Rapid high-dose Bup induction in the Emergency Department and by Paramedics: initial observations and future directions

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ALAMEDA HEALTH SYSTEM

HIGHLAND HOSPITAL
A member of Alameda Health System

UCSF

CA BRIDGE

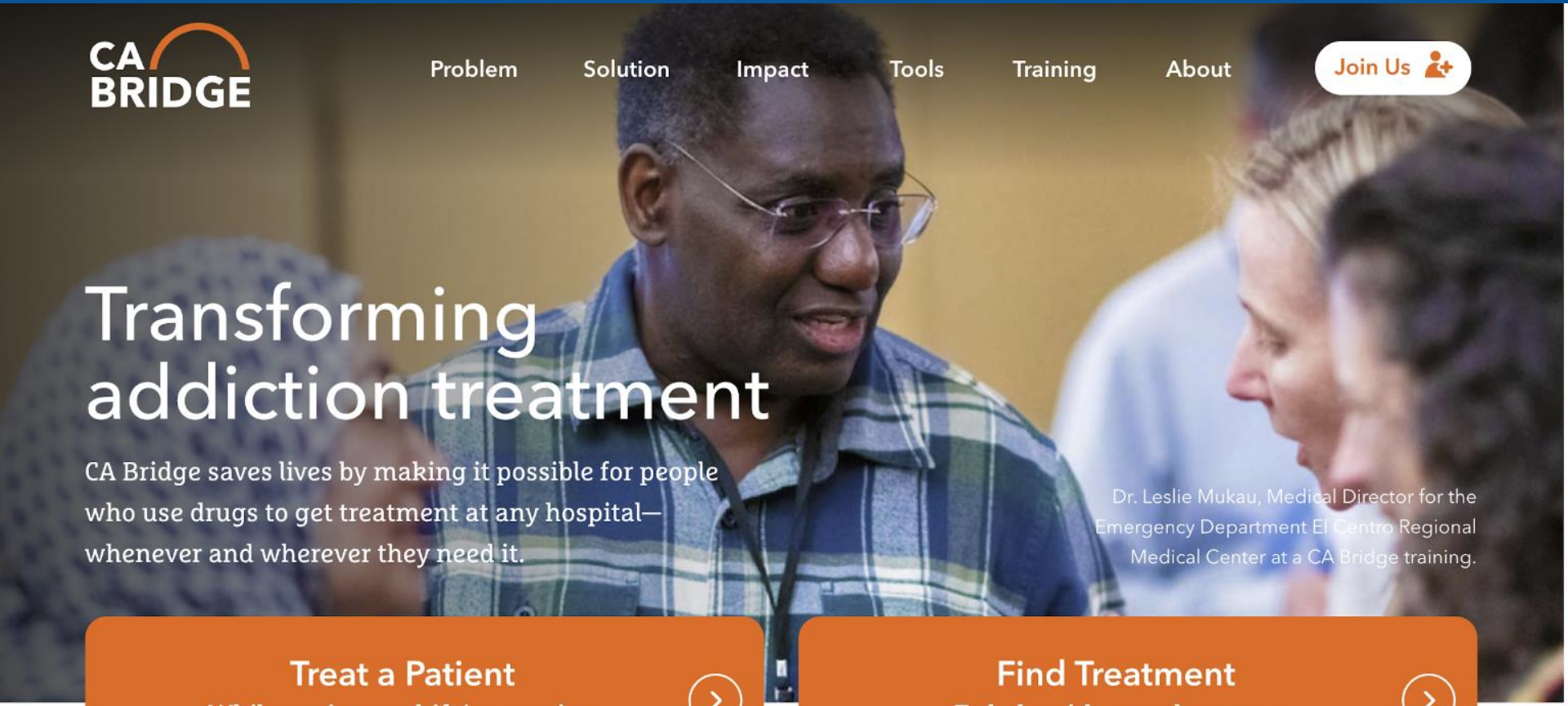
Disclosures:

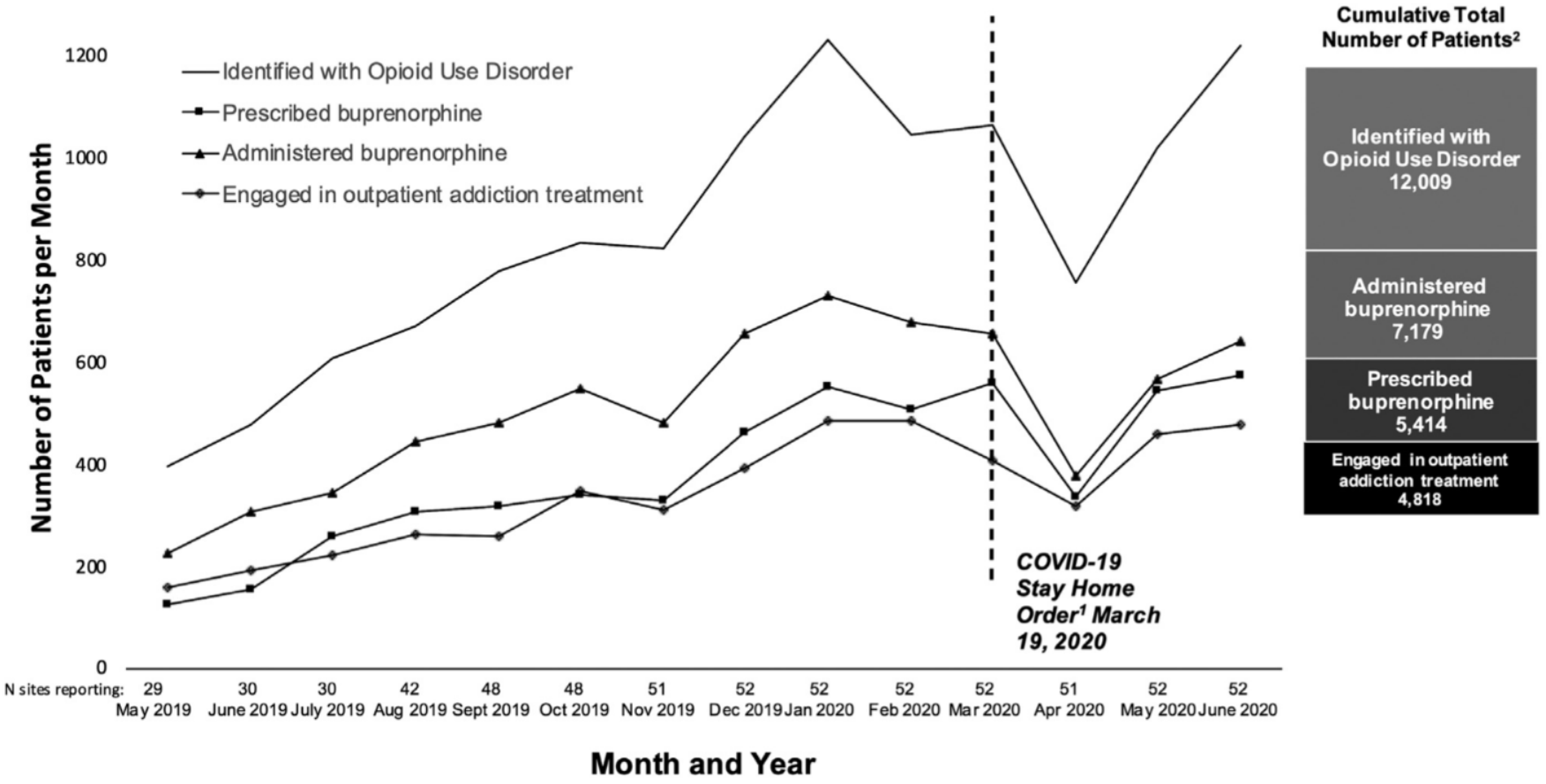
Funding: Alameda Health System/East Bay Medical Group; Alameda County Behavioral Healthcare Services. NIDA CTN; Public Health Institute/CA Bridge; Honoria for various single talk presentations for health systems/organizations including Vituity, Team Health, and Kaiser.

Decriminalize drug use

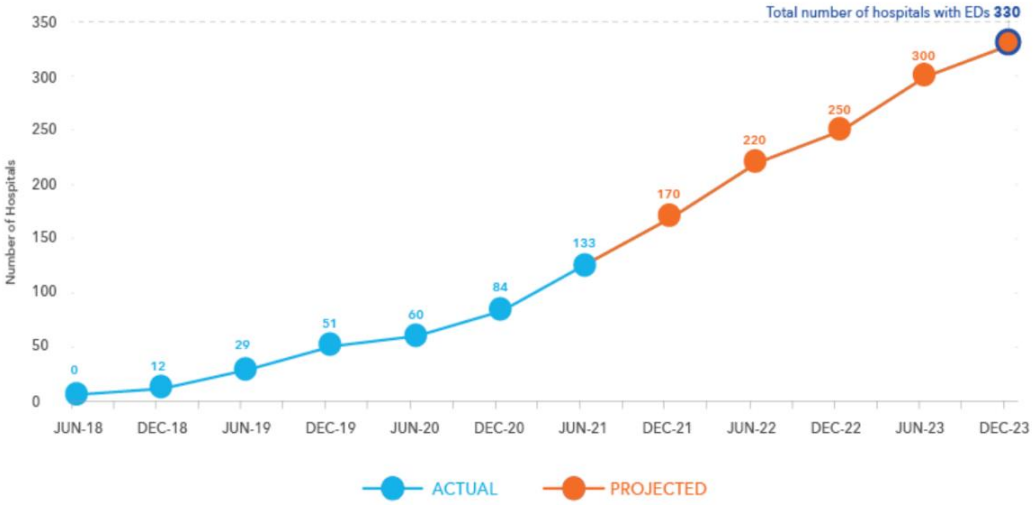
Photo: Brian L. Frank for The New York Ti

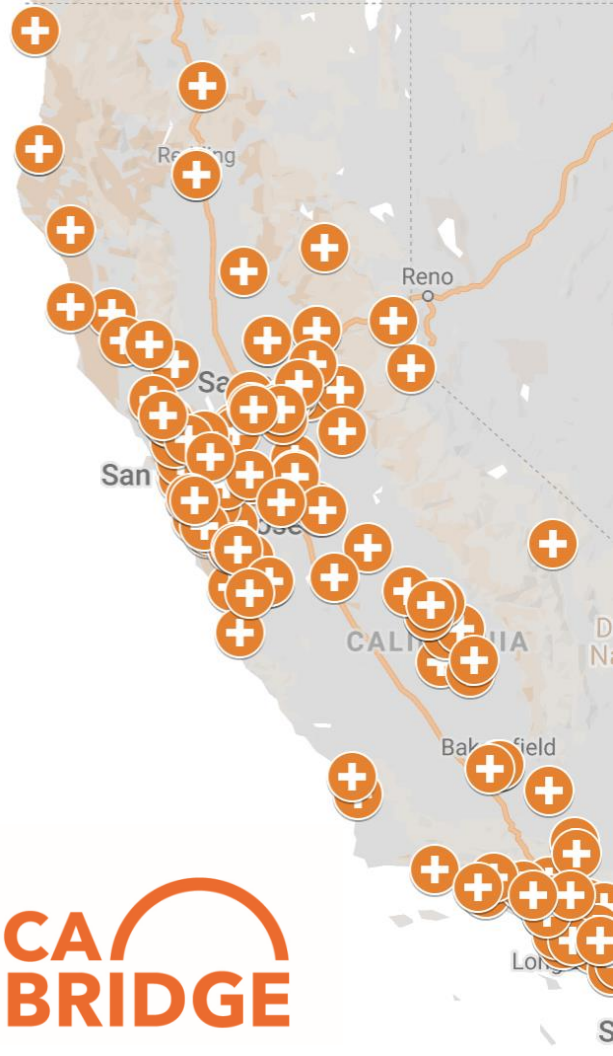
We are the Drug Policy Alliance.


CA BRIDGE
Problem
Solution
Impact
Tools
Training
About
Join Us
Transforming addiction treatment
CA Bridge saves lives by making it possible for people who use drugs to get treatment at any hospital—whenever and wherever they need it.
Dr. Leslie Mukau, Medical Director for the Emergency Department El Centro Regional Medical Center at a CA Bridge training.
Treat a Patient
While you're on-shift/on-service.
Find Treatment
To help with your drug use.


Identified with Opioid Use Disorder
Prescribed buprenorphine
Administered buprenorphine
Engaged in outpatient addiction treatment
Number of Patients per Month
1200
1000
800
600
400
200
0
COVID-19 Stay Home Order[1] March 19, 2020
N sites reporting: 29 30 30 42 48 48 51 52 52 52 52 51 52 52
May 2019 June 2019 July 2019 Aug 2019 Sept 2019 Oct 2019 Nov 2019 Dec 2019 Jan 2020 Feb 2020 Mar 2020 Apr 2020 May 2020 June 2020
Month and Year
Cumulative Total Number of Patients[2]
Identified with Opioid Use Disorder 12,009
Administered buprenorphine 7,179
Prescribed buprenorphine 5,414
Engaged in outpatient addiction treatment 4,818

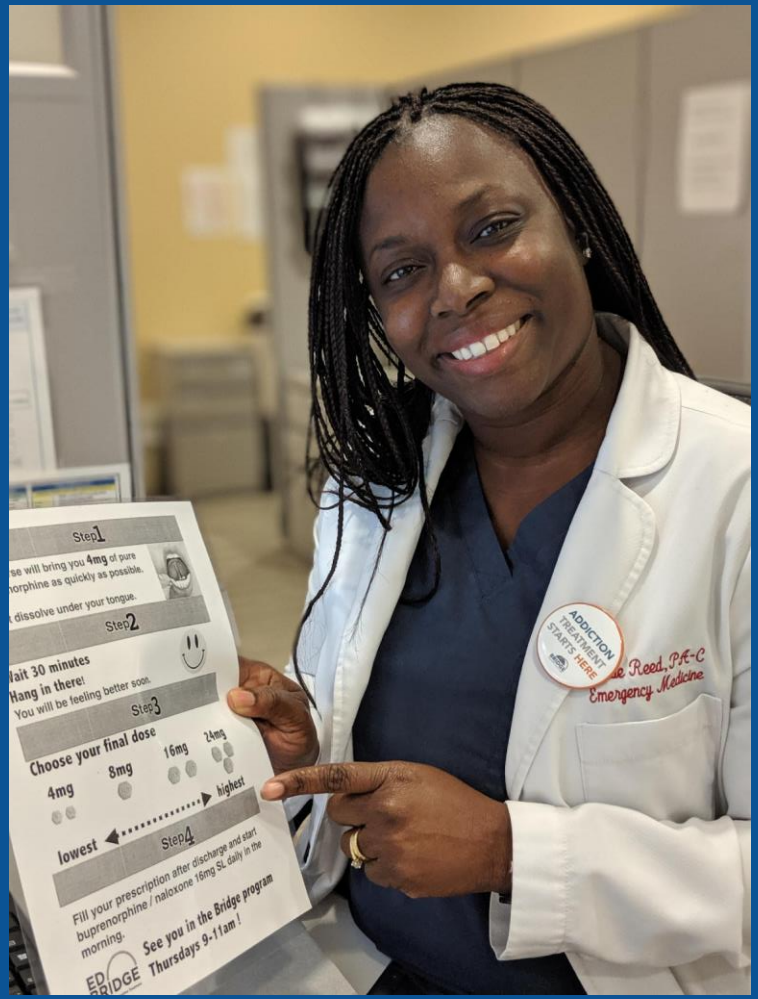
282 CA Bridge Hospitals in California





Implementation Goal

Friendly, on demand buprenorphine, dosed right, the first time



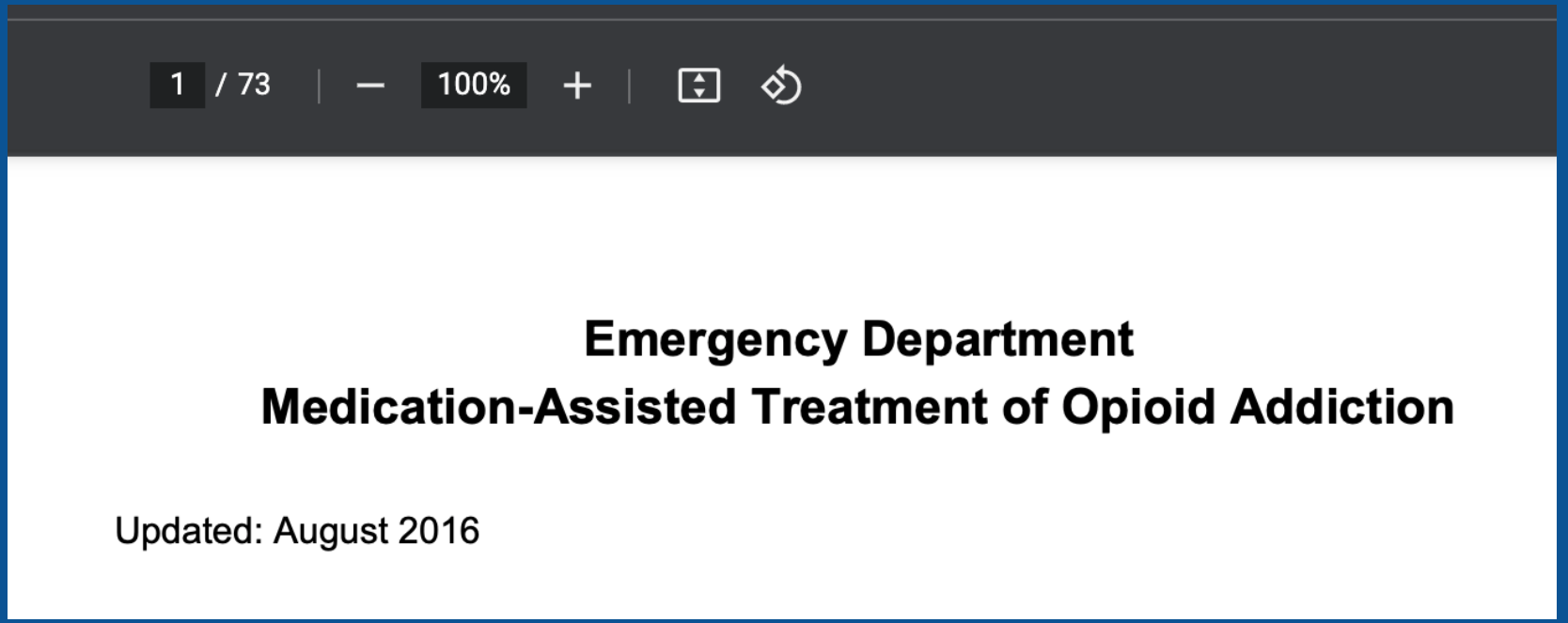
Objectives:

1. A pharmacologic model for the complex interaction of buprenorphine and full agonist opioids (both illicit and medically administered) in variety of commonly encountered clinical scenarios.

1. Strategies to optimize both buprenorphine and full agonist dosing and titration to promote successful induction.

1. Effectively adapt treatment plans when buprenorphine induction becomes complex using buprenorphine and additional medications such as full agonist opioids and ketamine.

Getting started in 2016



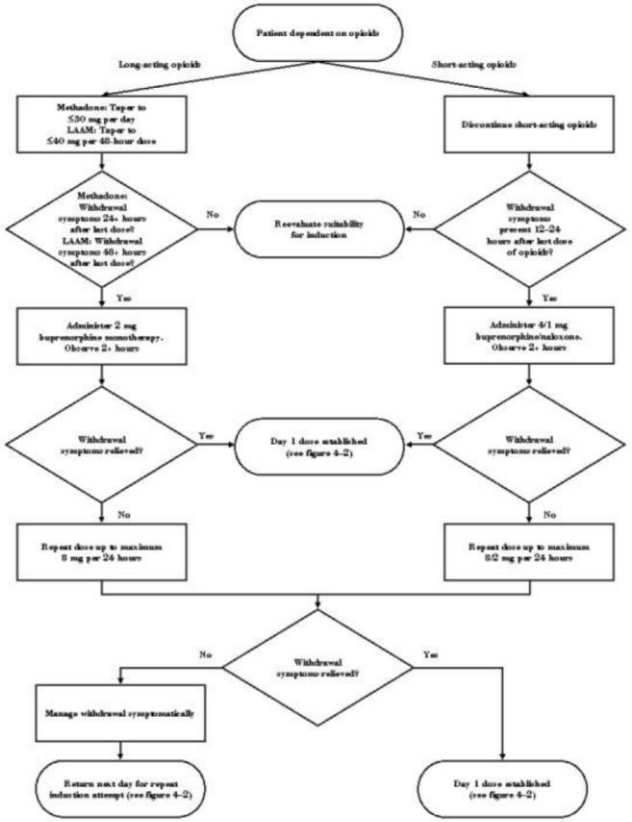


Figure 4-1. Induction Days 1–2

*If buprenorphine monotherapy was administered on Day 1, switch to buprenorphine/naloxone on Day 2 (for a patient who is not pregnant).

**Dose may be increased by 2/0.5–4/1 mg increments on subsequent days as needed for symptom relief. Target dose of 12/3–16/4 mg buprenorphine/naloxone per day by the end of the first week.

Figure 4-2. Induction Day 2 Forward

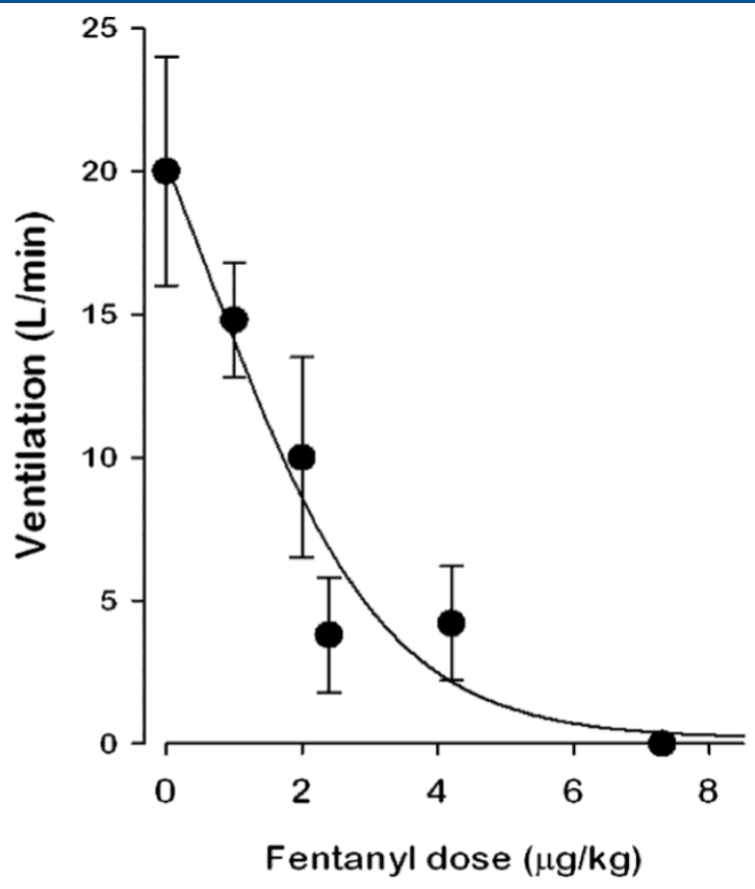
Problems

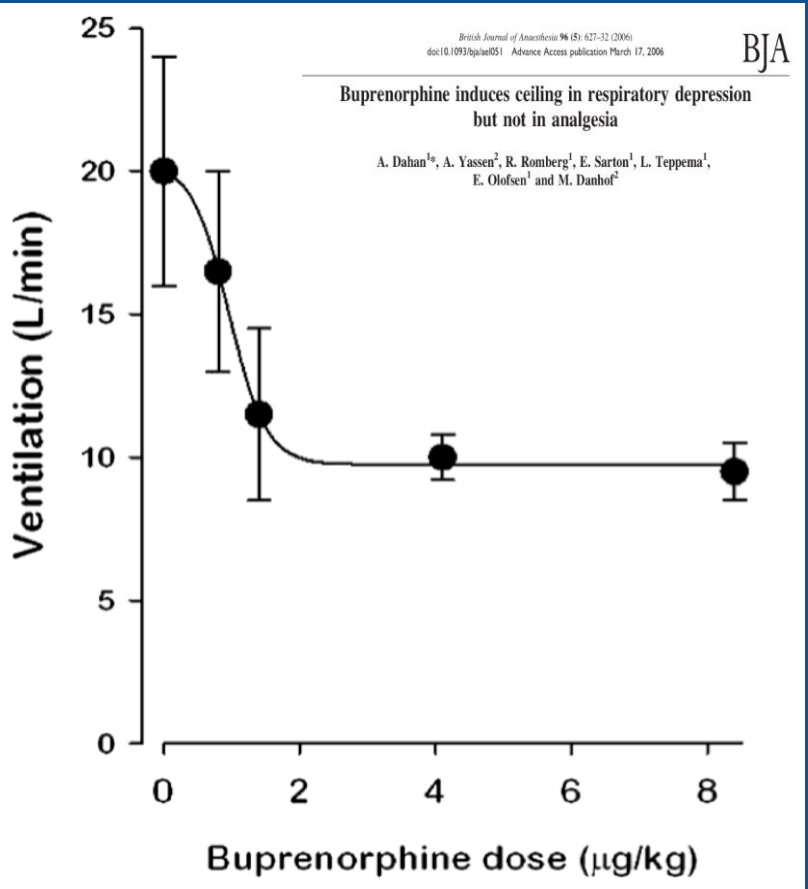
- Fear of getting it wrong
- Fear of hurting someone
- Frustratingly slow
- Partial treatment
- Tenuous follow up – bounce back

2017 – start from scratch

- Make it fast
- Make it last

Ceiling on Respiratory depression





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]

Cowan 1977

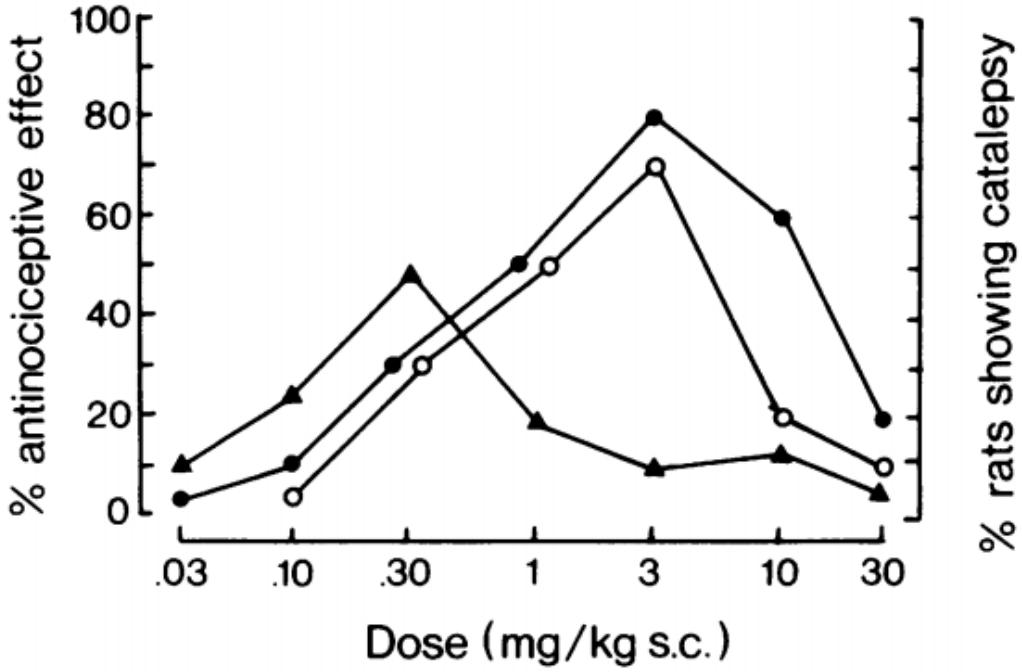
Early Observation:

Bup dose effects are not linear

Br. J. Pharmac. (1977), **60**, 537–545

AGONIST AND ANTAGONIST PROPERTIES OF BUPRENORPHINE, A NEW ANTINOCICEPTIVE AGENT

A. COWAN[1], J.W. LEWIS & I.R. MACFARLANE
Department of Pharmacology, Reckitt & Colman, Dansom Lane, Kingston-upon-Hull HU8 7DS

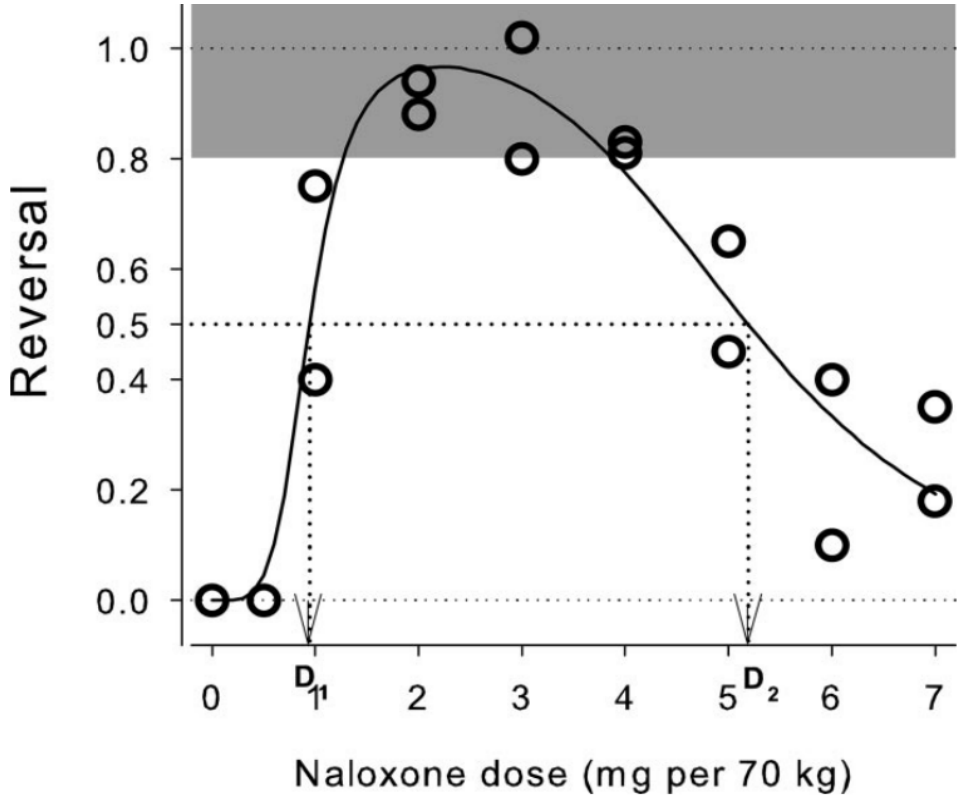


Van Dorp 2006

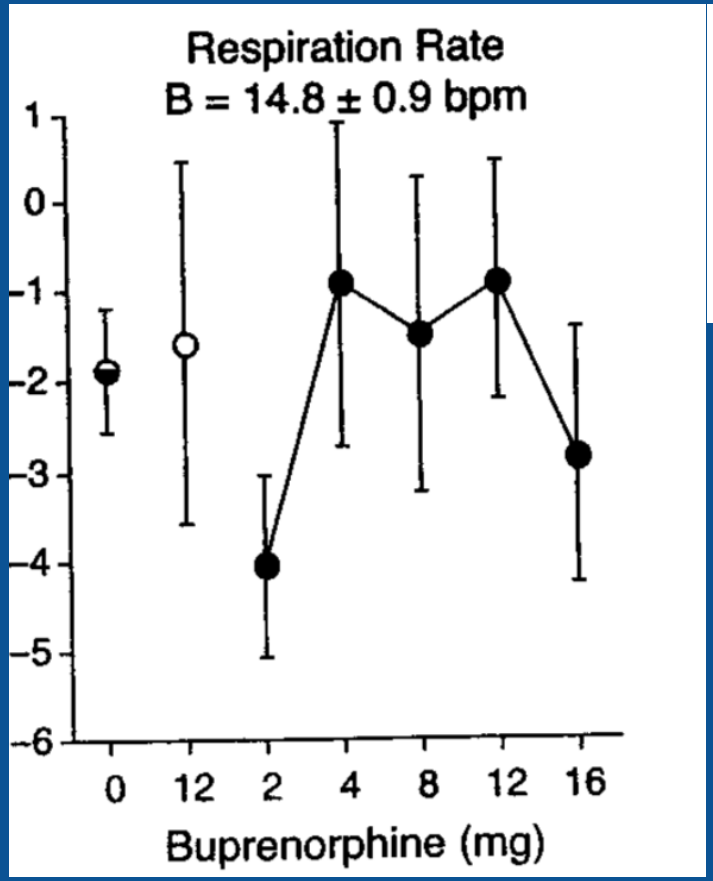
Anesthesiology 2006; 105:51–7

Naloxone Reversal of Buprenorphine-induced Respiratory Depression

Eveline van Dorp, M.D., Ashraf Yassen, M.Sc.,† Elise Sarton, M.D., Ph.D.,‡ Raymonda Romberg, M.D., Ph.D.,§ Erik Olofsen, M.Sc.,‖ Luc Teppema, Ph.D.,# Meindert Danhof, Ph.D.,** Albert Dahan, M.D., Ph.D.††*



Ceiling on Respiratory depression



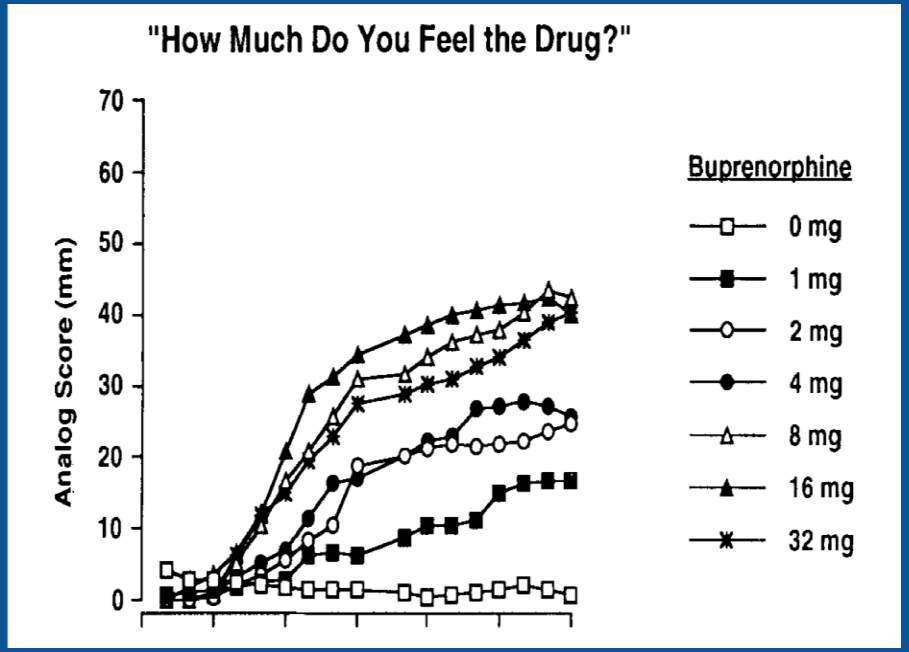
ORIGINAL CONTRIBUTION

Effects of High-Dose Intravenous Buprenorphine in Experienced Opioid Abusers

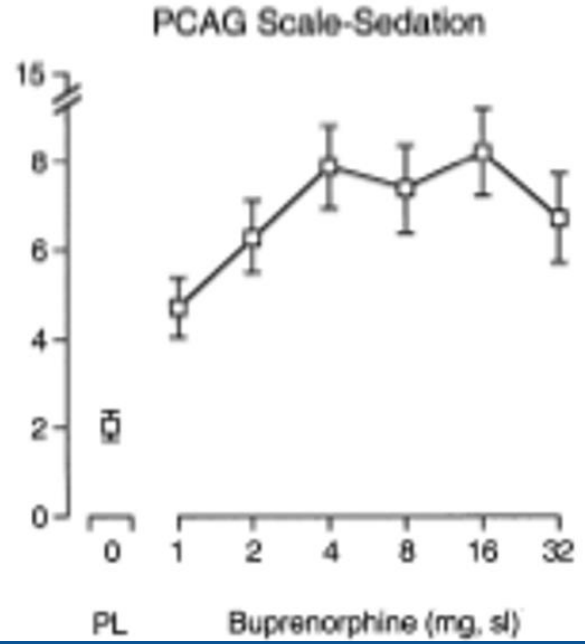
Annie Umbricht, MD,† Marilyn A. Huestis, PhD,* Edward J. Cone, PhD,*‡ and Kenzie L. Preston, PhD**

Bup 16 mg IV push
Non-dependent subjects

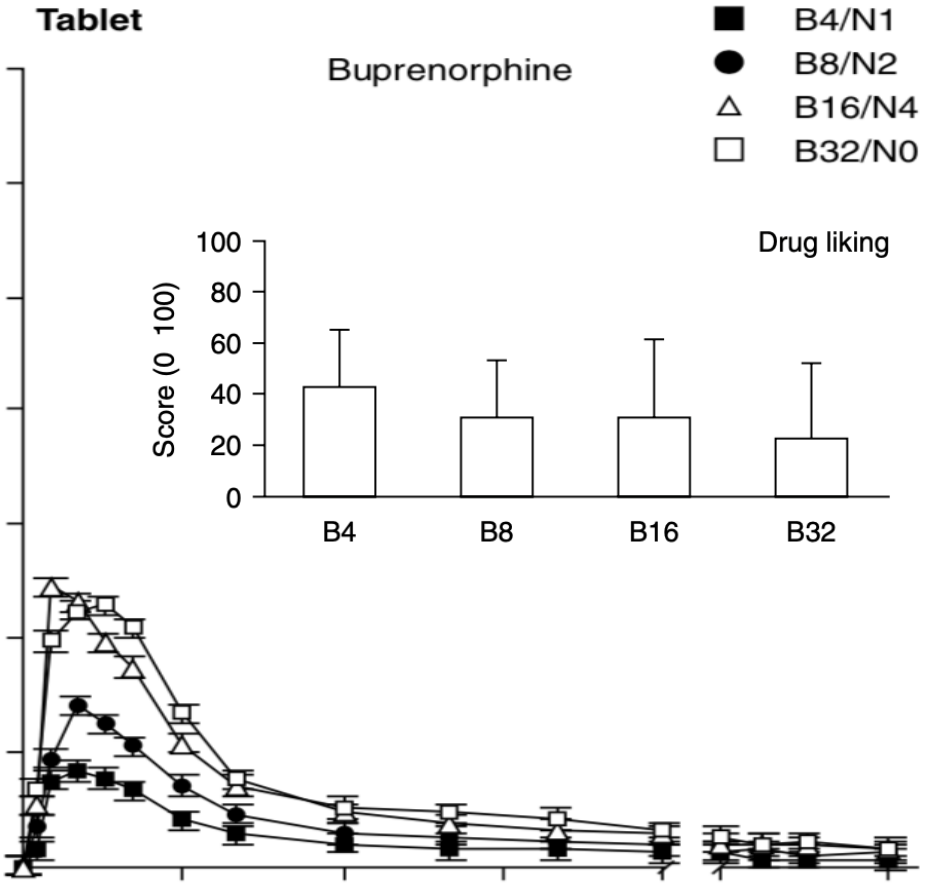
Ceiling on sedation



Clinical pharmacology of buprenorphine: Ceiling effects at high doses



Walsh, Sharon L., et al. "Clinical pharmacology of buprenorphine: ceiling effects at high doses." *Clinical Pharmacology & Therapeutics* 55.5 (1994): 569-580.



ORIGINAL RESEARCH ARTICLE
Clin Pharmacokinet 2004; 43 (5): 329-340
0312-5963/04/0005-0329/$31.00/0

Pharmacokinetics and Subjective Effects of Sublingual Buprenorphine, Alone or in Combination with Naloxone

Lack of Dose Proportionality

Debra S. Harris,[1] John E. Mendelson,[1] Emil T. Lin,[2] Robert A. Upton[2] and Reese T. Jones[1]

1 Drug Dependence Research Center, Langley Porter Psychiatric Institute, University of California, San Francisco, San Francisco, California, USA
2 Department of Biopharmaceutical Sciences, University of California, San Francisco, San Francisco, California, USA

No differences were found between dose strengths for most subjective and physiological effects.

Observations of Ceiling suggest safety

Avens Publishing Group
J Addiction Prevention
February 2016 Vol.:4, Issue:1

Instant Detoxification of Heroin with High Dose of Buprenorphine

Keywords: Buprenorphine; Single high dose; Heroin detoxification

Abstract

Background: Heroin dependence is a raising problem.

Objective: To investigate the effect of a single dose of 120 mg of buprenorphine for the detoxification of heroin dependence.

Results: A single dose of 120 mg of buprenorphine is very useful for the treatment of heroin dependents.

Discussion: This study describes that one high dose of buprenorphine is beneficial for the management of heroin dependence. This finding is outstanding.

Conclusion: We concluded that a single high dose of buprenorphine may treat heroin withdrawal symptoms very well. This finding is a considerable addition to the literature of heroin detoxification.

Open Access **Case Report**

Journal of
Addiction &
Prevention

Jamshid Ahmadi*

Substance Abuse Research Center, Department of Psychiatry, Shiraz University of Medical Sciences, Iran

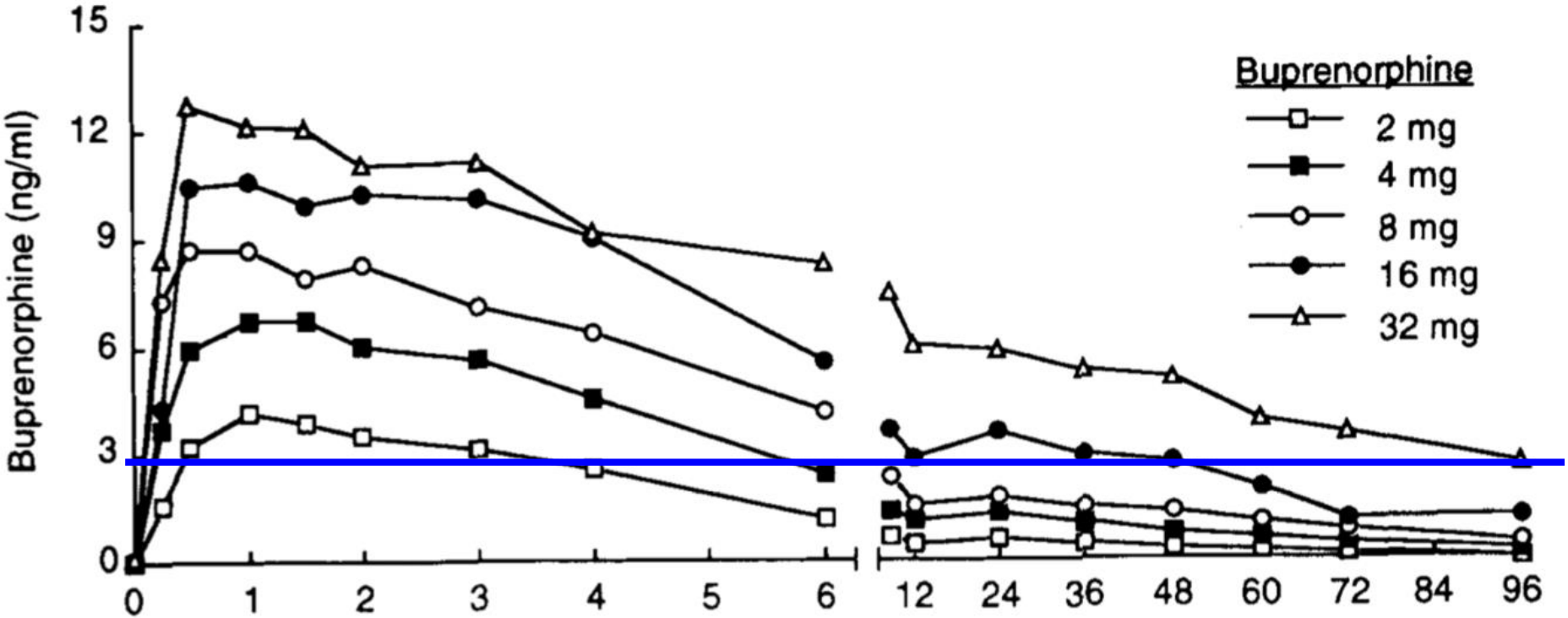
***Address for Correspondence**
Jamshid Ahmadi, Professor and Founding Director, Substance Abuse Research Center, Department of Psychiatry, Shiraz University of Medical Sciences, Shiraz, Iran, Tel/Fax: +98-71-3627 93 19; E-mail: Jamshid_Ahmadi@yahoo.com

Submission: 08 February, 2016
Accepted: 16 February, 2016
Published: 20 February, 2016

Reviewed & Approved by: Dr. Thomas Heffernan, Department of Psychology and Faculty of Life and Health Sciences, Northumbria University, UK

Pain and Craving Scale of measurement: *0-1-2-3-4-5-6-7-8-9-10.*

Long lasting effects to bridge early challenges after discharge



Walsh, Sharon L., et al. "Clinical pharmacology of buprenorphine: ceiling effects at high doses." *Clinical Pharmacology & Therapeutics* 55.5 (1994): 569-580.

Alternate day dosing: 44mg SL

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Drug and Alcohol Dependence 55 (1999) 157–163

DRUG and ALCOHOL DEPENDENCE

Plasma concentrations of buprenorphine 24 to 72 hours after dosing

M.C. Chawarski [a,*], R.S. Schottenfeld [a], P.G. O'Connor [b], J. Pakes [a]

[a] *Department of Psychiatry, CMHC/SAC, Suite S214, Yale University School of Medicine, 34 Park Street, New Haven, CT 06519, USA*
[b] *Department of Medicine, Yale University School of Medicine, New Haven, CT, USA*

Received 15 January 1998; accepted 3 December 1998

Short communication

Limits to buprenorphine dosing: a comparison between quintuple and sextuple the maintenance dose every 5 days

Anke Gross [a,*], Eric A. Jacobs [a,1], Nancy M. Petry [a,2], Gary J. Badger [b], Warren K. Bickel [a]

[a] *Substance Abuse Treatment Center, University of Vermont, 1 South Prospect Street, Burlington, VT 05401, USA*
[b] *Department of Psychiatry and Department of Psychology, Medical Statistics, University of Vermont, Burlington, VT 05401, USA*

Received 2 May 2000; received in revised form 15 November 2000; accepted 15 November 2000

14 subjects
Maximum dose 76mg
+ **Subjective withdrawal after 96 hours**
+ **No objective withdrawal at 120 hours**

Detoxification

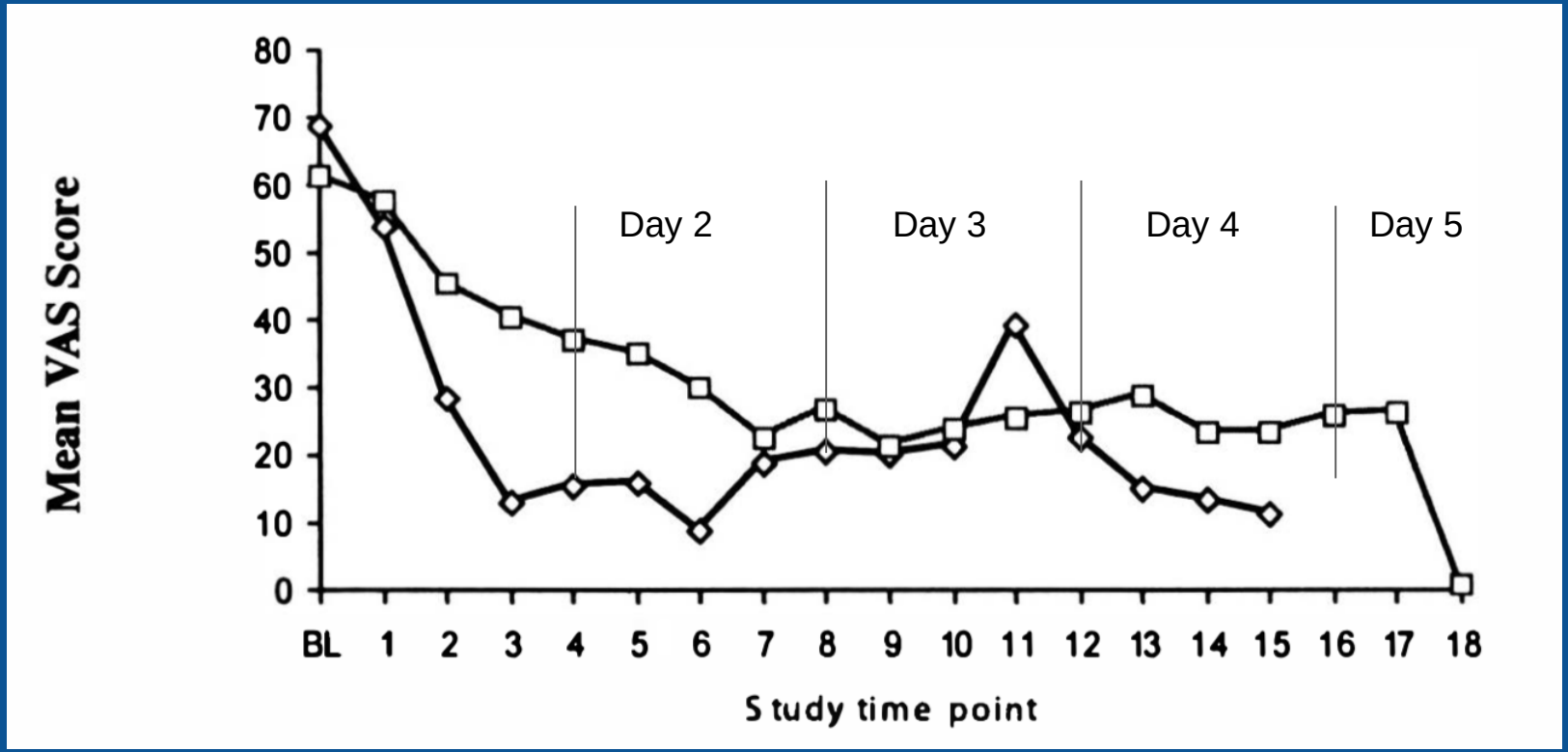
Rapid Heroin Detoxification Using a Single High Dose of Buprenorphine

Ilan Kutz & Victor Reznik (2001), Journal of Psychoactive Drugs, 33:2, 191-193, DOI: 10.1080/02791072.2001.10400484

10 Heroin addicted patients abstinent for 24 hours
32mg liquid buprenorphine over 20 minutes
8mg given every 5 minutes

VAS score of withdrawal intensity

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



Precipitated Withdrawal Risk

Strain 1995

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

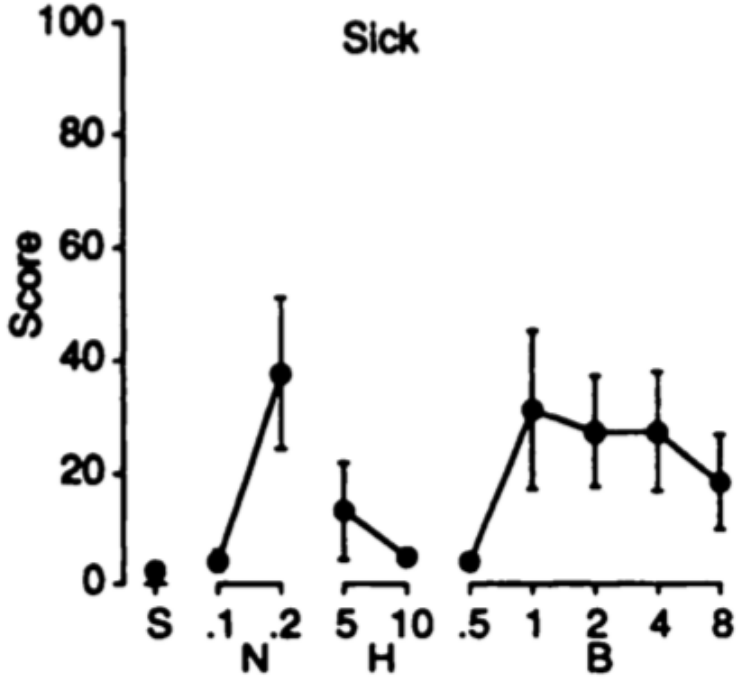
"Less withdrawal was seen at the lowest (0.5 mg) and highest (8 mg) doses. These results suggest that higher doses of buprenorphine produce less antagonist effects and may be better tolerated than moderate doses in methadone maintained patients, when given at a short time interval."

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

0022-3565/95/2722-0628$00.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 1995 by The American Society for Pharmacology and Experimental Therapeutics
JPET 272:628–638, 1995
Vol. 272, No. 2
Printed in U.S.A.

Buprenorphine Effects in Methadone-Maintained Volunteers: Effects at Two Hours after Methadone[1]

ERIC C. STRAIN,[2] KENZIE L. PRESTON,[3] IRA A. LIEBSON[2] and GEORGE E. BIGELOW[2]
Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, Maryland
Accepted for publication October 26, 1994



Schuh 1996

0022-3565/96/2782-0836$00.00/0
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 1996 by The American Society for Pharmacology and Experimental Therapeutics
JPET 278:836–846, 1996
Vol. 278, No. 2
Printed in U.S.A.

Buprenorphine, Morphine and Naloxone Effects during Ascending Morphine Maintenance in Humans[1]

KORY J. SCHUH,[2] SHARON L. WALSH, GEORGE E. BIGELOW, KENZIE L. PRESTON and MAXINE L. STITZER

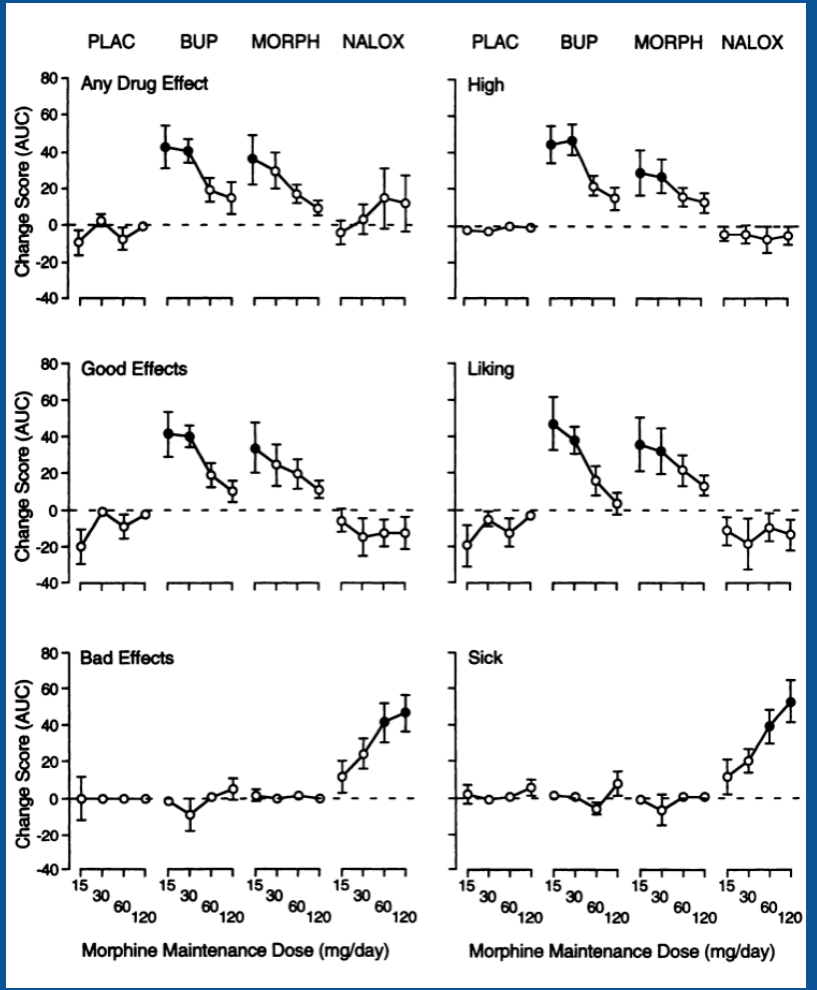
Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Science, Johns Hopkins University School of Medicine, Baltimore, Maryland

Accepted for publication April 22, 1996

Condition:
Morphine 120mg IM daily

Exposure: Buprenorphine 6mg IM
5 hrs after 30mg Morph IM

Result: No precipitated withdrawal



Fudala 1998

Condition: Morphine 60mg daily (15mg IM QID)
Exposure: Buprenorphine 2mg IV 4 hours after morphine
Result: No precipitated withdrawal

ELSEVIER

Drug and Alcohol Dependence 50 (1998) 1–8

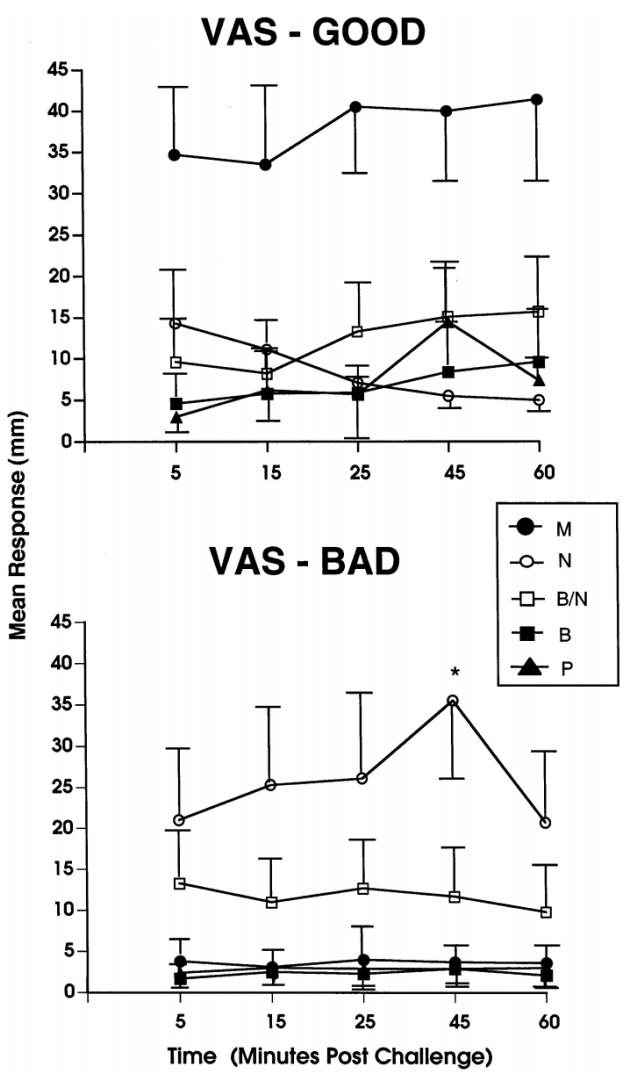
DRUG and ALCOHOL DEPENDENCE

Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts[1]

Paul J. Fudala [a,*], Elmer Yu [a], Wayne Macfadden [a], Chris Boardman [b], C. Nora Chiang [c]

[a] *Department of Psychiatry, University of Pennsylvania School of Medicine/Building 15 – Department of Veterans Affairs Medical Center, University and Woodland Avenues, Philadelphia, PA 19104, USA*
[b] *Children's Hospital of Philadelphia, Philadelphia, PA, USA*
[c] *National Institute on Drug Abuse, Medications Development Division, Rockville, MD, USA*

Received 2 July 1997; accepted 18 October 1997



Mendelson 1999

Psychopharmacology (1999) 141 : 37–46

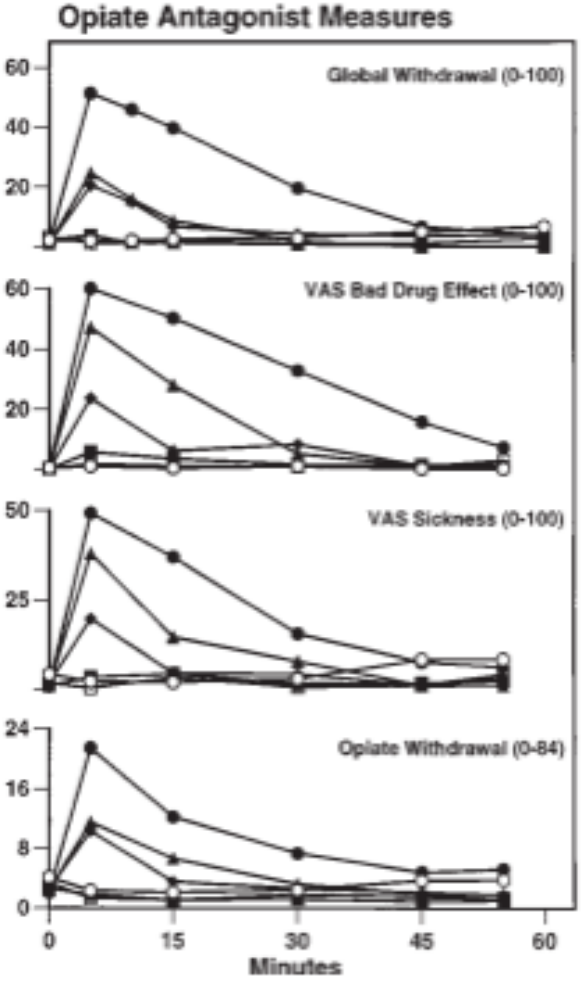
ORIGINAL INVESTIGATION

John Mendelson · Reese T. Jones · Susette Welm
Matthew Baggott · Isabella Fernandez
Ann K. Melby · Rajneesh P. Nath

Buprenorphine and naloxone combinations: the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers

Received: 9 February 1998/Final version: 8 May 1998

Fig. 1 Time course of subject-rated opiate agonist and antagonist effects. Each data point represents mean values for 12 subjects (*Time* = baseline value). Buprenorphine (2 mg) □, buprenorphine (2 mg) and naloxone (1 mg) ●, buprenorphine (2 mg) and naloxone (0.5 mg) ▲, buprenorphine (2 mg) and naloxone (0.25 mg) ◆, morphine (15 mg) ■, and placebo ○



Condition: IM morphine, 60mg daily. Morphine was administered in four 15mg doses at 0600, 1100, 1600, and 2200.

Exposure: IV buprenorphine 2 mg and naloxone placebo **4 hours** after IM Morphine

Result: No precipitated withdrawal

Stoller 2001

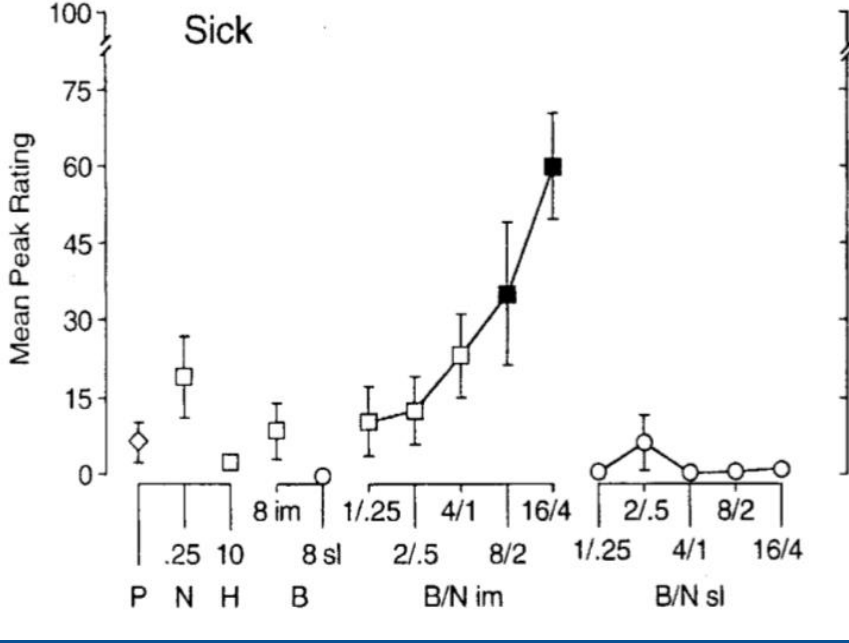
Psychopharmacology (2001) 154:230–242
DOI 10.1007/s002130000637

ORIGINAL INVESTIGATION

Kenneth B. Stoller · George E. Bigelow
Sharon L. Walsh · Eric C. Strain

Effects of buprenorphine/naloxone in opioid-dependent humans

Condition: Hydromorphone 10mg PO QID (40mg/d)
Exposure: Buprenorphine 8mg IM and SL 3 h after the last dose of hydromorphone
Result: No Precipitated Withdrawal.



Rosado 2007

Drug Alcohol Depend. 2007 October 8; 90(2-3): 261–269.

Sublingual Buprenorphine/Naloxone Precipitated Withdrawal in Subjects Maintained on 100 mg of Daily Methadone*

James Rosado[1,2], **Sharon L. Walsh**[1,3], **George E. Bigelow**[1], and **Eric C. Strain**[1]

1*Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224 USA*

2*Miami Dade College, Wolfson Campus, 300 N.E. 2nd Avenue, Suite 3506-3, Miami, FL 33132-2297 USA*

3*Department of Behavioral Sciences, University of Kentucky, 515 Oldham Court, Lexington, KY 40502 USA*

What dose precipitates withdrawal?

- *16 subjects – 100mg Methadone daily*
- *6 dropped out*
- *3 / 10 tolerated up to 32 mg SL*
- *4 @ 4mg*
- *2 @ 8mg*
- *1 @ 16mg*

2017 – Starting from scratch

Carpe Diem!

- Make it fast and simple

Make it last

Step1 2-8mg

The nurse will bring you
pure buprenorphine as quickly as possible.

We usually start with a single 8mg tablet

If you are a heavy user with a big habit
consider starting with two (16 mg)

Let the tablet dissolve under your tongue.

Step2 wait

Wait 15-30 minutes... HANG IN THERE!

You will be feeling better soon!

Step3 Final dose

Choose your final TOTAL dose

8 mg	16 mg	24 mg	32 mg

LOWEST ⬅️----------➡️HIGHEST
(Light habit) (Big Habit)

Step4 Rest & Relax

Pick up your prescription after discharge and start
buprenorphine/naloxone as prescribed the next morning.

The protocol is patient directed dosing:

"How much buprenorphine would you like?"

Guidance: high-dose best for heavier user in more severe withdrawal

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

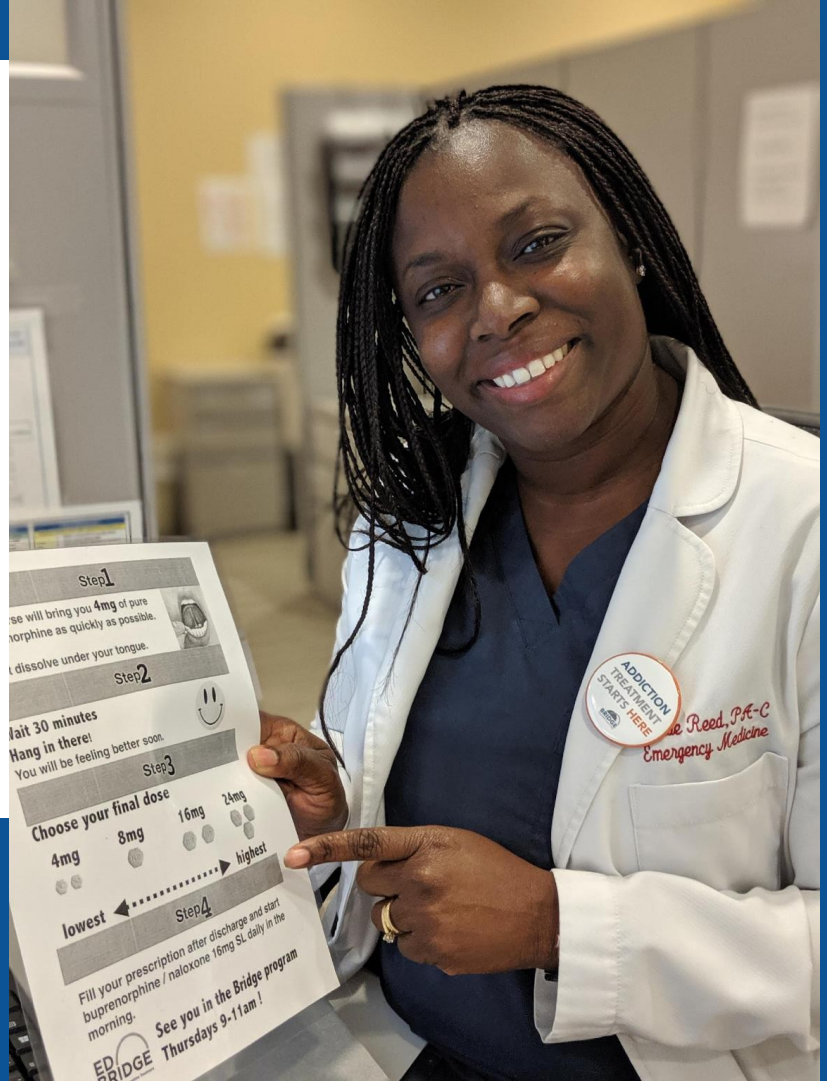
Light user

8mg

Medium heroin

16mg

Heavy heroin



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Original Investigation | Substance Use and Addiction

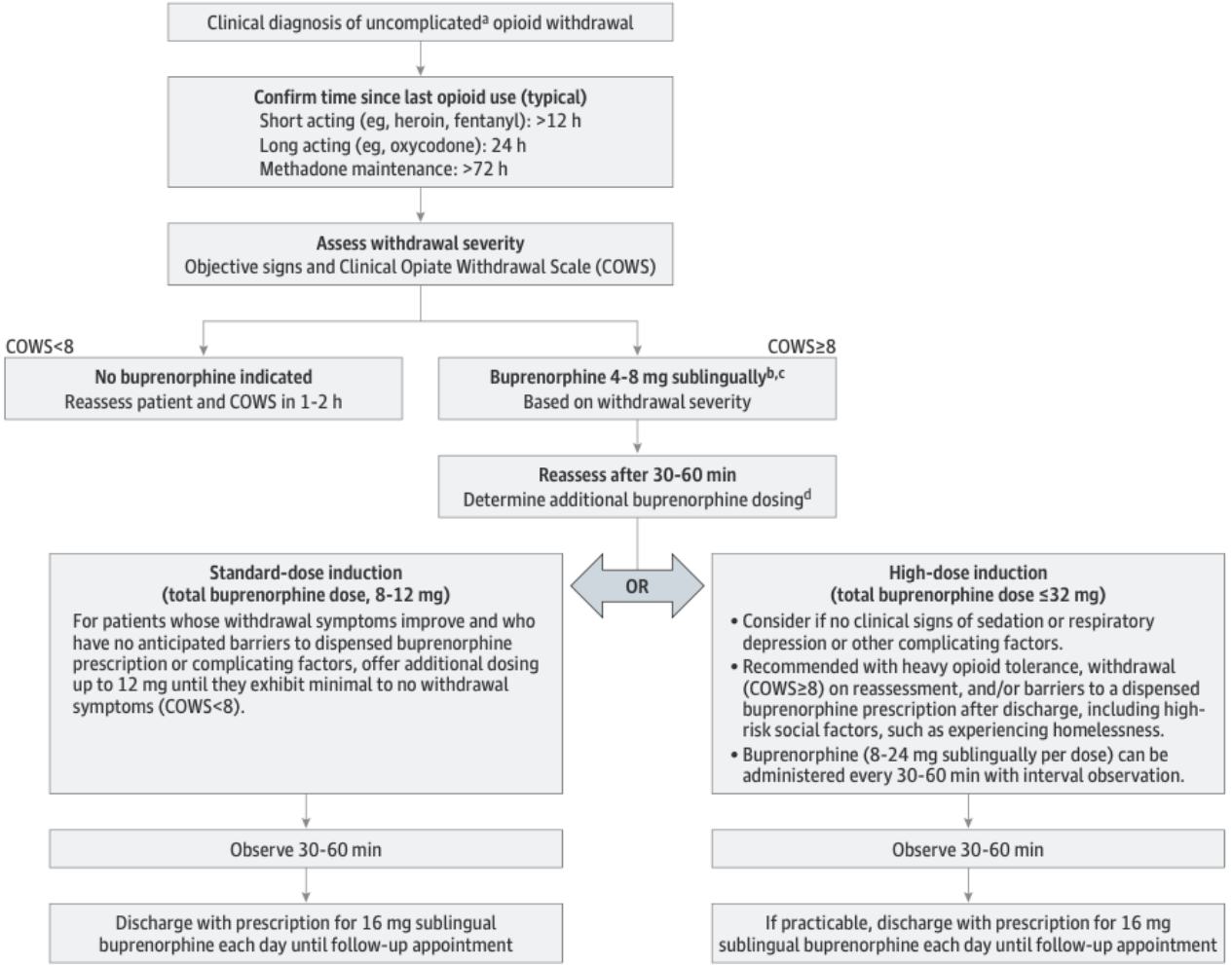
High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder

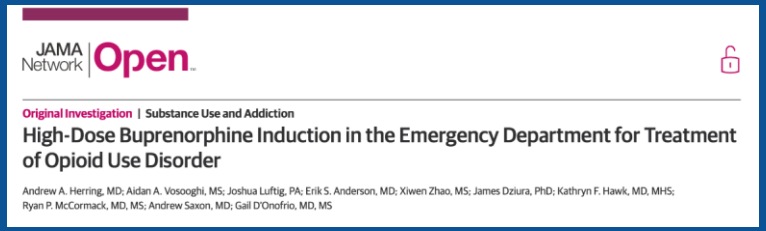
Andrew A. Herring, MD; Aidan A. Vosooghi, MS; Joshua Luftig, PA; Erik S. Anderson, MD; Xiwen Zhao, MS; James Dziura, PhD; Kathryn F. Hawk, MD, MHS; Ryan P. McCormack, MD, MS; Andrew Saxon, MD; Gail D'Onofrio, MD, MS

Retrospective case series

Examined the safety and tolerability of high-dose(>12mg)buprenorphine induction for patients with OUD presenting to an ED.

Figure 1. High-Dose Buprenorphine Treatment Pathway





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Measures:

What are all the ways BUP can go wrong?

Precipitate withdrawal – COWS

Excessive agonism – Opiate 32 scale (Schuster), clinical observation and vital signs

"Side effects" – OR SDS (nausea, itch, headache)

Table 1. Baseline Demographic and Clinical Characteristics of Patients Receiving Sublingual Buprenorphine Induction for Opioid Use Disorder

Characteristic	Patients, No. (%) (n = 391)
Sex	
Male	267 (68.3)
Female	124 (31.7)
Age, y	
18-25	38 (9.7)
26-34	138 (35.3)
35-44	93 (23.8)
45-54	60 (15.3)
55-64	48 (12.3)
65-73	14 (3.6)
Race[a]	
Black	170 (43.5)
White	148 (37.8)
Other race[b]	73 (18.7)
Ethnicity[a]	
Hispanic or Latino	57 (14.6)
Non-Hispanic or non-Latino	334 (85.4)
Insurance status	
Medi-Cal	274 (70.1)
Medicare	26 (6.7)
Military	1 (0.3)
Other public insurance	12 (3.1)
Private	23 (5.9)
No insurance	49 (12.5)
Homeless[c]	
Yes	88 (22.5)
No	303 (77.5)
Psychiatric diagnosis[d]	
Yes	161 (41.2)
No	230 (58.8)
Buprenorphine exposure history[e]	
No	209 (53.5)
Yes	176 (45.0)
Emergency department visits, No.[f]	
1	292 (74.7)
2-4	86 (22.0)
5-14	13 (3.3)

Summary

- 579 cases, 391 unique patients
- 59 providers
- 68% male
- Racial/ethnically diverse
- Safety net
  - > 80% Medi-Cal or no payer
  - > 20% homeless
- 40% with psychiatric dx
- 50% had bup before

Table 2. Clinical Characteristics of Sublingual Buprenorphine Induction for Opioid Use Disorder During Emergency Department Visits

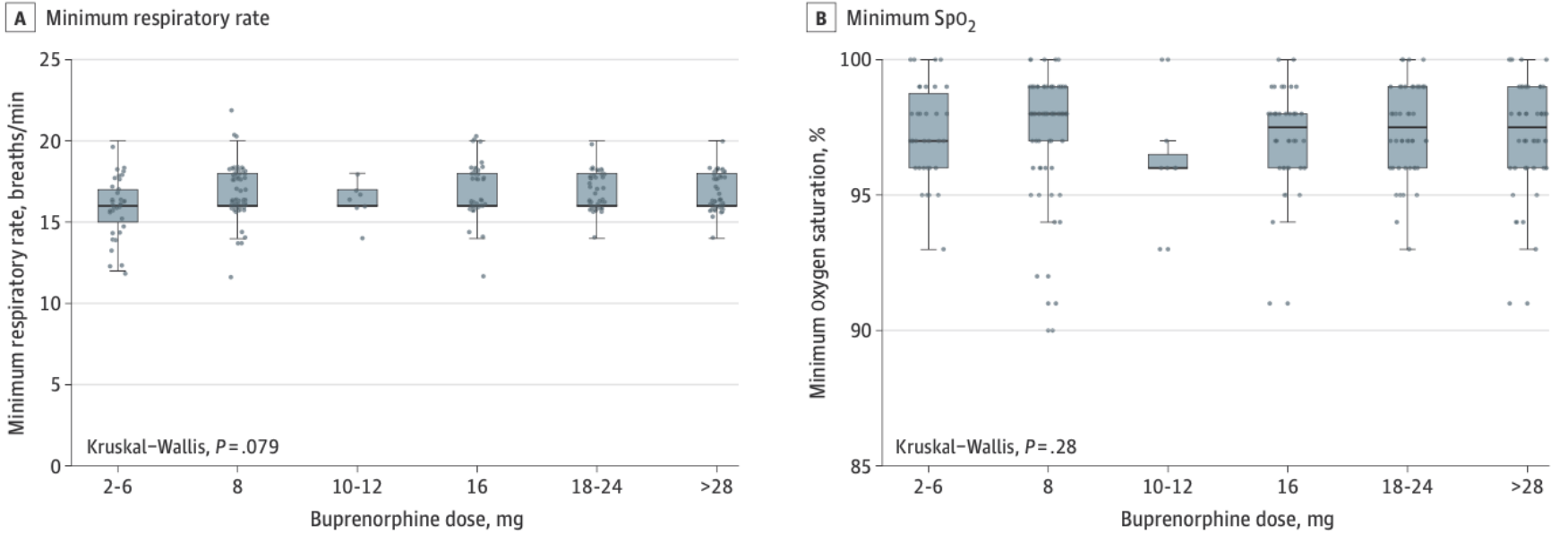
Characteristic	Total buprenorphine dose sublingual						*P* value[a]
	2-6 mg (n = 55)	8 mg (n = 136)	10-12 mg (n = 22)	16 mg (n = 106)	20-24 mg (n = 122)	≥28 mg (n = 138)	
Systolic blood pressure, median (IQR), mm Hg							
At triage	133 (120-150)	132 (120-150)	132 (110-140)	128 (120-140)	128 (120-150)	130 (120-140)	.75
Maximum	135 (130-160)	140 (130-160)	140 (130-150)	133 (120-150)	134 (120-150)	142 (120-160)	.48
Minimum	118 (110-130)	117 (110-130)	103 (97-130)	116 (100-130)	116 (110-130)	121 (110-140)	.83
Respiratory rate, median (IQR), breaths/min							
At triage	18 (16-18)	18 (16-18)	18 (16-18)	18 (16-18)	18 (17-18)	18 (17-18)	.26
Maximum	18 (18-18)	18 (18-20)	18 (17-18)	18 (18-20)	18 (18-20)	18 (18-20)	.23
Minimum	16 (15-17)	16 (16-18)	16 (16-17)	16 (16-18)	16 (16-18)	16 (16-18)	.08
Heart rate, median (IQR), beats/min							
At triage	84 (70-98)	89.5 (78-100)	87 (81-94)	83.5 (75-95)	88 (80-100)	87 (79-99)	.16
Maximum	87 (77-100)	92.5 (82-100)	88 (76-98)	90 (80-100)	95.5 (87-100)	96.5 (81-100)	.73
Minimum	71 (63-80)	76 (68-85)	64 (60-84)	77 (66-86)	80 (70-89)	76 (71-88)	.26
Temperature, °F	98 (97-98)	97.8 (97-98)	97.6 (97-98)	97.5 (97-98)	97.9 (97-98)	97.8 (97-98)	.24
Oxygen saturation, median (IQR), %							
At triage	99 (98-100)	99 (98-100)	98 (97-100)	99 (98-100)	99 (98-100)	99 (98-100)	.29
Maximum	100 (99-100)	99 (99-100)	100 (98-100)	99 (98-100)	99 (98-100)	99 (99-100)	.13
Minimum	97 (96-99)	98 (97-99)	96 (96-96)	97.5 (96-98)	97.5 (96-99)	97.5 (96-99)	.25
Supplemental oxygen, patients, No. (%)	6 (11)	3 (2.2)[b]	1 (4.5)	4 (3.8)	2 (1.6)[b]	1 (0.72)[b]	.01
Chronic obstructive pulmonary disease diagnosis, patients, No. (%)	17 (2.9)	2 (3.6)	3 (2.2)	1 (4.5)	4 (3.8)	2 (1.6)	.76
Emergency Severity Index, patients, No. (%)							
1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	.10
2	7 (13)	9 (6.6)	0 (0)	5 (4.7)	4 (3.3)	5 (3.6)	
3	24 (44)	38 (28)	5 (23)	31 (29)	38 (31)	33 (24)	
4	15 (27)	63 (46)	11 (50)	46 (43)	64 (52)	81 (59)	
5	9 (16)	26 (19)	6 (27)	24 (23)	16 (13)	19 (14)	
Length of stay, median (IQR), h	3.5 (2.4-5.8)	2.6 (1.7-4.4)[b]	2.6 (2.1-3.7)	2.1 (1.5-3.5)[b,c]	2.2 (1.4-3.3)[b]	2.3 (1.7-3.6)[b]	.002
Clinician type, No. (%)							
Advance practice provider	22 (40)	72 (53)	15 (68)[b]	64 (60)[b]	87 (71)[b,c]	99 (72)[b,c]	<.001[d]
Medical doctor	33 (60)	64 (47)	7 (32)	42 (40)	35 (29)	39 (28)	
Adverse events, No. (%)							
Precipitated withdrawal	0	4 (2.9)	0	0	0	1 (0.7)	.20
Hospitalization	5 (9.1)	4 (2.9)	1 (4.5)	3 (2.8)	8 (6.6)	4 (2.9)	.26
Return to ED within 24 h	2 (3.6)	10 (7.4)	3 (14.0)	9 (8.5)	6 (4.9)	15 (11.0)	.32
Time to return to ED within 24 h, median (IQR), h	13.8 (12-16)	11.4 (5.9-14)	17.8 (11-20)	.4 (6.5-23)	15.1 (13-18)	18.4 (14-22)	.52

Dose categories Mg (*N*)

2-6 (55)
8 (136)
10-12 (22)
16 (106)
20-24 (122)
≥ 28 (138)

No observed respiratory depression

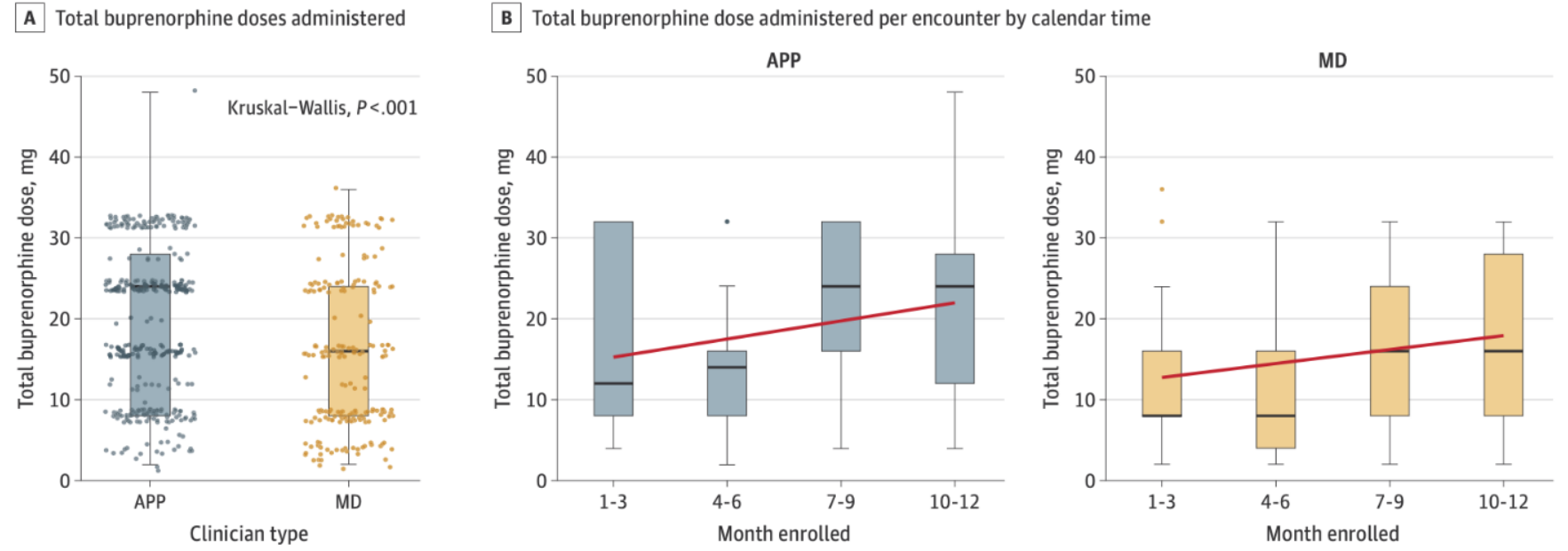
Figure 2. Minimum Respiratory Rate and Oxygen Saturation (SpO_2) Following Initial Dose by Buprenorphine Dose



Boxes correspond to 25th and 75th percentiles, with lines in boxes denoting medians. Dots denote outliers. Error bars denote 95% CIs. Kruskal-Wallis test compares distributions of respiratory rate and oxygen saturation across buprenorphine dose categories.

Patients and providers liked the high-dose option

Figure 3. Buprenorphine Doses Administered by Physicians (MDs) and Advanced Practice Practitioners (APPs)

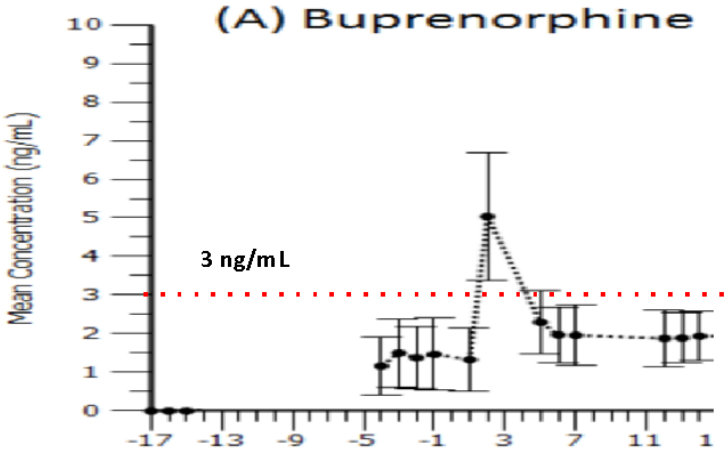



Need help with
pain pills or heroin?
Ask about trying Buprenorphine.
BRIDGE

Injectable Bup is High-dose Bup

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

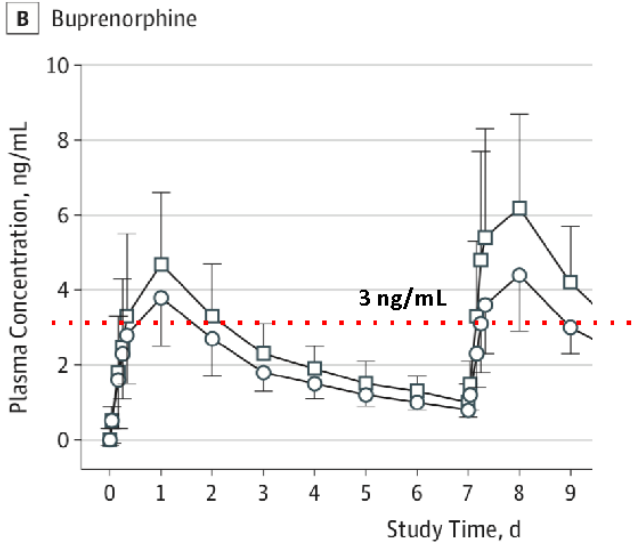
Barbara R Holight, Susan M Learned, Celine M Laffont, Paul J Fudala, Yue Zhao, Amanda S Garofalo, Mark K Greenwald, Vijay R Nadipelli, Walter Ling, Christian Heidbreder, for the RB-US-13-0001 Study Investigators*



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 Tiberg, PhD; Behshad Sheldon, BS; Sonnie Kim, PharmD



- **Sublocade 300mg creates steady state average plasma concentrations more than double that of 24mg daily SL buprenorphine**

Table 7 Comparison of Steady-state Buprenorphine Plasma Exposure Between Daily Transmucosal Buprenorphine and Once Monthly SUBLOCADE at Trough (C_{trough}), Average (C_{avg}) and Peak (C_{max}) Levels (Geometric Mean (CV%))

Pharmacokinetic parameters	Transmucosal Buprenorphine				SUBLOCADE	
	8 mg	12 mg	16 mg	24 mg	100 mg	300 mg
$C_{avg,ss}$ (ng/mL)	1.37 (40)	1.79 (40)	2.16 (40)	2.84 (40)	2.87 (32)	6.32 (32)
$C_{max,ss}$ (ng/mL)	4.27 (45)	5.60 (45)	6.77 (45)	8.86 (45)	5.10 (33)	11.81 (35)
$C_{trough,ss}$ (ng/mL)	0.66 (63)	0.87 (63)	1.04 (61)	1.37 (62)	2.46 (40)	5.47 (39)

Received: 25 September 2020 | Revised: 8 May 2021 | Accepted: 16 May 2021

DOI: 10.1111/ajad.13193

REGULAR ARTICLE

THE AMERICAN JOURNAL ON ADDICTIONS

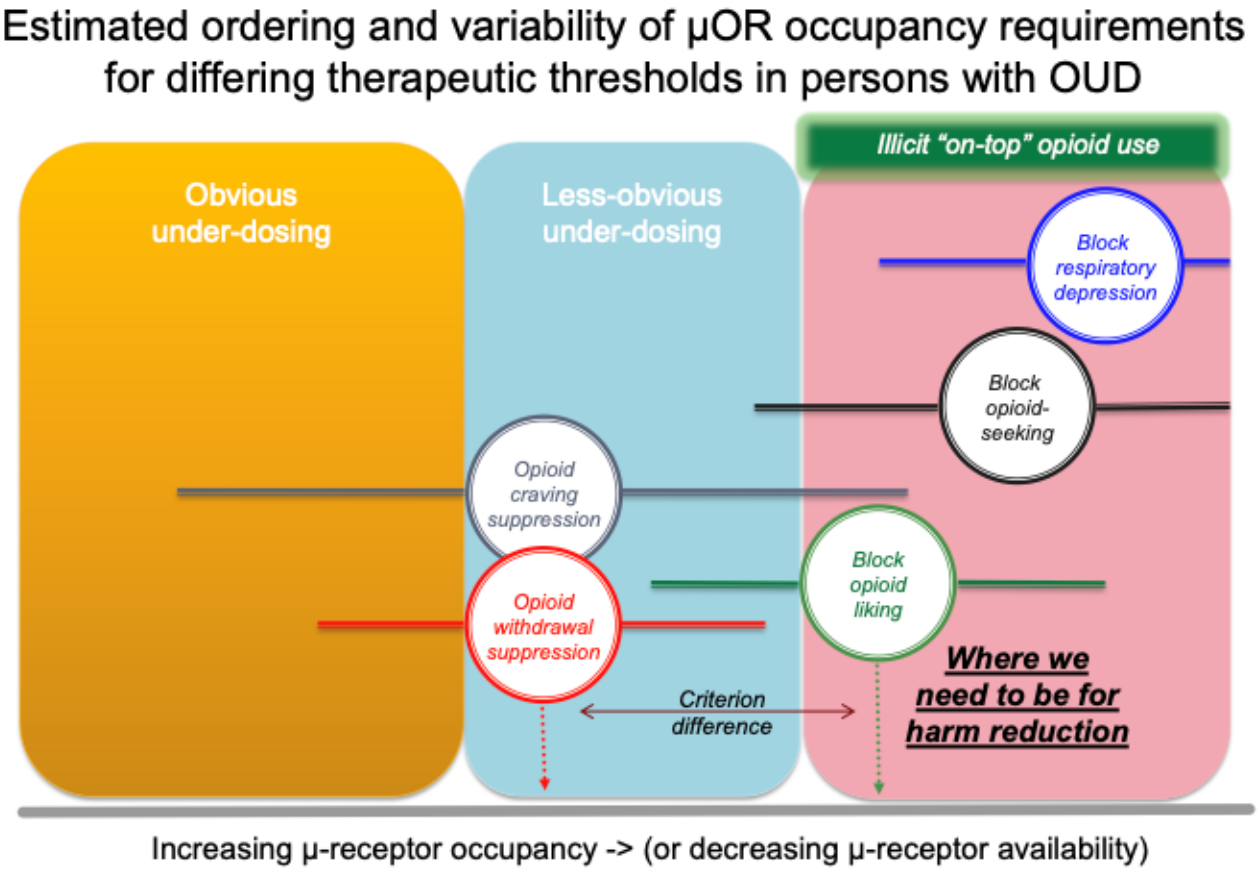
Open-label trial of a single-day induction onto buprenorphine extended-release injection for users of heroin and fentanyl

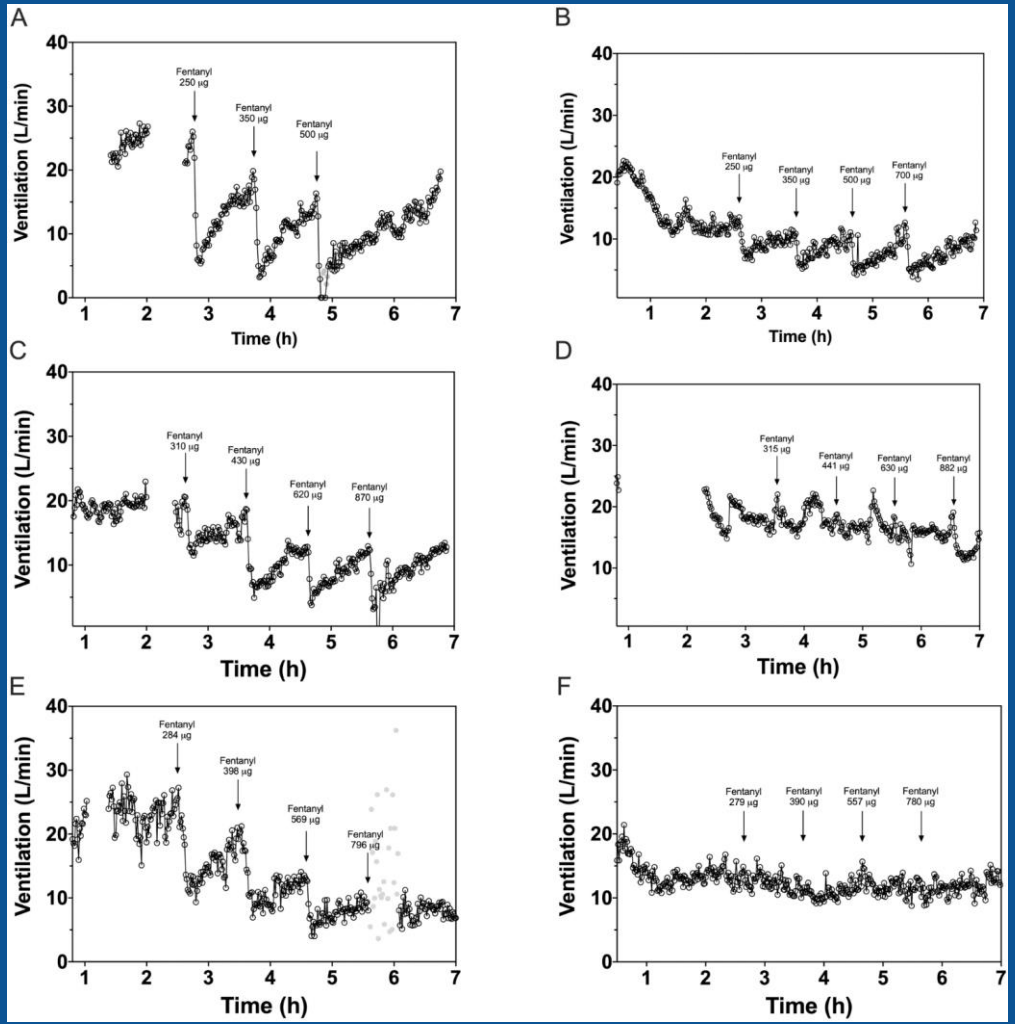
John J. Mariani MD[1,2] | Amy L. Mahony LMHC[1] | Samuel C. Podell BS[3] | Daniel J. Brooks LCSW[1] | Christina Brezing MD[1,2] | Sean X. Luo MD, PhD[1,2] | Nasir H. Naqvi MD, PhD[1,2] | Frances R. Levin MD[1,2]

ACP-008	1150	6	
	1240	9	Buprenorphine 2 mg SL
	1330	5	Buprenorphine 6 mg SL
	1415	5	Buprenorphine 8 mg SL
	1500	4	Buprenorphine 8 mg SL
	1530	5	XR-Buprenorphine 300 mg SC

Mariani JJ, Mahony AL, Podell SC, et al. Open-label trial of a single-day induction onto buprenorphine extended-release injection for users of heroin and fentanyl. Am J Addict. 2021;1-7. https://doi.org/10.1111/ajad.13193

Mark Greenwald, NIDA presentation Nov 2022





PLOS ONE

RESEARCH ARTICLE

Effect of sustained high buprenorphine plasma concentrations on fentanyl-induced respiratory depression: A placebo-controlled crossover study in healthy volunteers and opioid-tolerant patients

Laurence M. Moss[1,2], Marijke Hyke Algera[2], Robert Dobbins[3], Frank Gray[3], Stephanie Strafford[3], Amy Heath[3], Monique van Velzen[2], Jules A. A. C. Heuberger[1], Marieke Niesters[2], Erik Olofsen[2], Celine M. Laffont[3], Albert Dahan[2], Geert Jan Groeneveld[1,2]*

1 Centre for Human Drug Research (CHDR), Leiden, The Netherlands, **2** Department of Anesthesiology, Leiden University Medical Centre (LUMC), Leiden, The Netherlands, **3** Indivior Inc., North Chesterfield, Virginia, United States of America

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Paramedic administered Bup

Taylor & Francis

Prehospital Emergency Care

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipec20

Prehospital Initiation of Buprenorphine Treatment for Opioid Use Disorder by Paramedics

H. Gene Hern, David Goldstein, M Kalmin, S Kidane, S Shoptaw, Ori Tzvieli & Andrew A Herring

To cite this article: H. Gene Hern, David Goldstein, M Kalmin, S Kidane, S Shoptaw, Ori Tzvieli & Andrew A Herring (2021): Prehospital Initiation of Buprenorphine Treatment for Opioid Use Disorder by Paramedics, Prehospital Emergency Care, DOI: 10.1080/10903127.2021.1977440

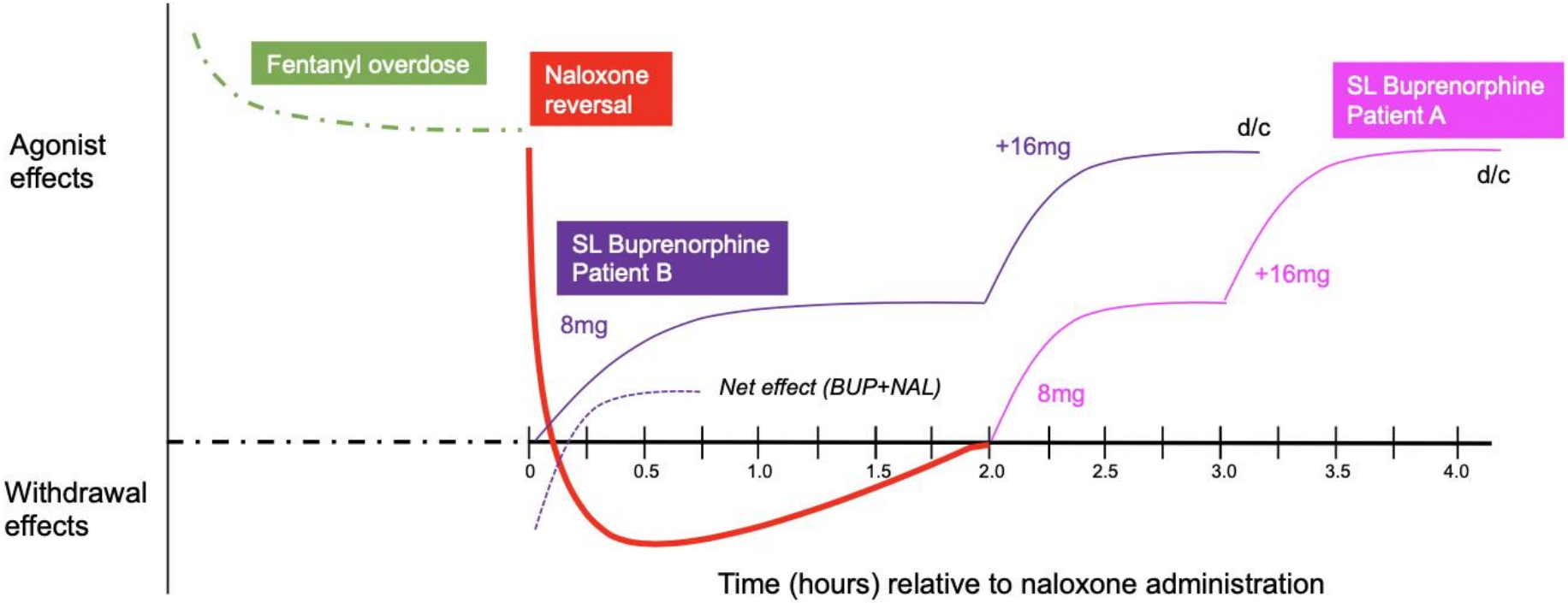
To link to this article: https://doi.org/10.1080/10903127.2021.1977440

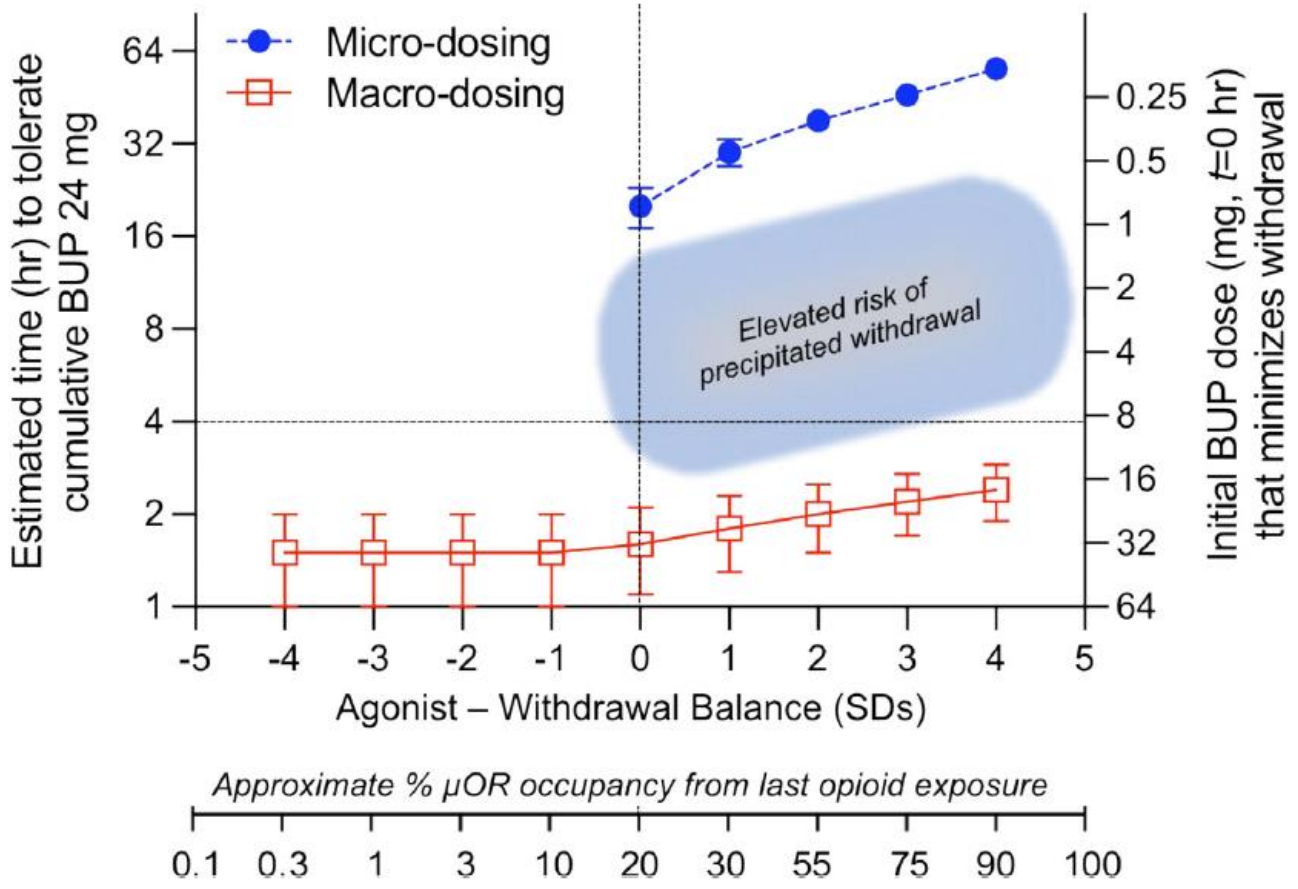
Contra Costa County
71 patients
COWS≥ 7
First dose 16mg SL
<50% post naloxone

32 (45%)
Continued on Bup
at 7 days

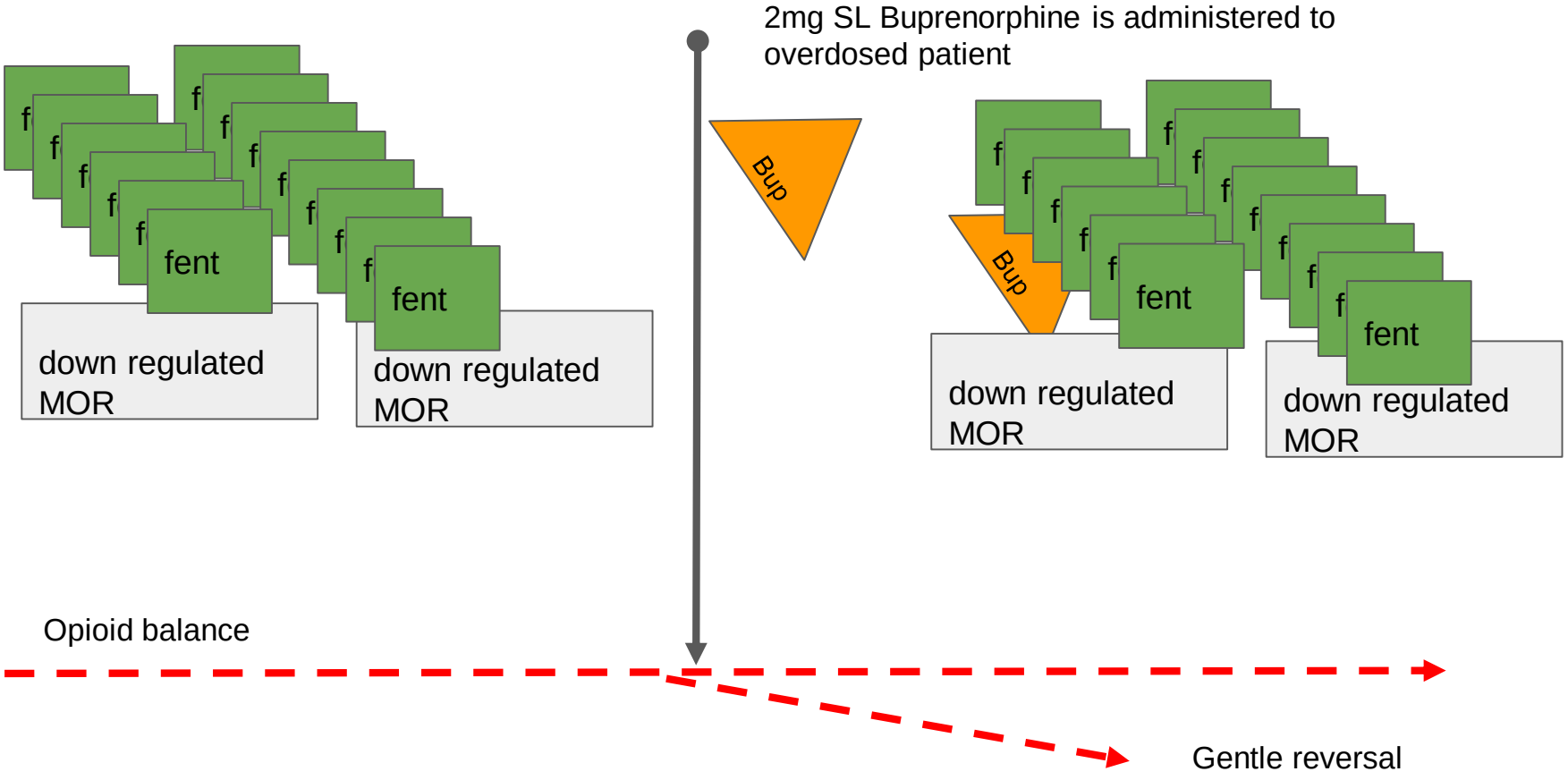
25 (35%)
Continued in Bup
care at 30 days

High-dose Bup after naloxone reversal




Micro-dosing
Macro-dosing
Elevated risk of precipitated withdrawal
Estimated time (hr) to tolerate cumulative BUP 24 mg
64
32
16
8
4
2
1
Initial BUP dose (mg, t=0 hr) that minimizes withdrawal
0.25
0.5
1
2
4
8
16
32
64
-5 -4 -3 -2 -1 0 1 2 3 4 5
Agonist – Withdrawal Balance (SDs)
Approximate % μOR occupancy from last opioid exposure
0.1 0.3 1 3 10 20 30 55 75 90 100

Example 1: Opioid overdose



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*]

Using IV Bup to reverse methadone overdose in Tehran

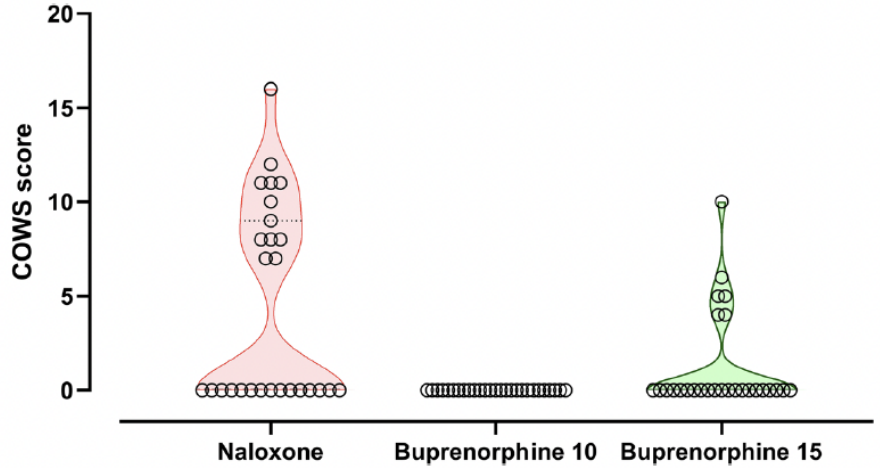
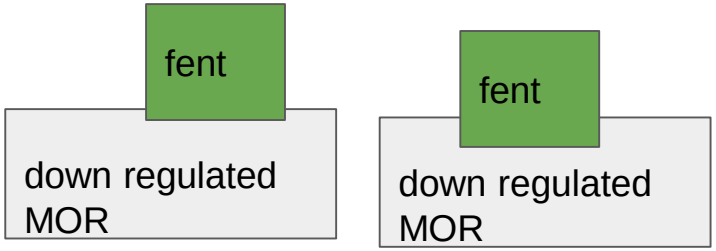


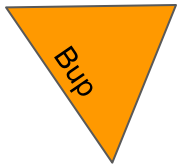
Fig. 4 Violin and scatter plot of withdrawal scores after initial doses of buprenorphine vs naloxone (COWS scale)

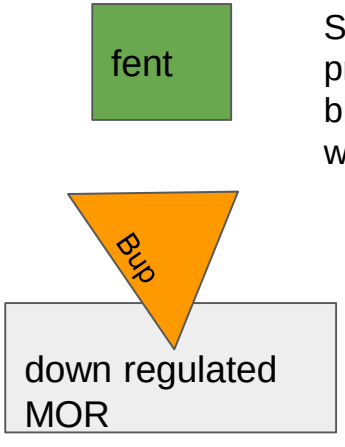
Ex: 2 Fentanyl wash out

Residual fentanyl metabolites limit tolerance reversal and continue MOR agonism



2mg SL Buprenorphine is administered to a patient 12 hrs after last fentanyl use





Small (not micro) dose of bup produces near complete blockade of fentanyl=abrupt worsening

Abrupt worsening of withdrawal

ORIGINAL ARTICLES

Interaction of Fentanyl and Buprenorphine in an Experimental Model of Pain and Central Sensitization in Human Volunteers

Tröster, Andreas MD*; Ihmsen, Harald PhD*; Singler, Boris MD*; Filitz, Jörg MD†; Koppert, Wolfgang MD†

Author Information

*Department of Anaesthesiology, University Hospital Erlangen, Erlangen

†Department of Anesthesiology and Intensive Care, Hannover Medical School, Hannover, Germany

This work was supported by a grant from Grunenthal GmbH, Aachen, Germany. The authors declare no conflict of interest. Presented, in part, at Euroanaesthesia, Vienna, Austria, May 28-31, 2005. A.T. and H.I. contributed equally.

Reprints: Harald Ihmsen, PhD, Department of Anaesthesiology, University Hospital Erlangen, Krankenhausstrasse 12, 91054 Erlangen, Germany (e-mail: harald.ihmsen@kfa.imed.uni-erlangen.de).

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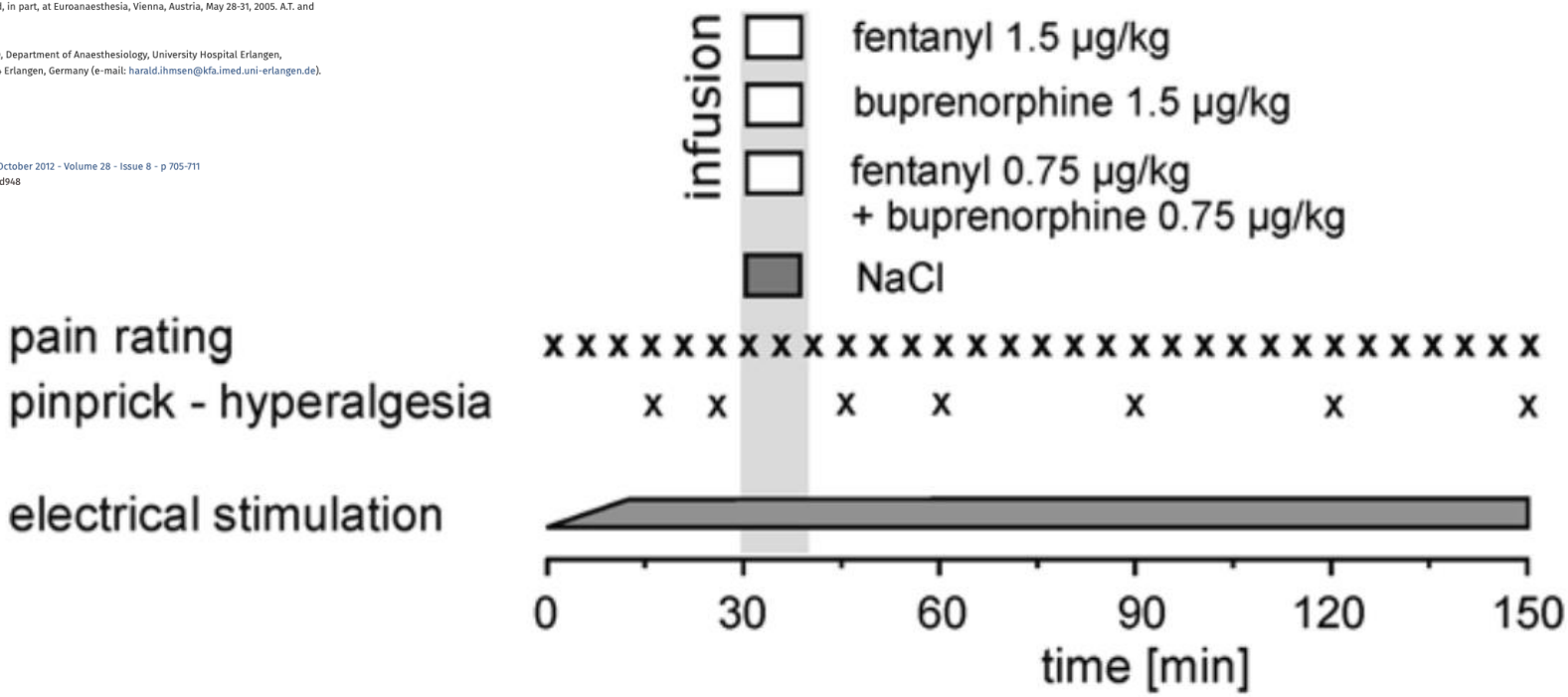
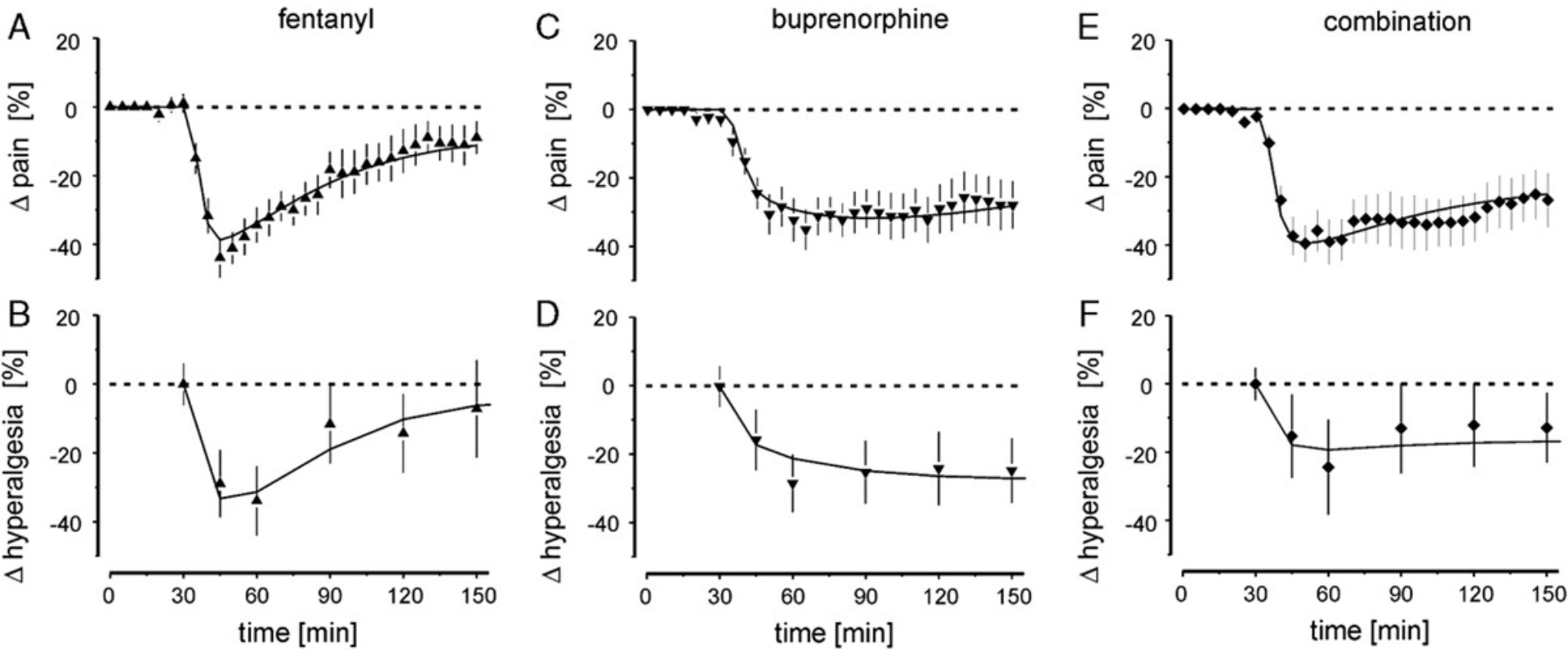
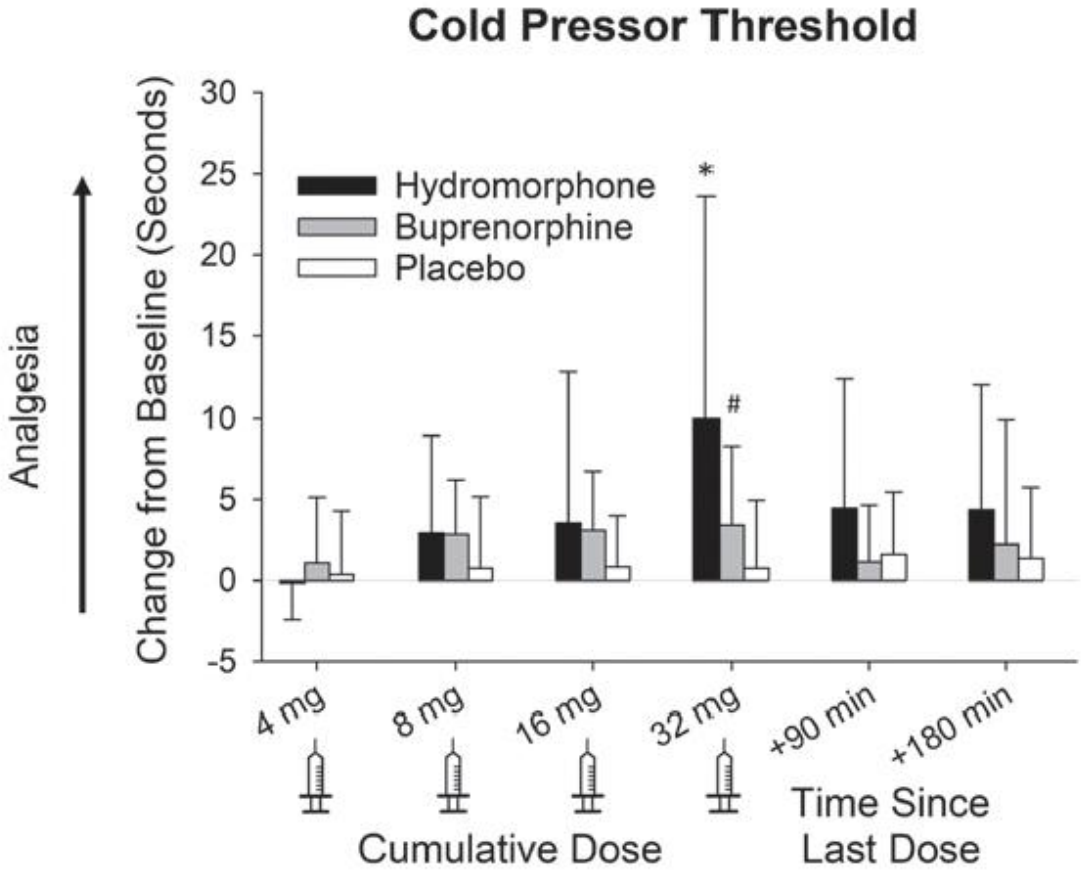
The Clinical Journal of Pain: October 2012 - Volume 28 - Issue 8 - p 705-711
doi: 10.1097/AJP.0b013e318241d948




A
fentanyl
C
buprenorphine
E
combination
Δ pain [%]
B
D
F
Δ hyperalgesia [%]
20
0
-20
-40
0
30
60
90
120
150
time [min]



PAIN MEDICINE

ANESTHESIOLOGY

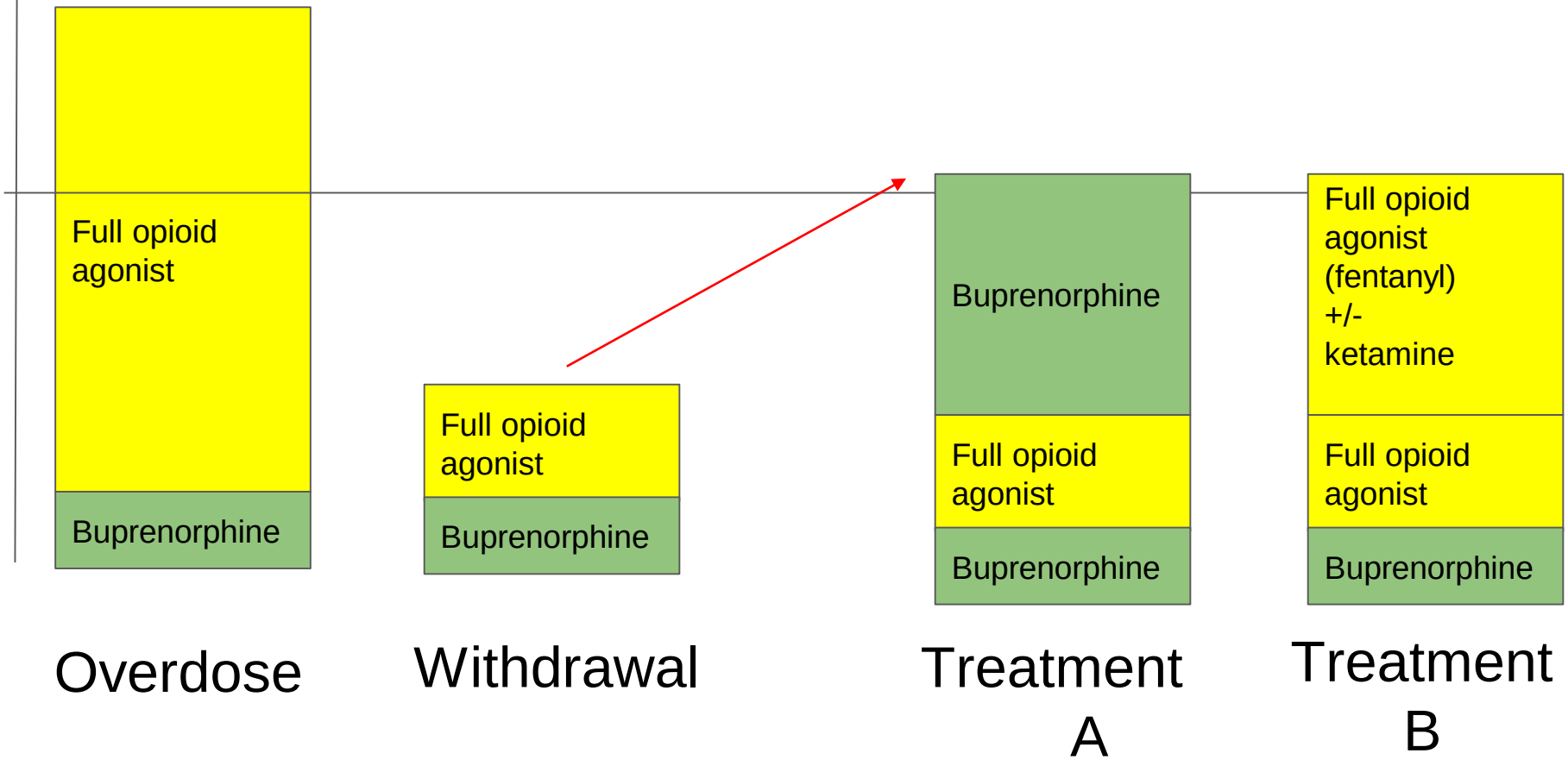
Analgesic Effects of Hydromorphone *versus* Buprenorphine in Buprenorphine-maintained Individuals

Andrew S. Huhn, Ph.D., Eric C. Strain, M.D., George E. Bigelow, Ph.D., Michael T. Smith, Ph.D., Robert R. Edwards, Ph.D., D. Andrew Tompkins, M.D., M.H.S.

Anesthesiology 2019; 130:131–41

This study did not address the first issue but does provide controlled evidence that doses up to 32 mg of IV hydromorphone or IV buprenorphine may be given safely without respiratory depression in select buprenorphine-maintained individuals. This finding is specific to persons maintained on 12 to 16 mg sublingual buprenorphine/naloxone for opioid use disorder, who are approximately 17 h removed from their last dose and in the absence of concomitant medications that may cause further respiratory depression or other negative effect

Opioid balance



Rapid high-dose induction in the Emergency Department and by Paramedics: initial observations and future directions

Andrew A Herring
aherring@alamedahealthsystem.org