

Reaching our Most Vulnerable Patients with MAT through Long Acting Injectables

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Educational Objectives

After attending this presentation, participants will be able to:

1. Interpret pharmacokinetic data on intravenous, sublingual and extended release subcutaneous buprenorphine.
2. Discuss emerging potential applications of extended release subcutaneous buprenorphine in the emergency and pre-hospital (emergency medical services) setting.
3. Describe specific case histories of emergency department patients treated with extended release subcutaneous buprenorphine.

Disclosure Information

- Arianna D. Sampson, PA-C – Physician Assistant, Emergency Department, Marshall Medical Center
- Andrew Herring, MD – Physician, Alameda Health System
- Loni Jay, MD – faculty, Addiction Medicine, Sutter Family Medicine Residency Program
- Aimee Moulin, MD – Physician, Emergency Department, UC Davis Medical Center
- Hannah Snyder, MD – Assistant Professor, Dept. of Family and Community Medicine, UCSF
- Monish Ullal, MD – Physician, Associate Medical Director, AHS Bridge Program, Buprenorphine Clinic, Highland Hospital/Alameda Health System



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

Impact: From March 2019 - July 2020 over 50 hospitals treated patients with substance use disorders

Update: 208 hospitals implement the CA Bridge model in 2020

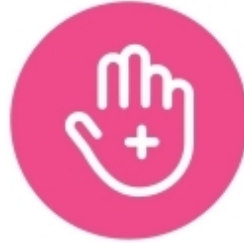


CA Bridge Model

Revolutionizing The System Of Care



Rapid, Evidence-based Treatment



Connection to Ongoing Care



Culture of Respect

CA Bridge Model: Treatment

- Evidence-based substance use disorder treatment (medication for addiction treatment, MAT) is accessible in the ED *and in all other hospital departments*.
- Treatment is provided rapidly (same day) & efficiently in response to patient needs.



CA Bridge Model: Connection

- Linkage to ongoing care involves active support and follow up with patients.
- Outreach to people who use drugs to increase access to care, equity, & harm reduction.



CA Bridge Model: Culture

- Hospital culture is welcoming and does not stigmatize substance use.
- Human relationships that build trust are integral to how substance use disorder treatment is provided.



CA Bridge Impact

Cumulative totals across all reporting CA Bridge sites (n = 52) as of June 30, 2020



11954

patients identified
with OUD



7718

patients provided
with treatment



5818

patients given a
prescription for MAT



4994

patients linked to
follow-up MAT care

OUD Opioid Use Disorder

MAT Medication for Addiction Treatment



1.

Patient with SUD
is identified

2.

SUN talks to
patient

3.

SUN consults with
provider to start
treatment

4.

SUN guides patient
through next steps
of ongoing care

Inductionology

The art and science of starting Bup

“The optimal dose-induction procedure for a partial agonist used in treatment as a replacement therapy should produce maximal morphine-like effects, opiate blockade, and minimal opiate-withdrawal effects, and it should be accomplished as rapidly as possible to retain individuals in treatment and to minimize illicit opiate use.”

Tip 40

4 mg



Wait 2 hours



4 mg



Total 8mg

"Why are you are only giving me 4mg?"



"I still feel terrible"



"It's not working"



"The patient left"



"The ED is not the right place to start MAT"

After Discharge



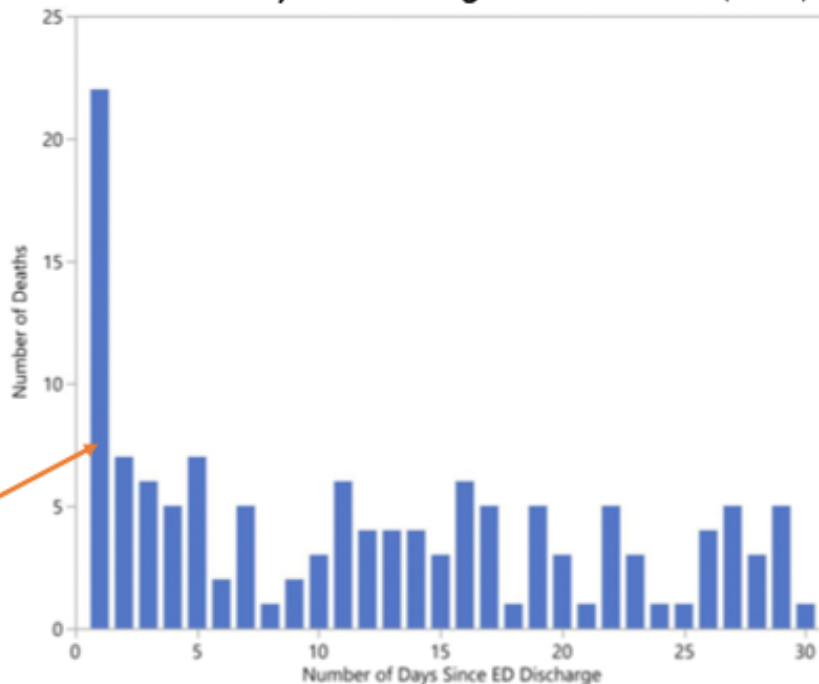
After Discharge

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

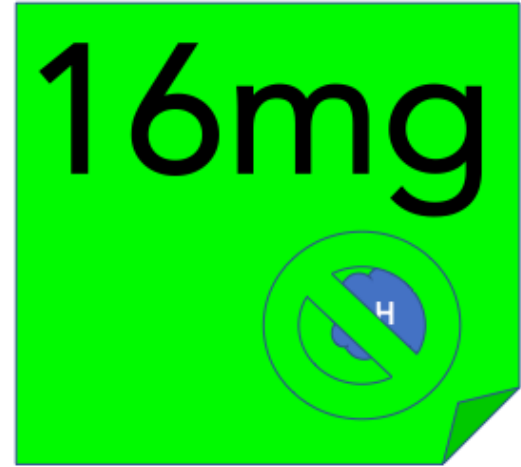
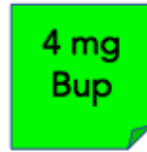
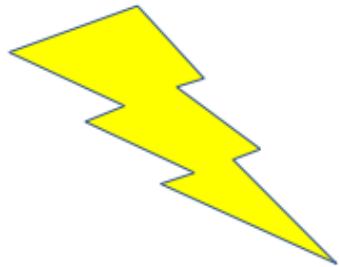
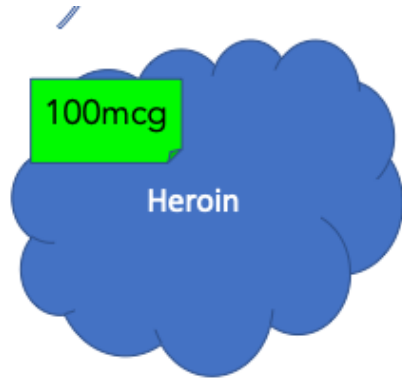
Scott G. Weiner, MD, MPH¹, Olesya Baker, PhD², Dana Bernson, MPH³, Jeremiah D. Schuur, MD, MHS⁴

- 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)



Micro Standard Loading



Strain 1995

Condition: Methadone 30mg Daily
Exposure: Buprenorphine 0.5-8mg IM 2 hrs after methadone

“Less withdrawal was seen at the lowest (0.5 mg) and highest (8 mg) doses. These results suggest that higher doses of buprenorphine produce less antagonist effects and may be better tolerated than moderate doses in methadone maintained patients, when given at a short time interval.”

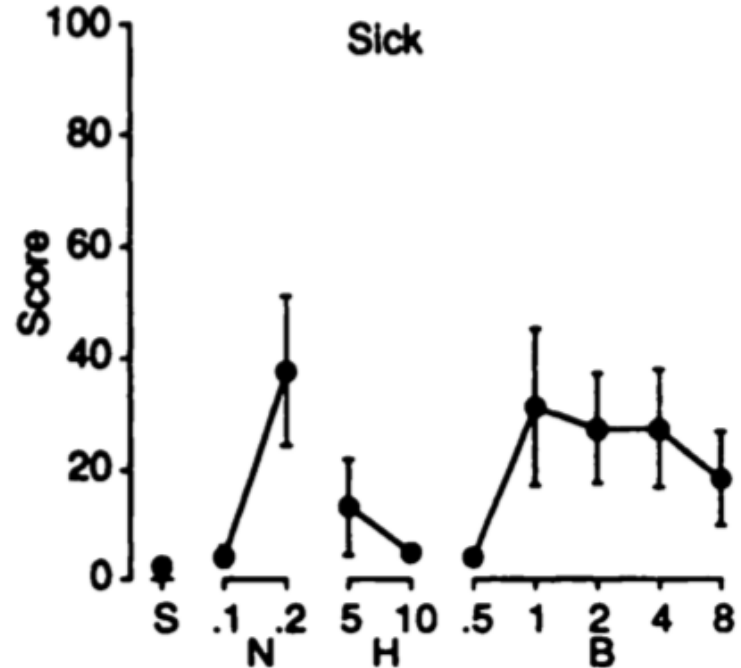
“The present demonstration of diminished antagonist effects of buprenorphine at higher doses may be an example of noncompetitive autoinhibition. “

Buprenorphine Effects in Methadone-Maintained Volunteers: Effects at Two Hours after Methadone¹

ERIC C. STRAIN,² KENZIE L. PRESTON,³ IRA A. LIEBSON² and GEORGE E. BIGELOW²

Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, Maryland

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ED Bup Initiations

Demographics of Unique Patients	
(N=404)	%
Gender	
Male	68
Age	
18-25	9
26-34	36
35-44	24
45-54	15
55-64	12
65+	4
Homeless	
	23
Race	
Black	43.32
White	37.87

N=599 Encounters*

2-4 mg	n=60 (10%)
8 mg	n=143 (24%)
10-12 mg	n=23 (3.8%)
16 mg	n=108 (18%)
18-24 mg	n=124 (21%)
> 24 mg	n=141 (24%)

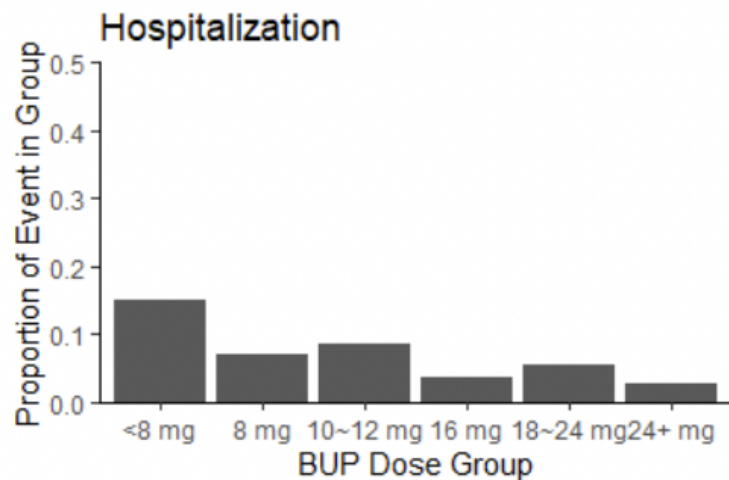
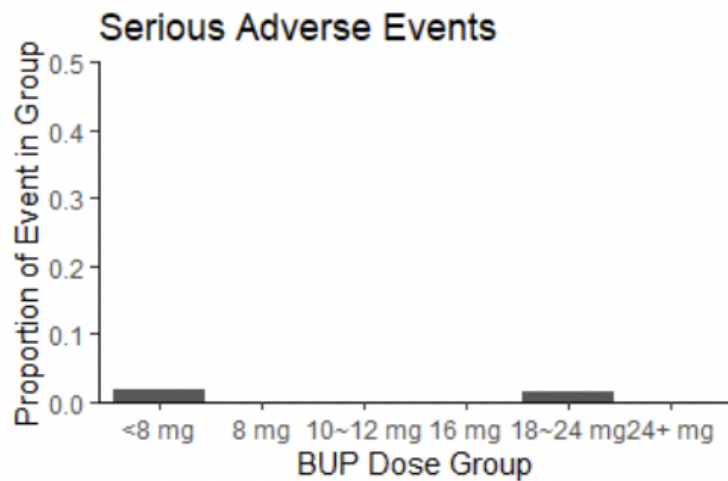
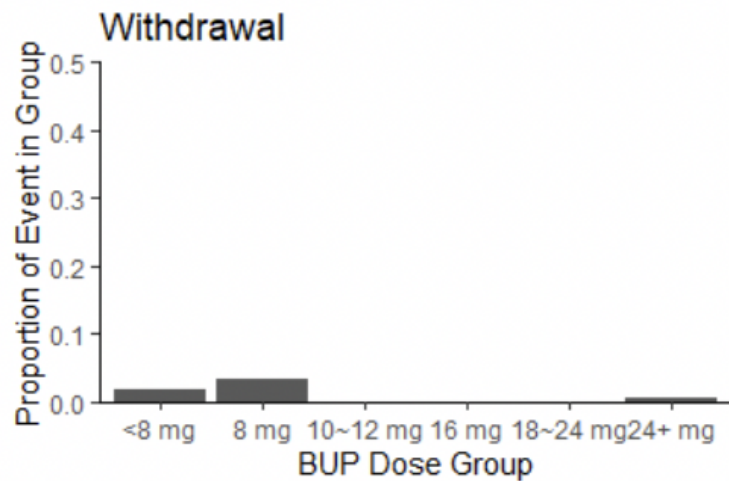
**loading
dose**

* Number of Encounters

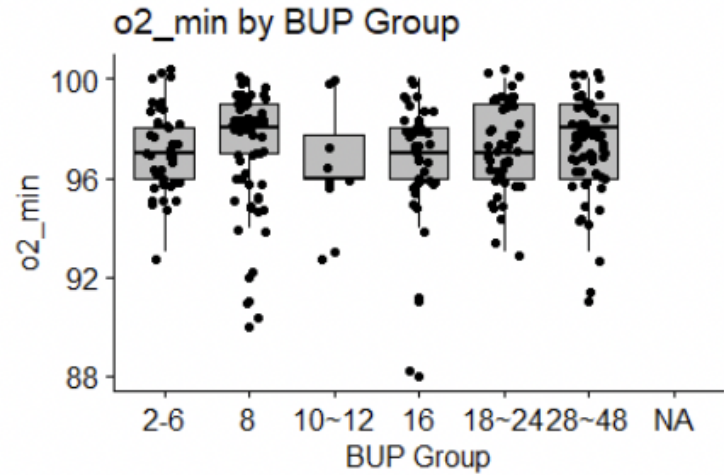
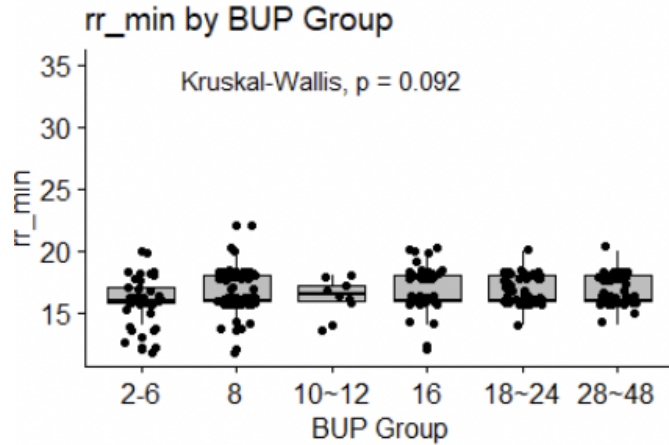
- 1 301 (75%)
- 2-4 88 (22%)
- ≥ 5 13 (3%)

<i>Bup Dose</i>	<i>Precipitated Withdrawal</i>	<i>Group Size</i>	<i>Event Rate</i>
<8mg	1	60	0.017
8mg	5	146	0.034
10-12mg	0	23	0
16mg	0	107	0
18-24mg	0	124	0
24+mg	1	139	0.007

<i>Bup Dose</i>	<i>Adverse Events</i>	<i>group_size</i>	<i>event rate</i>
<8mg	1	60	0.017
8mg	0	143	0
10-12mg	0	23	0
16mg	0	108	0
18-24mg	2	124	0.016
24+mg	0	141	0



Respiratory Status



Lessons Learned

*Loading Bup is practical
and safe.*

Review

Pharmacokinetics of the combination tablet of buprenorphine and naloxone

C. Nora Chiang*, Richard L. Hawks

Division of Treatment Research and Development, National Institute on Drug Abuse, 6001 Executive Blvd, Room 4123 Bethesda, MD 20892, USA

Received 19 December 2002; accepted 4 February 2003

C.N. Chiang, R.L. Hawks / Drug and Alcohol Dependence 70 (2003) S39–S47

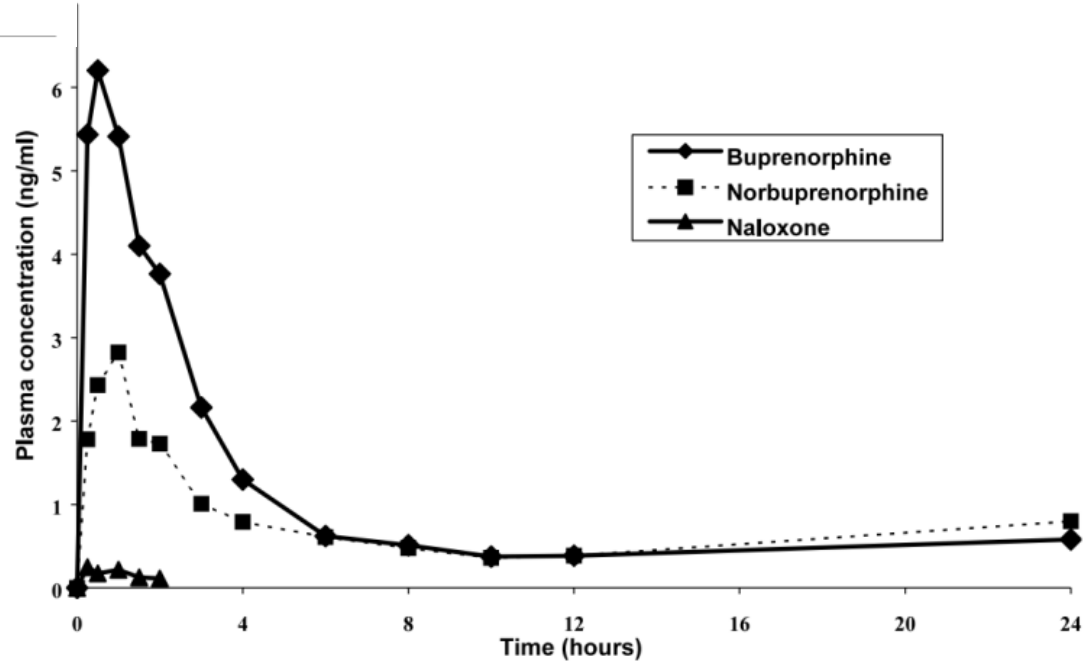


Fig. 4. The time course of plasma levels of buprenorphine, norbuprenorphine and naloxone for a subject receiving a sublingual dose of the combination tablet of buprenorphine (16 mg) and naloxone (4 mg) (data from Jones et al., 1997).

8mg SL Tablet

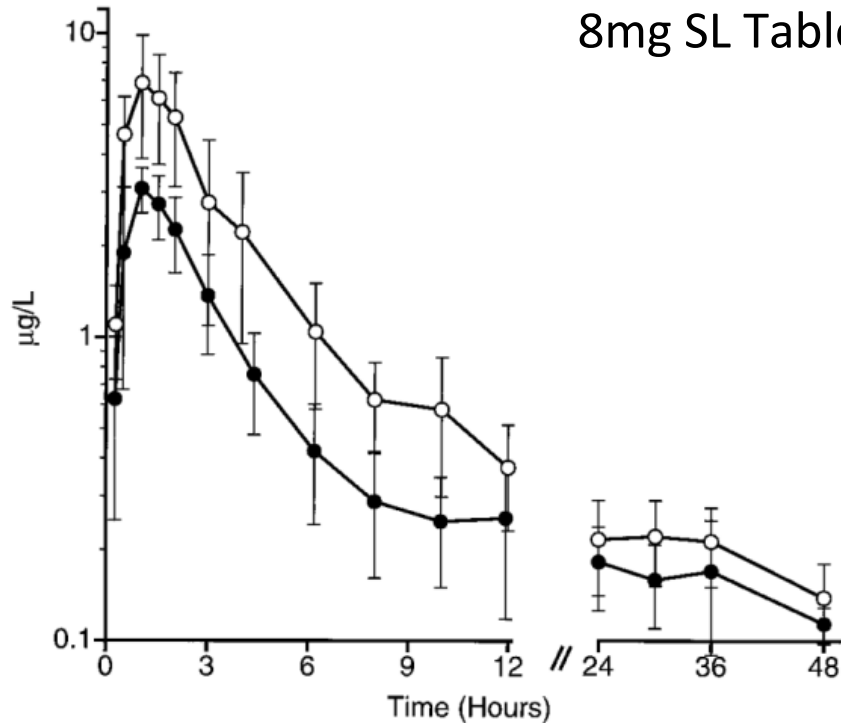


Fig. 7. Plasma concentration–time profile of buprenorphine (mean ± SD) in six human volunteers receiving 8 mg of buprenorphine in 1 mL of 300 mL/L ethanol sublingually for 5 min (○) and an 8-mg buprenorphine tablet sublingually for 5 min (●).

AUC (extrapolated) h · µg/L
Peak concentration, µg/L
Peak time, h

Subnanogram-concentration measurement of buprenorphine in human plasma by electron-capture capillary gas chromatography: application to pharmacokinetics of sublingual buprenorphine

E. THOMAS EVERHART,* POLLY CHEUNG, PETER SHWONEK, KAREN ZABEL, EILEEN C. TISDALE, PEYTON JACOB III, JOHN MENDELSON, and REESE T. JONES

Tablet (n = 6) (mean ± SD) Dose B

17.8 ± 7.5

3.12 ± 0.52

1.20 ± 0.27

Bioavailability of an 8-mg tablet relative to that from an 8-mg solution

Liquid (n = 6) (mean ± SD) Dose A

35.7 ± 13.9

7.14 ± 2.80

0.85 ± 0.27

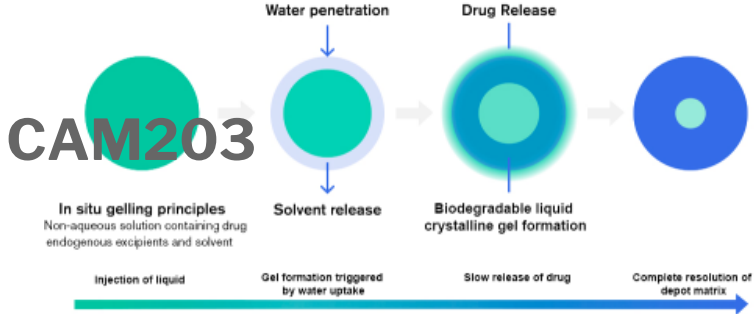
Tablet (n = 6) (mean ± SD) Dose B

17.8 ± 7.5

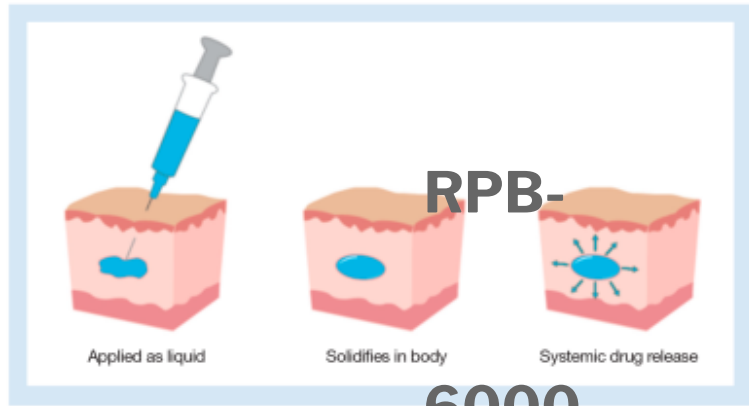
3.12 ± 0.52

1.20 ± 0.27

XR Bup

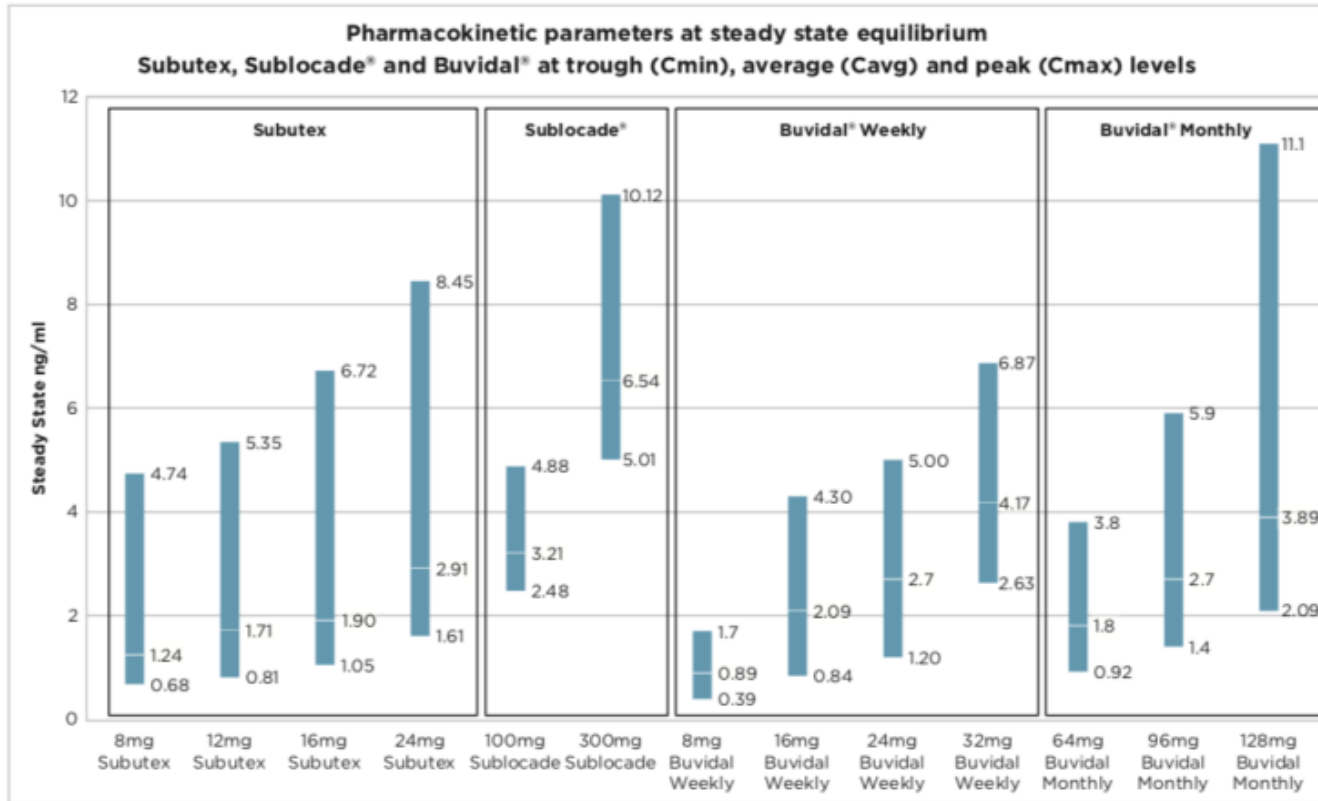


8



6000

Figure 1: Pharmacokinetic parameters - steady state



Lintzeris N, Dunlop A, Masters D (2019) Clinical guidelines for use of depot buprenorphine (Bupival® and Sublocade®) in the treatment of opioid dependence. NSW Ministry of Health, Sydney Australia

Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

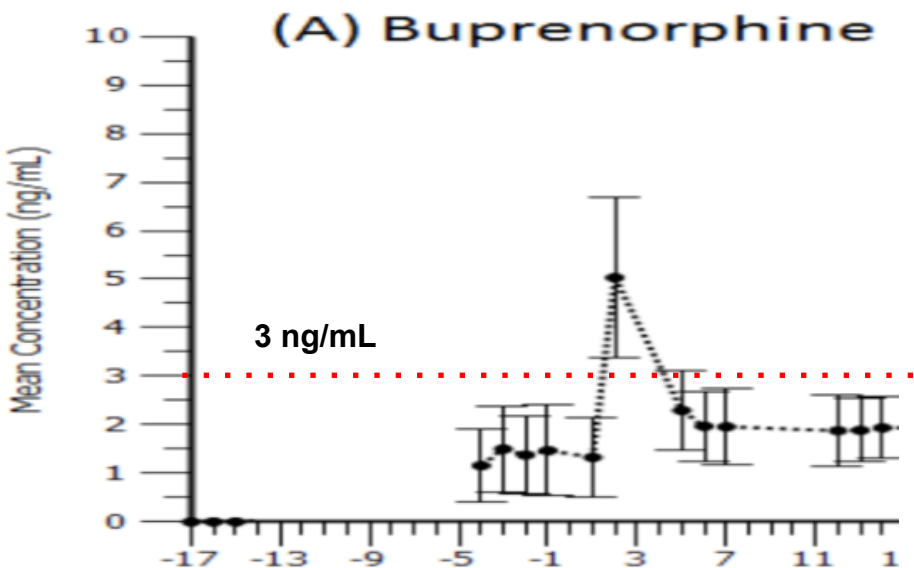
Barbara R Haight, Susan M Learned, Celine M Laffont, Paul J Fudala, Yue Zhao, Amanda S Garofalo, Mark K Greenwald, Vijay R Nadipelli, Walter Ling, Christian Heidbreder, for the RB-US-13-0001 Study Investigators*

111

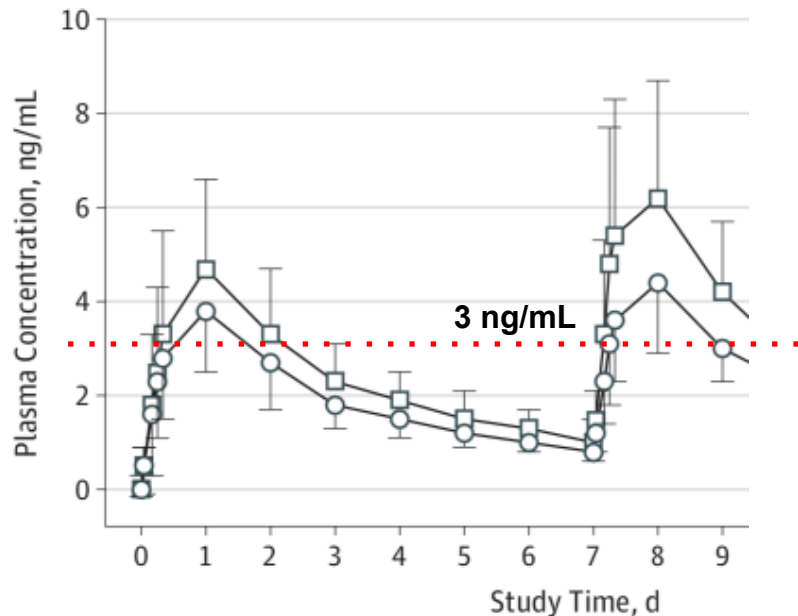
JAMA Psychiatry | Original Investigation

Effect of Buprenorphine Weekly Depot (CAM2038) and Hydromorphone Blockade in Individuals With Opioid Use Disorder A Randomized Clinical Trial

Sharon L. Walsh, PhD; Sandra D. Comer, PhD; Michelle R. Lofwall, MD; Bradley Vince, DO; Naama Levy-Cooperman, PhD; Debra Kelsh, MD; Marion A. Coe, BA; Jermaine D. Jones, PhD; Paul A. Nuzzo, MA; Fredrik Tibergh, PhD; Behshad Sheldon, BS; Sonnie Kim, PharmD

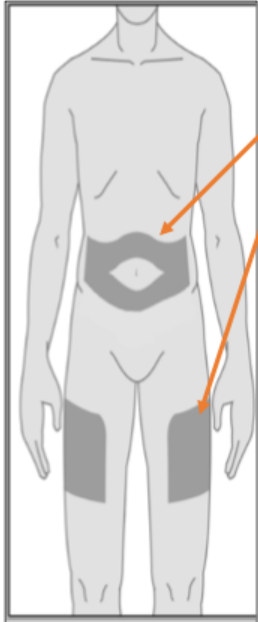


B Buprenorphine

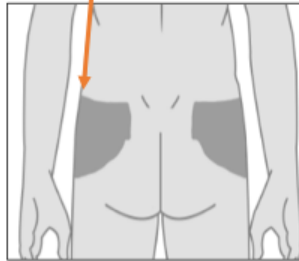


XR-BUP (CAM2038) Injection Guidelines

Injection Placement

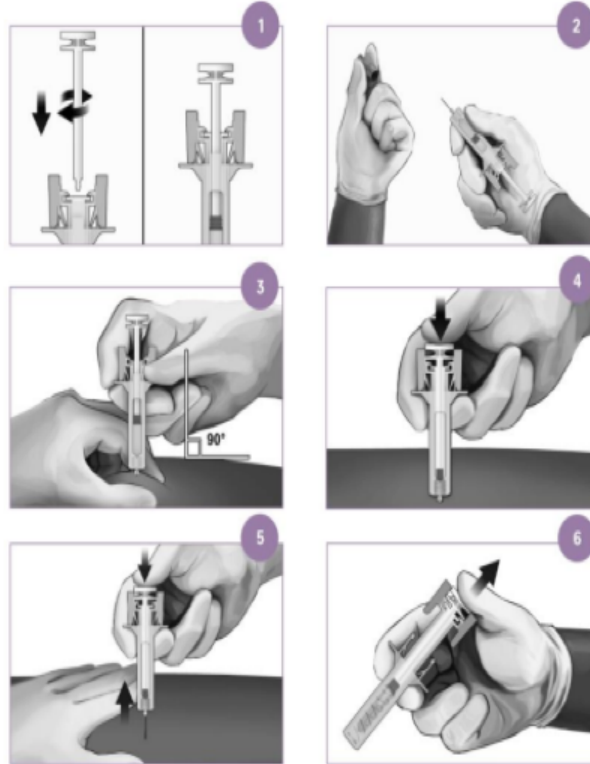


First injections should use, *abdomen, outer gluteal area and thighs*



Avoid waistline or within 5 cm of the navel

Injection Instructions



1. Gently insert plunger rod into plunger stopper, turning clockwise until secured.
2. Carefully remove needle shield.
3. **Pinch skin** at injection site between thumb and finger. Fully insert needle at **90° angle**, perpendicular to skin.
4. Slowly depress plunger until it latches between the guard wings and all solution is injected. **Hold for 2 seconds.**
5. Gently pull needle from skin, keeping plunger fully depressed.
6. Slowly remove thumb from plunger to retract the needle.

DO NOT RUB INJECTION SITE

May gently wipe away blood from injection site with cotton ball or gauze

Inspect the safety syringe closely: May see a small bubble

***Do not use if liquid not clear or past expiration date**

Case Discussions



Case Discussions

Candidates for XR-Bup

1. Stable patients
2. Unstable patients
3. Induction

Marshall CARES

Program philosophy: low threshold, patient centered, early promotion of XR-bup for all patients.

Marshall CARES

Patient Case: women down from Tahoe, XR-bup overcomes geographic barriers to access.

Marshall CARES

Patient Case: women just gave birth, husband still using in home and women can't stop, undergoes XR-bup induction, helps overcome significant psychosocial barriers.

Marshall CARES

CAREs Patient Case: guy that stops using meth and alcohol after stabilizing on XR- bup, overcomes dysfunction of comorbid SUDs.

Marshall CARES

CARES slide of total numbers in program, graph of XR-bup program numbers over time.

Marshall CARES

CARES slide of XR-bup patient characteristics: used for high risk patients.

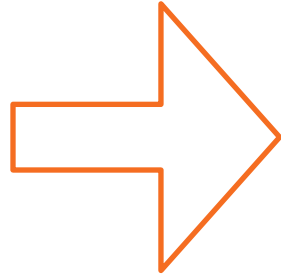
Case Discussions

XR-Bup is liberating

1. No Diversion
2. No Urine Drug Screening
3. No Frequent visits
4. No pharmacy hassles

Case Discussions

Emergency



Bridge Clinic

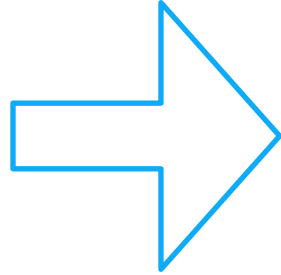
Department

Case Discussion: Mr. L

- 40 yo man with OUD (IV heroin, fentanyl)
- Presented to Emergency Department → CAM-2038 (Bup-XR 24 mg)
- Loss to follow-up → fentanyl overdose two weeks later → CPR and naloxone → admitted with rib fractures, pneumonia and bacteremia
- Hospital Day #2 given Bup-XR 300 mg → hydromorphone PRN pain added → discharged to Skilled Nursing Facility, weaned off hydromorphone → Bup-XR 300 mg #2 one month later
- 6 months later remains engaged in care with us receiving Bup-XR ~q28 days

Case Discussion

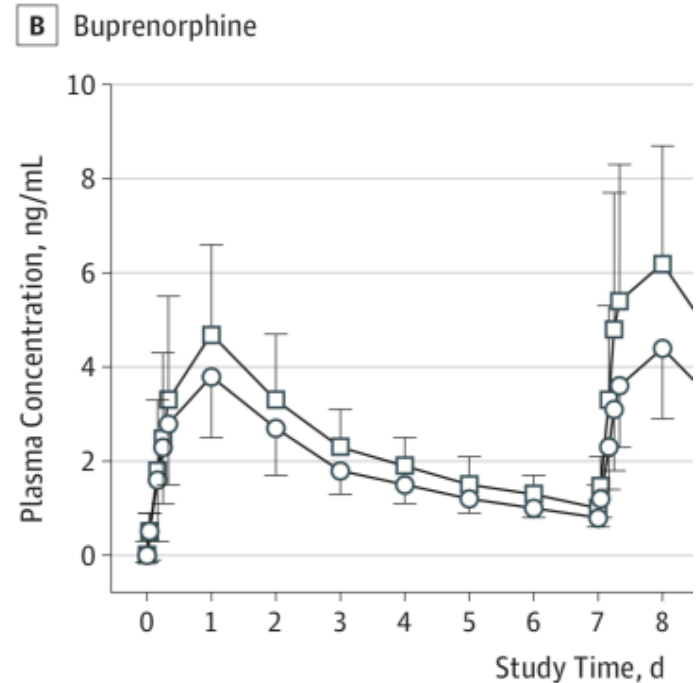
**Bridge
Clinic**



**Emergency
Department**

Case Discussion

- XR Bup has a rapid onset.
- Great for induction.



Incarceration

30 day XR

*No Diversion

*No daily dosing



Case Discussions

Problems

1. Injection hurts
2. Lots of variability in response
3. Stocking / pharmacy
4. Occasionally too strong

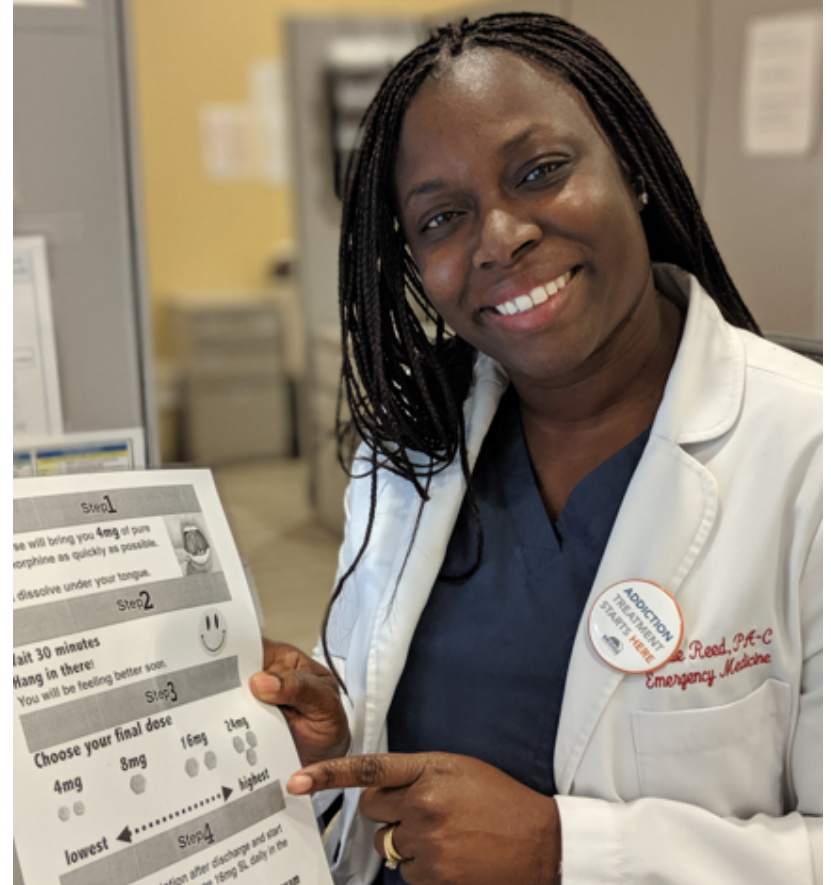
Case Discussions

Promises

1. Meth + Fentanyl
2. Diversion
3. Light touch
4. Discontinuation

Summary

- SL Bup wears off too fast. It's a problem
- XR Bup has many applications
- Suitable for induction and maintenance
- Long term effectiveness is unknown



References

- Lintzeris, N., A. Dunlop, and D. Masters. "Clinical guidelines for use of depot buprenorphine (Buvidal® and Sublocade®) in the treatment of opioid dependence." *NSW Ministry of Health: Sydney* (2019).
- Ling, Walter, Steve Shoptaw, and David Goodman-Meza. "Depot buprenorphine injection in the management of opioid use disorder: From development to implementation." *Substance Abuse and Rehabilitation* 10 (2019): 69.
- Phillips-Jackson, Helen, et al. "Budget Impact Analysis of the Introduction of Injectable Prolonged-Release Buprenorphine on Opioid Use Disorder Care Resource Requirements." *Clinicoeconomics and Outcomes Research: CEOR* 12 (2020): 233.
- Coe, Marion A., Michelle R. Lofwall, and Sharon L. Walsh. "Buprenorphine pharmacology review: update on transmucosal and long-acting formulations." *Journal of addiction medicine* 13.2 (2019): 93-103.
- Phillips-Jackson, Helen, et al. "Budget Impact Analysis of the Introduction of Injectable Prolonged-Release Buprenorphine on Opioid Use Disorder Care Resource Requirements." *Clinicoeconomics and Outcomes Research: CEOR* 12 (2020): 233.