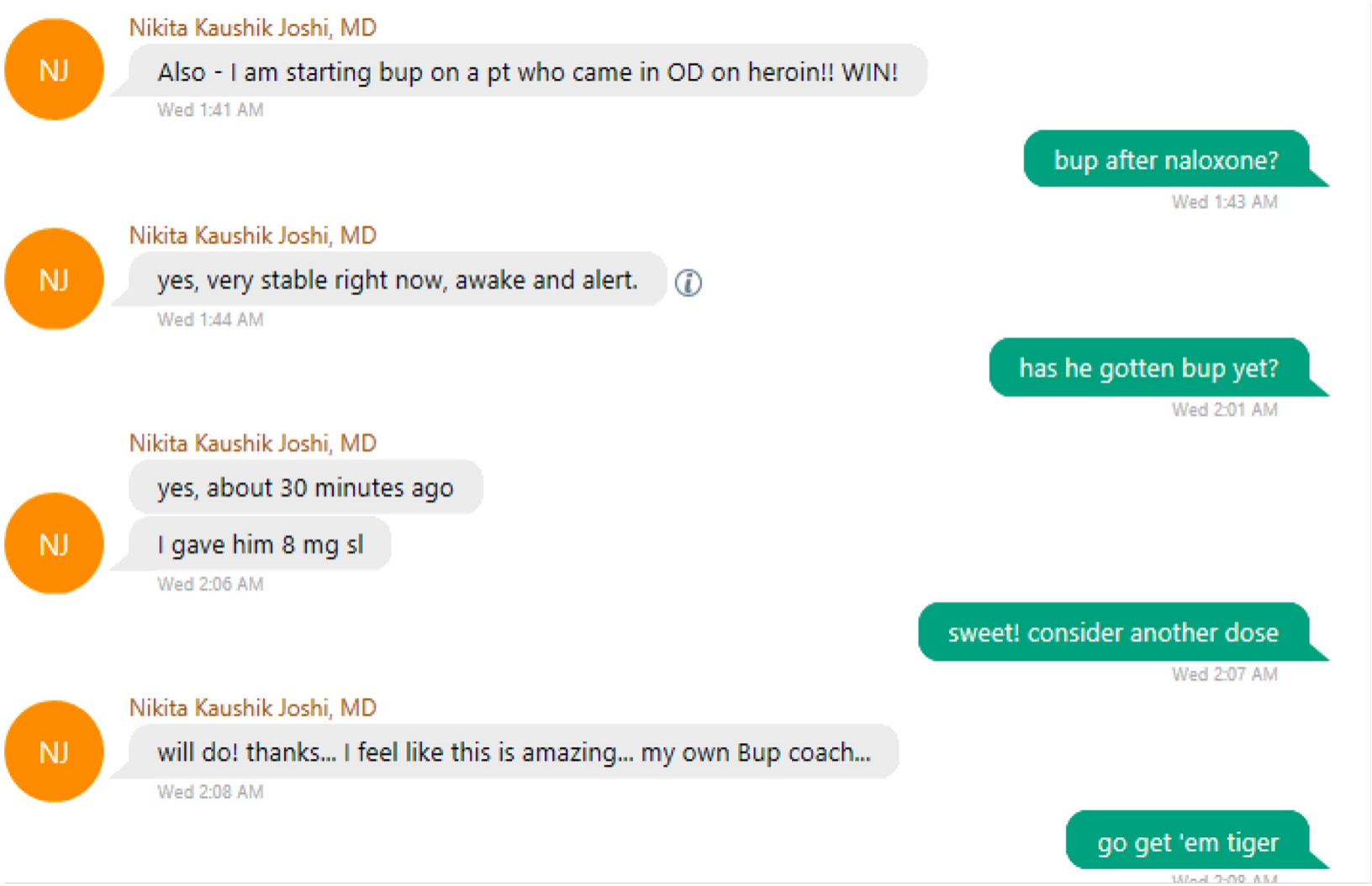


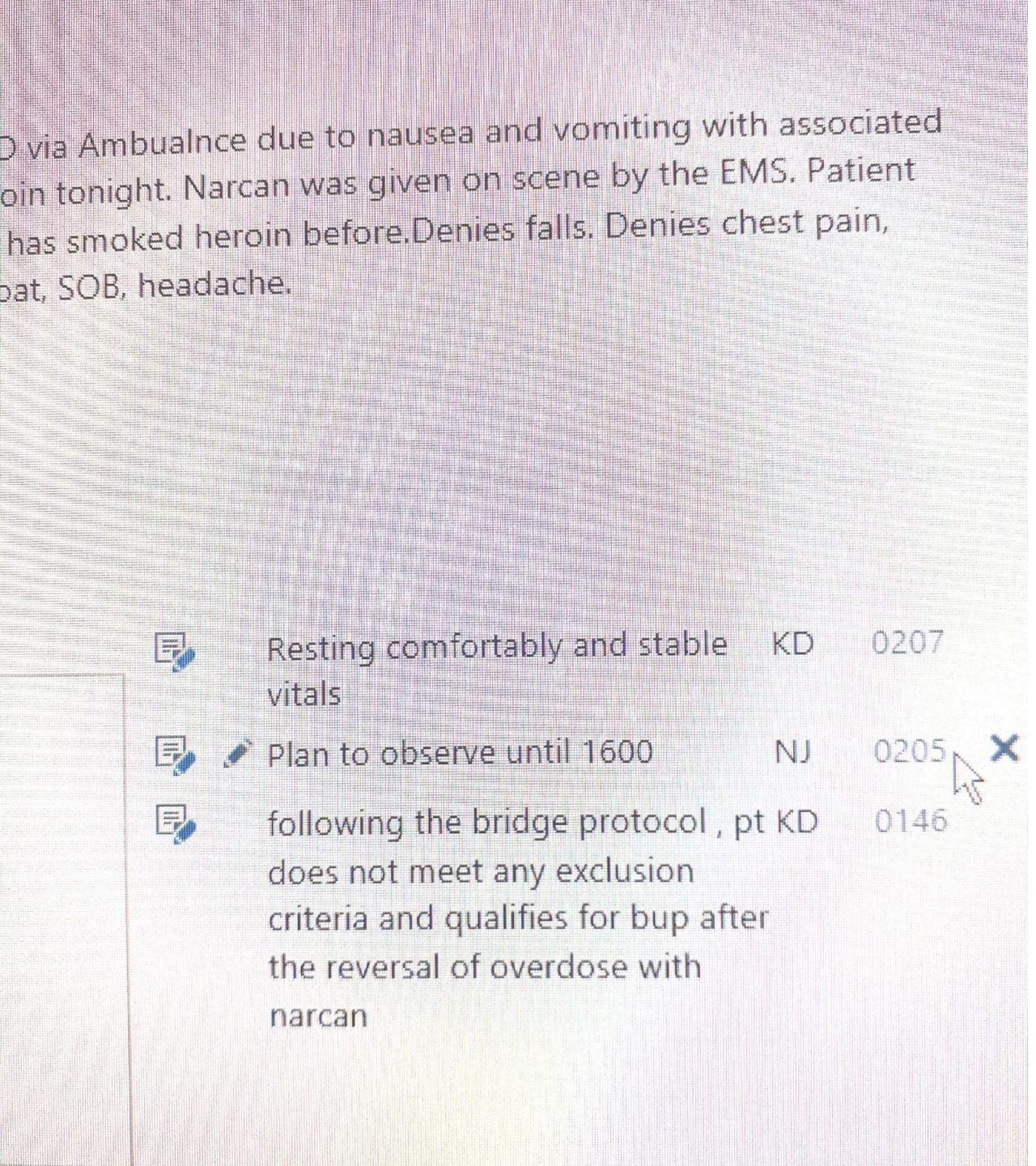
Blockade


Heroin
Bup
Agonism
Bup
Displacement
Blockade
Abstinence x
dependency
"Feel good"
"Feel bad"

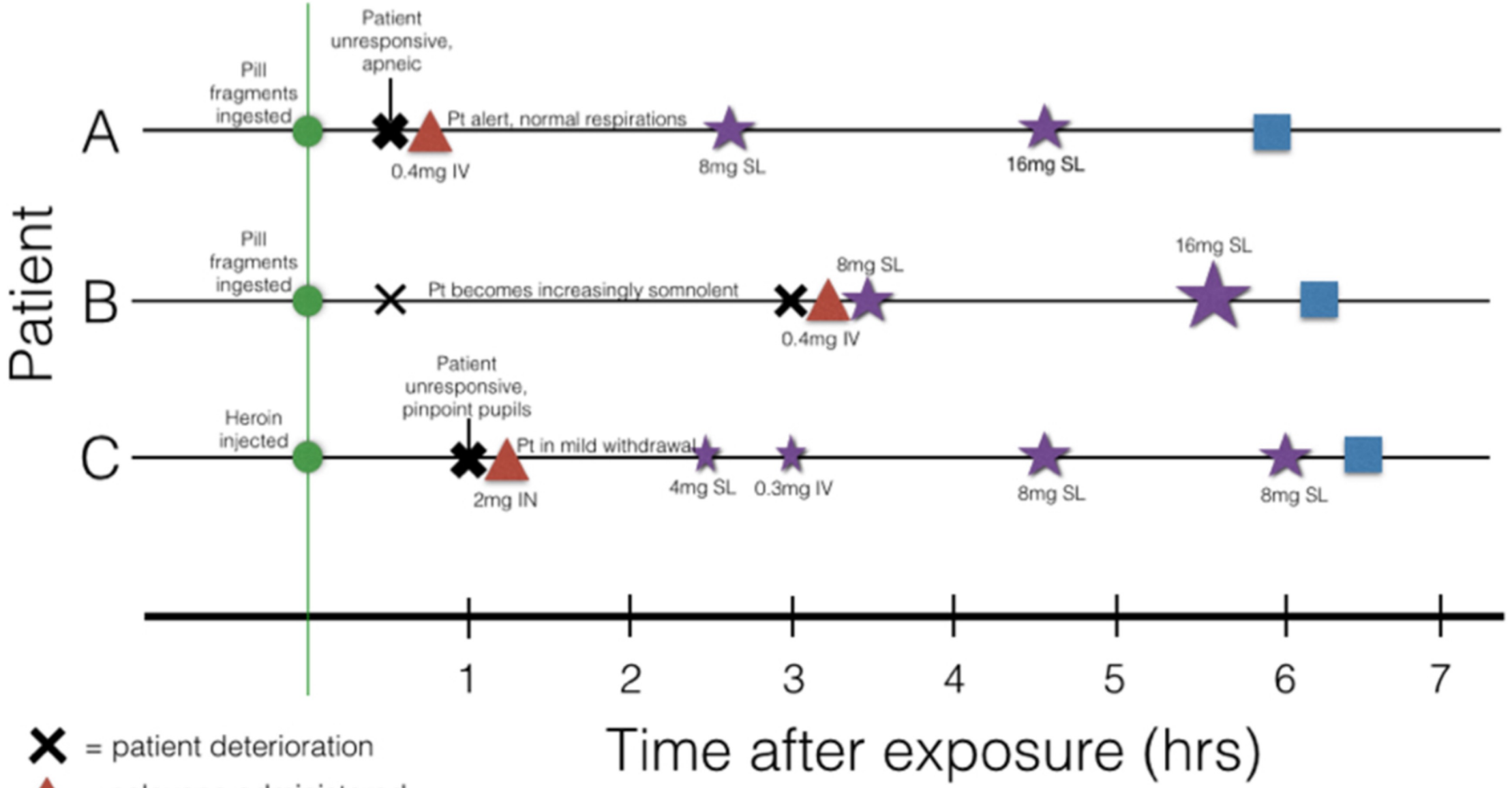
Bup After Overdose

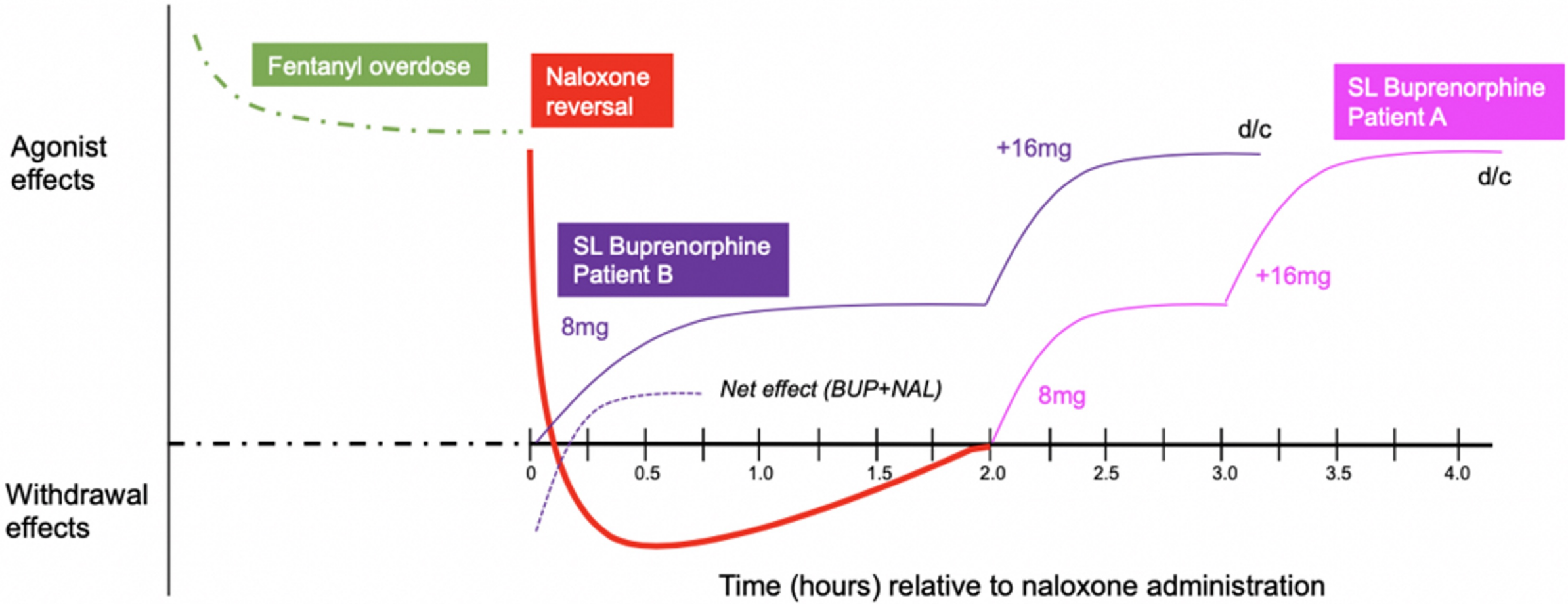
Bup After Overdose



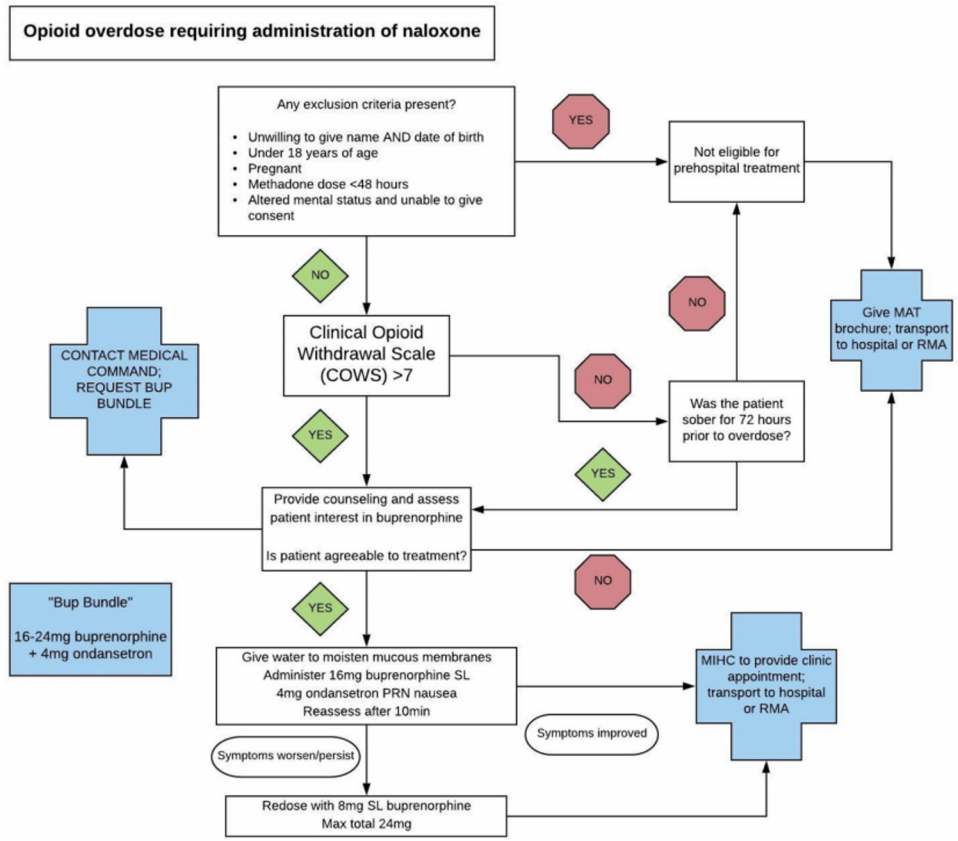


Bup After Overdose


Patient
A
B
C
Pill fragments ingested
Patient unresponsive, apneic
Pt alert, normal respirations
0.4mg IV
8mg SL
16mg SL
Pill fragments ingested
Pt becomes increasingly somnolent
8mg SL
0.4mg IV
16mg SL
Heroin injected
Patient unresponsive, pinpoint pupils
Pt in mild withdrawal
2mg IN
4mg SL
0.3mg IV
8mg SL
8mg SL
1
2
3
4
5
6
7
Time after exposure (hrs)
= patient deterioration
= naloxone administered
= buprenorphine administered
= discharge from ED in good condition


Fentanyl overdose
Naloxone reversal
SL Buprenorphine Patient A
d/c
+16mg
d/c
SL Buprenorphine Patient B
+16mg
8mg
Net effect (BUP+NAL)
8mg
Agonist effects
Withdrawal effects
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours) relative to naloxone administration

New Jersey first state to authorize paramedics to provide addiction-treatment drug to overdose victims

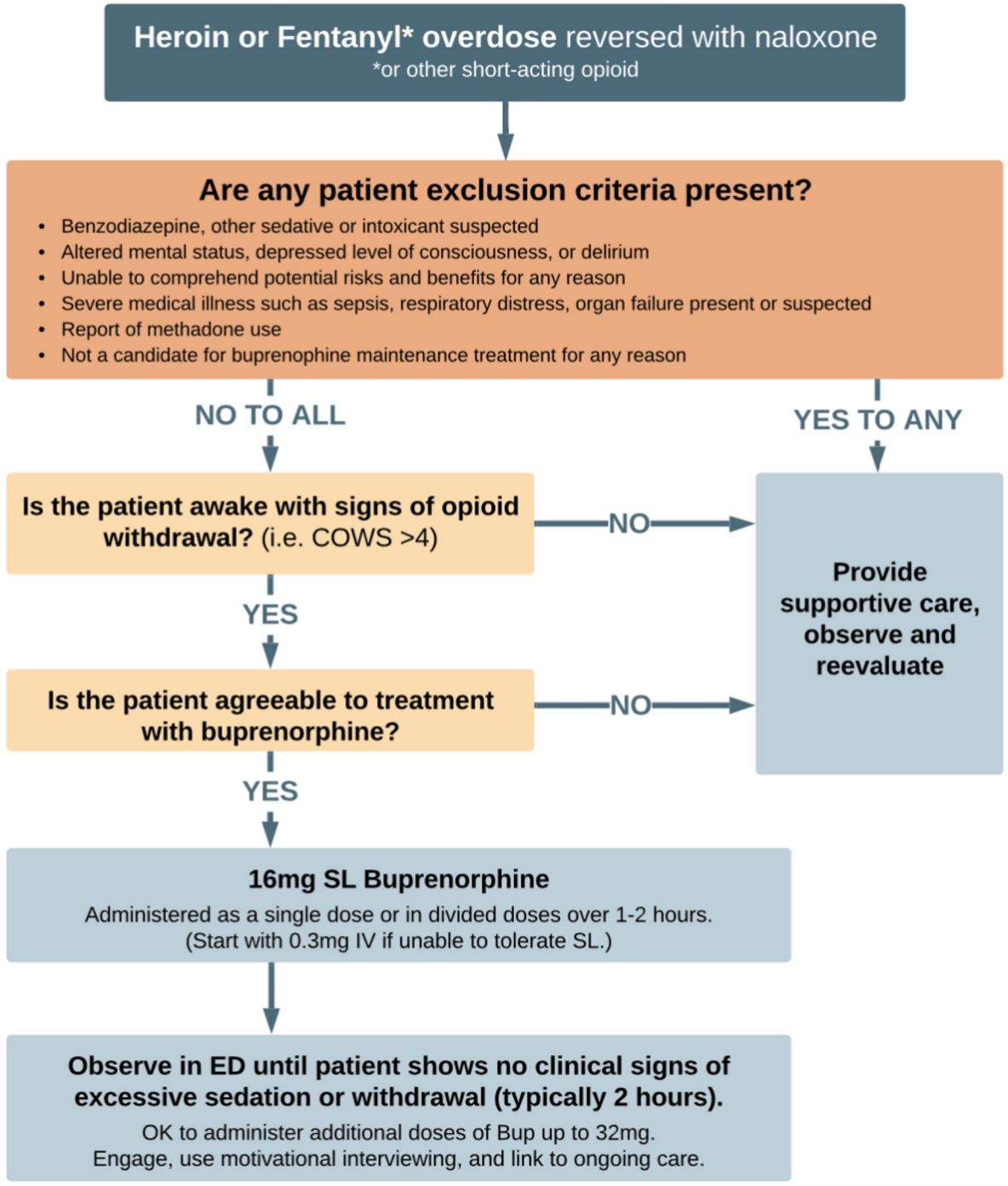


Buprenorphine Field Initiation of ReScue Treatment by Emergency Medical Services (Bupe FIRST EMS): A Case Series

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

Table 1. Patient Characteristics and Treatment

Patient	Naloxone given	Initial COWS	Buprenorphine given	Repeat COWS	1st visit	30 day retention
A	2 mg IM	13	16 mg	3	Yes	Yes
B	2mg IM	15	16-32 mg	3	Yes	No
C	4 mg IN	12	16 mg	4	Yes	Yes



Bup Induction after Overdose

Need help with pain pills or heroin?

We want to help you get off opioids and started on Suboxone (Buprenorphine).

Ask for more information here.

Andrew Herring, MD

Highland Hospital

Andrew@BridgeToTreatment.org

MORE RESOURCES AVAILABLE: BridgeToTreatment.org/resources

Questions

1. The affinity of buprenorphine for the Mu Opioid Receptor is:
   a. Less than fentanyl and naloxone
   b. Greater than fentanyl but less than naloxone
   c. Greater than both fentanyl and naloxone
   d. Less than fentanyl but greater than naloxone

Questions

1. The affinity of buprenorphine for the Mu Opioid Receptor is:
   a. Less than fentanyl and naloxone
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   c. Greater than both fentanyl and naloxone
   d. Less than fentanyl but greater than naloxone

Questions

2. Buprenorphine has shown a ceiling effect on respiratory depression. This means:
   a. buprenorphine does not cause respiratory depression
   b. buprenorphine combined with benzodiazepines can cause respiratory arrest
   c. respiratory depression is never a concern with buprenorphine
   d. at common doses larger amounts of buprenorphine does not cause a greater degree of respiratory depression

Questions

2. Buprenorphine has shown a ceiling effect on respiratory depression. This means:
   a. buprenorphine does not cause respiratory depression
   b. buprenorphine combined with benzodiazepines can cause respiratory arrest
   c. respiratory depression is never a concern with buprenorphine
   d. at common doses larger amounts of buprenorphine does not cause a greater degree of respiratory depression

Questions

3. After naloxone reversal of opioid overdose, buprenorphine:
   a. can be given to anyone without concern
   b. should be avoided in patients who regularly take methadone, are intoxicated with alcohol, or are sedated with benzodiazepines
   c. should not be given to patients who are not committed to long term addiction treatment
   d. Can only be given at least 2 hours after the last naloxone dose

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   b. is expected to displace any full agonist opioids but not the naloxone
   c. has been shown to cause a prolonged state of withdrawal because of it's very long half life.
   d. should be "micro-dosed" because that is the only safe way to administer buprenorphine without at least 12 hours of abstinence

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