

Virginia Opioid Addiction ECHO* Clinic April 1, 2022

*ECHO: Extension of Community Healthcare Outcomes



Helpful Reminders

Unmute		🗰 Gallery View			
Katy	Unmute My Audio Alt + A				
2	Start Video				
	Rename Rename				
	Hide Non-Video Participants				
	Hide Self View				

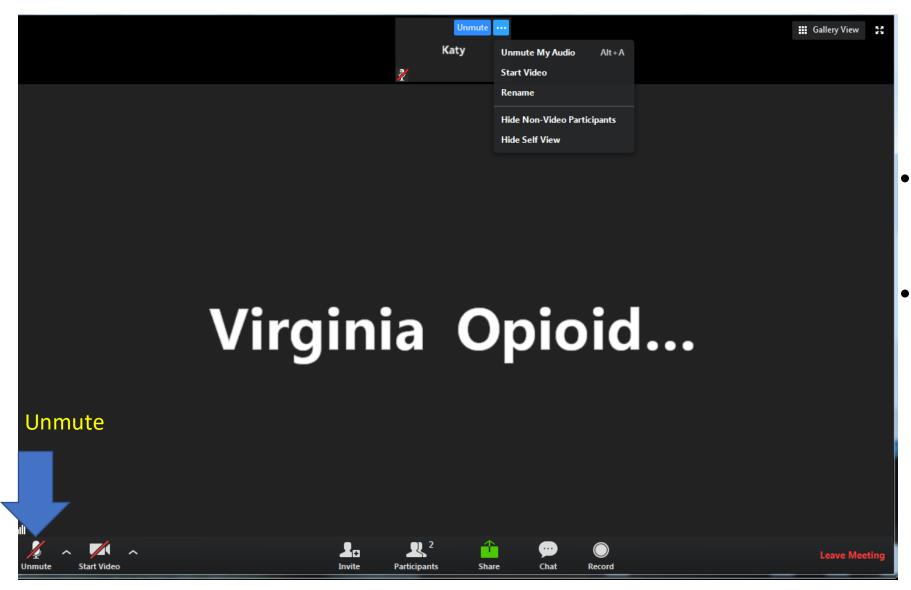
Virginia Opioid...





 Rename your Zoom screen, with your name and organization

Helpful Reminders



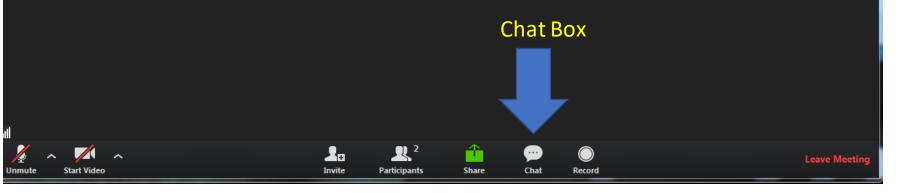


- You are all on mute please unmute to talk
 - If joining by telephone audio only, *6 to mute and unmute

Helpful Reminders

Unmute	Galler	y View 🚦
Katy	Unmute My Audio Alt+A	
2	Start Video	
	Rename	
	Hide Non-Video Participants	
	Hide Self View	

Virginia Opioid...





- Please type your full name and organization into the chat box
- Use the chat function to speak with IT or ask questions

VCU Opioid Addiction ECHO Clinics



WDH^{VIRGINIA} VDHLiveWell.com

VCU School of Medicine

- Bi-Weekly 1 hour tele-ECHO Clinics
- Every tele-ECHO clinic includes a 30 minute didactic presentation followed by case discussions
- Didactic presentations are developed and delivered by inter-professional experts
- Website Link: <u>www.vcuhealth.org/echo</u>

Hub and Participant Introductions



VCU Team					
Clinical Director	Gerard Moeller, MD				
Administrative Medical Director ECHO Hub	Vimal Mishra, MD, MMCi				
Clinical Experts	Lori Keyser-Marcus, PhD Courtney Holmes, PhD Albert Arias, MD Megan Lemay, MD Katie Adams, PharmD				
Didactic Presentation	Brandon Wills, DO				
Program Manager	Bhakti Dave, MPH				
Acute Telehealth Manager	Tamera Barnes, MD				
IT Support	Vladimir Lavrentyev, MBA				

@VCU

- Name
- Organization

Reminder: Mute and Unmute screen to talk

*6 for phone audio Use chat function for Introduction

What to Expect

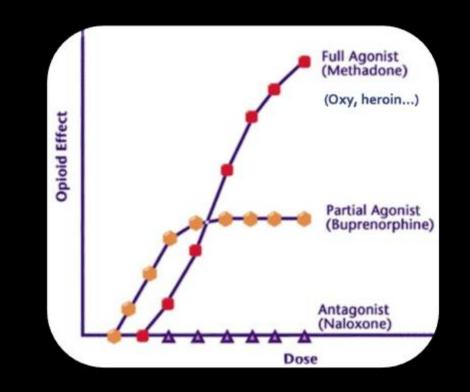


- I. Didactic Presentation I. Brandon Wills, DO
- II. Case presentations
 - I. Case 1
 - I. Case summary
 - II. Clarifying questions
 - III. Recommendations
- III. Closing and questions





Buprenorphine Macrodosing



Brandon Wills, DO, FACEP, FAACT

Fellowship Director, Medical Toxicology Division of Clinical Toxicology VCU Medical Center Virginia Poison Center





Disclosures

None

My background...





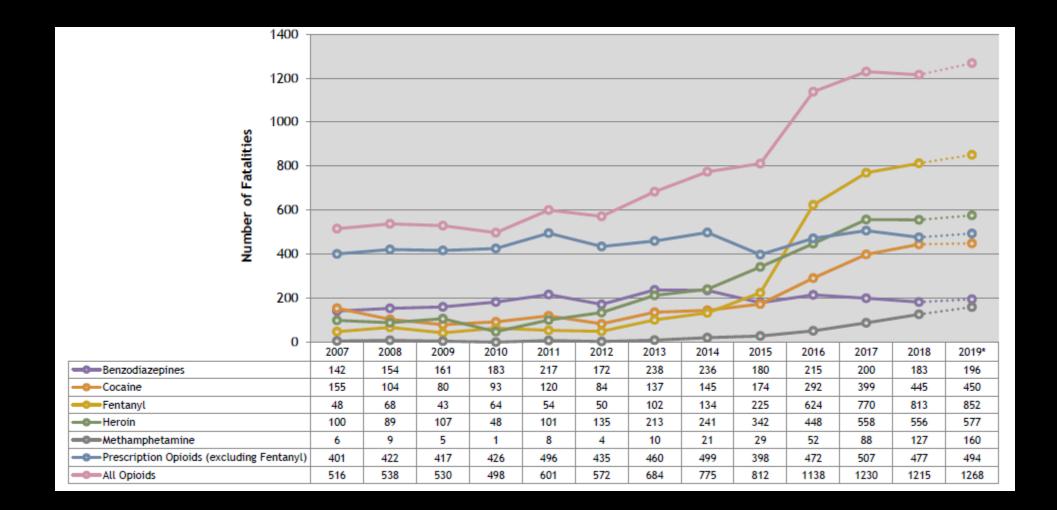
Objectives

- Distinguish dosing strategies for buprenorphine induction
- Discuss why we "need" alternative induction strategies
- Summarize literature on using higher dose buprenorphine (macrodosing)

Traditional Buprenorphine Induction

- 2-4mg Q 2h
- Potential **problems** with this approach?

The Rise of Fentanyl



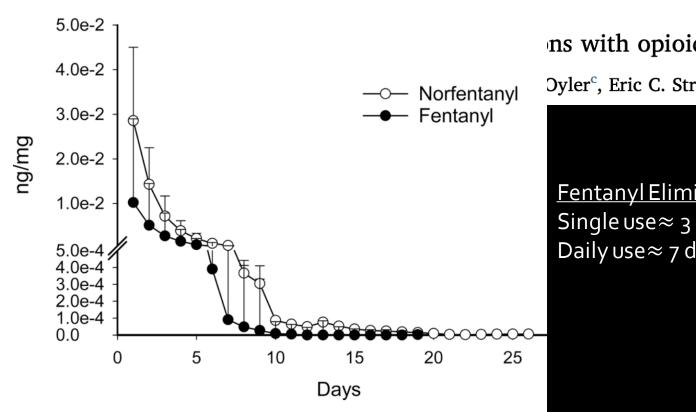
Drug and Alcohol Dependence 214 (2020) 108147



Contents lists available at ScienceDirect

Drug and Alcohol Dependence

Fentanyl and Norfentanyl Elimination



ns with opioid use disorder

Oyler^c, Eric C. Strain^a

r.com/locate/drugalcdep

Fentanyl Elimination: Single use \approx 3 hrs Daily use \approx 7 days

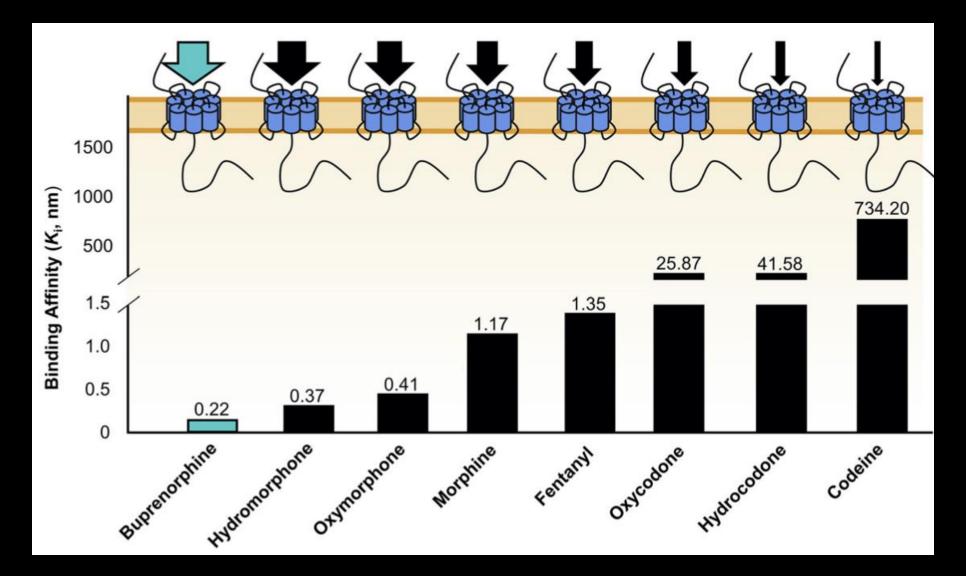
> Huhn, *Drug Alc Dep*, 2020 Mather, *Clin Pharmacokinet*, 1983 Lotsch, *Clin Pharmacokinet*, 2013

µ-opioid Receptor

Affinity vs Potency

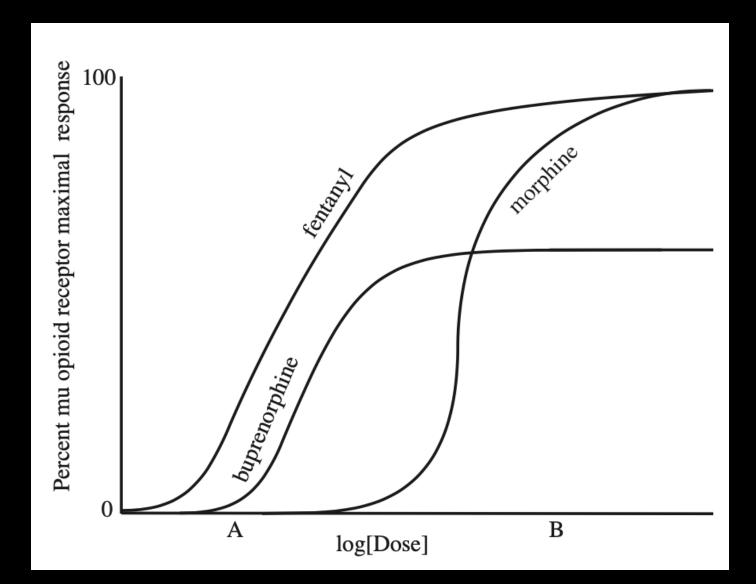


Affinity

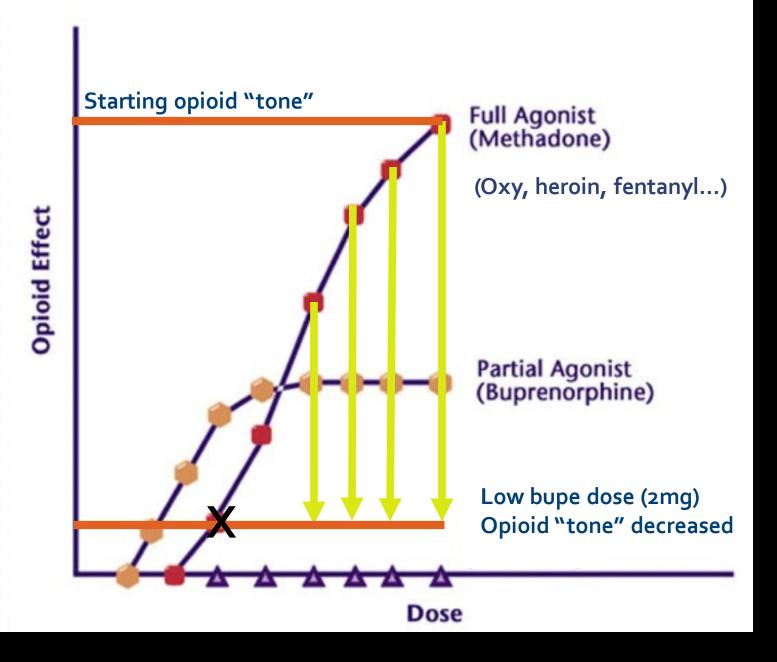


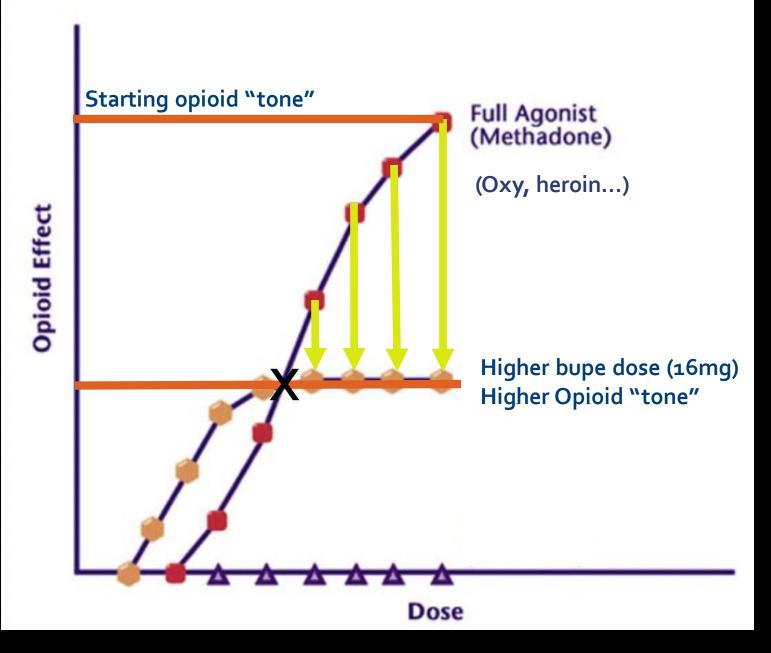
Pain Ther (2020) 9:41-54

Potency



J Addict Med • Volume 00, Number 00, Month/Month 2018





Goals of Buprenorphine Pharmacotherapy

- Abort withdrawal/ cravings
- Stop other opioid use
- Harm reduction in other domains...
- Avoid precipitating withdrawal
- Avoid adverse drug effects of buprenorphine

Microdose induction

- Useful for inpatients actively treated w/ full agonists
- Limited use in the outpatient setting

Day	Buprenorphine Dose (SL)
1	o.5 mg QD
2	o.5 mg BID
3	1 mg BID
4	2 mg BID
5	4mg BID
6	8 mg QD
7	8 mg am, 4mg pm
8	12 mg (stop full agonist)

Macrodose induction

2-4mg Q 2h
 Max day 1 dose: 16mg
 Max day 2 dose: 24mg

-Start with higher doses (8-16 mg) -Escalate quickly (Q 30-60 min) -Max doses ~32 mg Macrodosing buprenorphine

Macrodosing: Risks v Benefits

<u>Potential Benefits</u>

- Faster induction
- ↓ risk of P.O.W
 - Receptor saturation
 - Reduce withdrawal sx

<u>Potential Risks</u>

- ADR of high-dosing
 - Concurrent benzo's
 - Pregnancy
 - Transitioning from methadone
 - Concomitant medical co-morbidities

Evidence for using macrodosing?

I. Risk of respiratory depression?

II. Treatment of precipitated withdrawal?

III. Induction efficacy?

High-dose Buprenorphine

I. Risk of respiratory depression?

II. Treatment of precipitated withdrawal?

III. Induction efficacy?

Does High-Dose Buprenorphine Cause Respiratory Depression? Possible Mechanisms and Therapeutic Consequences

Bruno Mégarbane,^{1,2} Raymond Hreiche,¹ Stéphane Pirnay,^{1,3} Nicolas Marie¹ and Frédéric J. Baud^{1,2}

Review article

- Suggests most buprenorphine deaths are misuse/ co-ingestants
- Likely drug synergy (eg. benzodiazepines)

PLOS ONE

2022;17(1)

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 Algera², Robert Dobbins³, Frank Gray³, Stephanie Strafford³, Amy Heath³, Monique van Velzen², Jules A. A. C. Heuberger¹, Marieke Niesters², Erik Olofsen², Celine M. Laffont³, Albert Dahan², Geert Jan Groeneveld^{1,2}*

Randomized, single-blind, crossover

- 14 opioid naïve + 8 opioid tolerant (> 90 MME)
- IV Bupe vs IV placebo \rightarrow 4 escalating doses IV fentanyl
- Primary outcome: apnea & minute ventilation (V_E)

Table 2. Number and percentage of participants who experience <mark>d apnea that required stimulatio</mark> n (i.e. persister								
	Part A: Healthy Volunteers							
Fentanyl Dose	Fentanyl Dose Number	Placebo for 0.2 ng/mL (N = 6)	Buprenorphine 0.2 ng/mL (N = 6)	Placebo for 0.5 ng/mL (N = 6)	Buprenorphine 0.5 ng/mL (N = 6)			
0.075 mg/ 70 kg	1	0/6 (0)	0/6 (0)	0/6 (0)	0/6 (0)			
0.15 mg/70 kg	2	1/6 (17)	0/4 (0) ^b	0/6 (0)	0/6 (0)			
0.25 mg/70 kg	3	2/2 (100) ^b	2/4 (50)	3/4 (75) ^b	1/6 (17)			

Part B: Opioid-tolerant Patients							
Fentanyl Dose Number	Placebo (N = 8)	$\begin{array}{l} \text{Buprenorphine}^{\text{a}}\\ (\text{N}=8) \end{array}$					
1	0/8 (0)	0/8 (0)					
2	2/8 (25)	0/8 (0)					
3	1/6 (17)	0/8 (0)					
4 🤇	3/4 (75) ^b	0/8 (0)					

Main Results:

- Fentanyl reduced V_E
- Bupe attenuated reduction in V_E
- Presence of bupe was not fully protective

High-dose Buprenorphine

I. Risk of respiratory depression?

II. Treatment of precipitated withdrawal

III. Induction efficacy?

Case reports

Drug and Alcohol REVIEW

Drug and Alcohol Review (May 2021), 40, 567–571 DOI: 10.1111/dar.13228

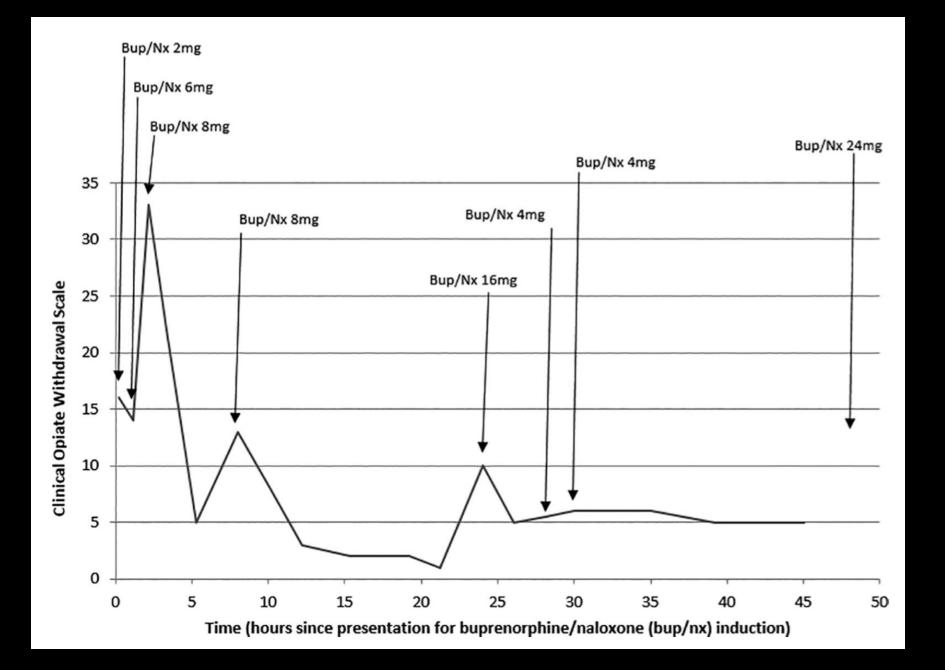
BRIEF REPORT

Managing opioid withdrawal precipitated by buprenorphine with buprenorphine

BRIDGET OAKLEY¹, HESTER WILSON^{1,2}, VICTORIA HAYES^{1,2} & NICHOLAS LINTZERIS^{1,3}

Single case report:

- -Pt with OUD reported heroin use 29 hrs earlier
- -COWS 16 \rightarrow 2mg bupe \rightarrow COWS 14 \rightarrow 6mg bupe \rightarrow COWS 33
- -Improvement after 16mg. Day 1= 24 mg bupe
- -Later reported taking 10 mg methadone < 1 week prior to induction



Family Practice, 2021, 1–3 doi:10.1093/fampra/cmab073

OXFORD

Case Report

A case of buprenorphine-precipitated withdrawal managed with high-dose buprenorphine

Thomas H N Quattlebaum^{a,*,}, Miki Kiyokawa^{b,c,e} and Kayla A Murata^a

Single case report:

- -Pt with OUD, daily oxycodone > 70 mg (Oxy ER 20 mg TID + IR prn)
- -Home induction
- -17 hours after last oxy ER, began bupe induction, 4 mg \rightarrow 30 min later= worse
- -Serial doses up to 16 mg \rightarrow worse \rightarrow to the ER (COWS 25)
- -Better after total day 1: 20 mg
- -Discharged the following day on 20 mg QD
- -5 months later, still doing good with 16 mg daily

High-dose Buprenorphine

I. Risk of respiratory depression?

II. Treatment of precipitated withdrawal

III. Induction efficacy? Case reports

Drug and Alcohol REVIEW

Drug and Alcohol Review (February 2020), 39, 135–137 DOI: 10.1111/dar.13017

BRIEF REPORT

High-dose buprenorphine for treatment of high potency opioid use disorder

MARLON DANILEWITZ^{1,2}
[©] & MARK McLEAN^{1,3}

29 y/o woman with OUD, non-pharmaceutical fentanyl Inpatient treatment, initial COWS 14

- Day 1 bupe= 16 mg (end of day COWS 12)
- Day 2 bupe= 30 mg (end of day COWS 5)
- Day 3 bupe= 32 mg (end of day COWS 2)
- Day 4 bupe= 40 mg (end of day COWS 3)
- Day 5 bupe= 40 mg (discharge dose)



Treatment of Opioid Use Disorder Attributed to Fentanyl With High-Dose Buprenorphine *A Case Report*

- 29 y/o hx of OUD x 9 years
- Non-pharmaceutical fentanyl (1,350 MME)
- 30 hours post-exposure, COWS 13
- 32 mg bupe needed to control WD and cravings

Journal of Clinical Psychopharmacology • Volume 41, Number 1, January/February 2021

TABLE 1. COWS Scoring, Total Daily Dosing of Buprenorphine/Naloxone, and Adjunctive Therapies	TABLE 1.	COWS Scoring,	Total Daily	Dosing	of Bu	orenor	phine/N	laloxone,	and Ad	junctive 1	Therapi	es
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Day	COWS, AM	COWS, PM	Buprenorphine/Naloxone, Total Daily Dose, mg	Baclofen 10 mg PRN, No. Doses	Clonidine 0.1 mg PRN, No. Doses
0	13	12	8	3	2
1	6	5	8	1	2
2	9	2	8	3	2
3	15	8	20	3	2
4	9	7	20	3	3
5	9	3	24	2	1
6	3	6	24	2	2
7	3	3	32	0	1
8	1	3	32	1	1
9	0	1	32	0	0
10	1	-	16*	0	0

High-dose Buprenorphine

I. Risk of respiratory depression?

II. Treatment for precipitated withdrawal

III. Induction efficacy? *Case Series/Studies*

2006;38(4):505

JOURNAL OF PSYCHOACTIVE DRUGS

Journal of Psychoactive Drugs



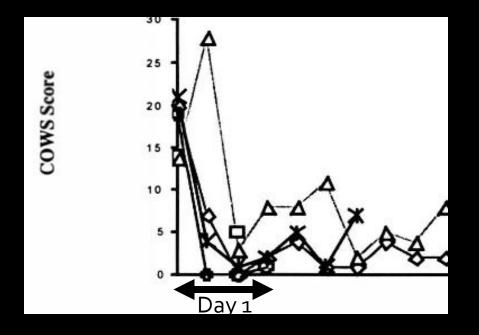
ISSN: 0279-1072 (Print) 2159-9777 (Online) Journal homepage: https://www.tandfonline.com/loi/ujpd20

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

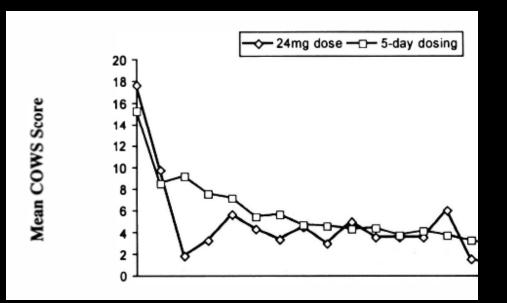
Kathleen Ang-Lee , Michael R. Oreskovich , Andrew J. Saxon , Craig Jaffe , Charles Meredith , Mei Ling K. Ellis , Carol A. Malte & Patricia C. Knox

Case Series

- n=5 vs historical controls, n=20
- Inpatient, supervised detox, COWS > 13
- 24 mg Bupe SL induction



One patient had precipitated withdrawal -Improved in 4 hours



The 24 mg group appears to have a faster normalization compared to escalating Bupe over 5 days



2014

Cochrane Database of Systematic Reviews

Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (Review)

Mattick RP, Breen C, Kimber J, Davoli M

■ Higher doses (≥ 16mg) = lower illicit use and increased retention

The American Journal on Addictions, 24: 667–675, 2015 Copyright © American Academy of Addiction Psychiatry ISSN: 1055-0496 print / 1521-0391 online DOI: 10.1111/ajad.12288

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

Petra Jacobs, MD,¹ Alfonso Ang, PhD,² Maureen P. Hillhouse, PhD,² Andrew J. Saxon, MD,³ Suzanne Nielsen, PhD,⁴ Paul G. Wakim, PhD,⁵ Barbara E. Mai, PhD,⁶ Larissa J. Mooney, MD,² Jennifer S. Potter, PhD,⁷ Jack D. Blaine, MD¹

Prospective Observational Study:

- Secondary analysis of START Data
- Different induction trajectories in the first 3 days
- Outcomes @ different induction dosing
- Bupe > 16 mg had less dropout and adverse events at 28 days
- Outcomes better with higher doses

RESEARCH

CrossMark

Open Access

Single high-dose buprenorphine for opioid craving during withdrawal

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

<u>RCT</u>

- Single buprenorphine dose for opioid withdrawal
- Gave 32 mg, 64 mg or 96 mg
- Observed *craving scores* for the next 5 days

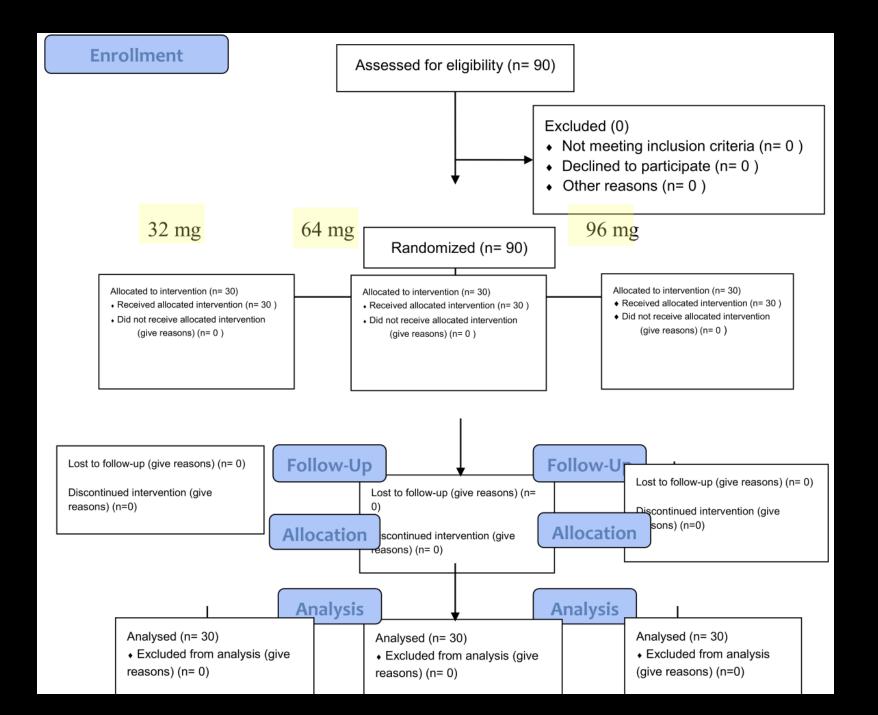


Table 3 Craving scores (means and standard deviations) of the three groups

Group (Buprenorphine, mg)	32	64	96
Day	n = 30	n = 30	n = 30
Baseline	7.23 ± 3.51	6.93 ± 3.54	7.56 ± 3.53
Day 1	4.46 ± 3.95	4.96 ± 2.90	4.00 ± 2.75
Day 2	2.56 ± 3.23	3.03 ± 2.23	1.00 ± 1.74
Day 3	1.70 ± 2.39	0.900 ± 1.37	0.366 ± 0.927
Day 4	1.23 ± 1.86	0.300 ± 0.749	0.233 ± 0.727
Day 5	0.700 ± 1.14	0.100 ± 0.402	0.00 ± 0.00

Results:

-64 mg worked better than 32 mg -96 mg did not work better than 64 mg

Adverse effects

To ensure safety, side effects, vital signs, respiration, and gastrointestinal effects were measured and monitored every hour for the first day, and then every 6 h. Nine patients developed notable side effects. Two (both in the 96-mg group) developed significant hypotension (blood pressure of 75/50 and 80/45, respectively) and were treated with hydration. Two (both in the 32-mg group) developed nausea. Five (two in the 64-mg group and three in the 96-mg group) developed both nausea and vomiting. Patients who had nausea or vomiting were treated with antiemetic medications. No severe respiratory, cardiovascular, or gastrointestinal adverse effects were observed.

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

Gerard G. Carroll, Deena D. Wasserman, Aman A. Shah, Matthew S. Salzman, Kaitlan E. Baston, Rick A. Rohrbach, Iris L. Jones & Rachel Haroz

Case Series: Pre-hospital

- n= 18
- Post-naloxone rescue, COWS > 7
- Buprenorphine 16 mg SL
- Next-day follow-up

- All 18 improved
- No P.O.W. observed
- 3 example cases summarized below

		TABLE 1. F	Patient Characteristics and	d Treatment		
Patient	Naloxone given	Initial COWS	Buprenorphine given	Repeat COWS	1 st visit	30 day retention
A	2 mg IM	13	16 mg	3	Yes	Yes
В	2mg IM	15	16-32 mg	3	Yes	No
С	4 mg IN	12	16 mg	4	Yes	Yes





Original Investigation | Substance Use and Addiction High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder

Andrew A. Herring, MD; Aidan A. Vosooghi, MS; Joshua Luftig, PA; Erik S. Anderson, MD; Xiwen Zhao, MS; James Dziura, PhD; Kathryn F. Hawk, MD, MHS; Ryan P. McCormack, MD, MS; Andrew Saxon, MD; Gail D'Onofrio, MD, MS JAMA Network Open. 2021;4(7):e2117128

Retrospective, observational study

- N= 579
- ED induction for OUD

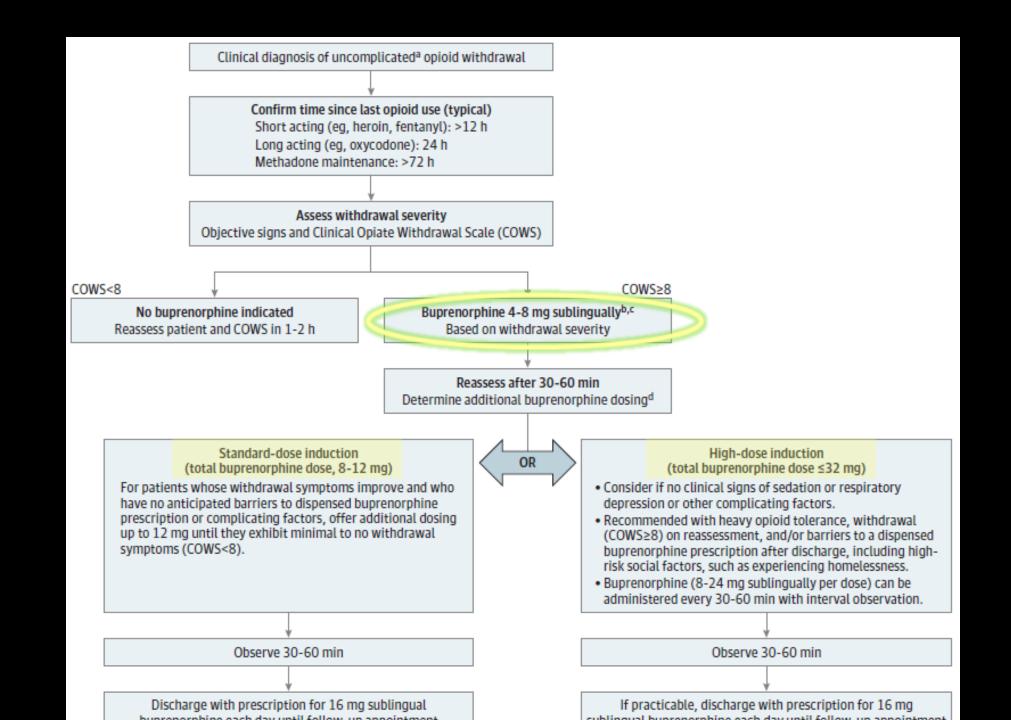
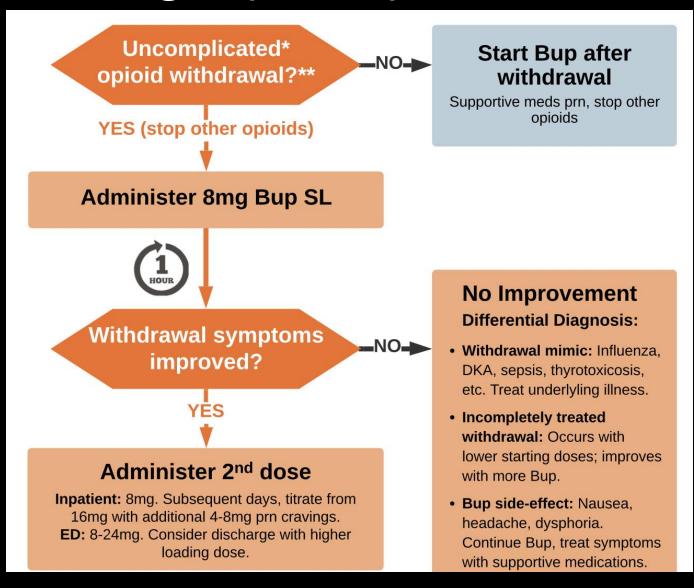


Table 2. Clinical Characteristics of Sublingual Buprenorphine Induction for Opioid Use Disorder During Emergency Department Visits						
	Total buprenorphine dose sublingual					
Characteristic	2-6 mg (n = 55)	8 mg (n = 136)	10-12 mg (n = 22)	16 mg (n = 106)	20-24 mg (n = 122)	≥28 mg (n = 138)
Adverse events, No. (%)						
Precipitated withdrawal	0	4 (2.9)	0	0	0	1 (0.7)
Hospitalization	5 (9.1)	4 (2.9)	1 (4.5)	3 (2.8)	8 (6.6)	4 (2.9)

<u>Bottom line</u>:

-Patients did well with high-dose -Zero cases of serious ADE

Starting buprenorphine in the ED



https://cabridge.org/

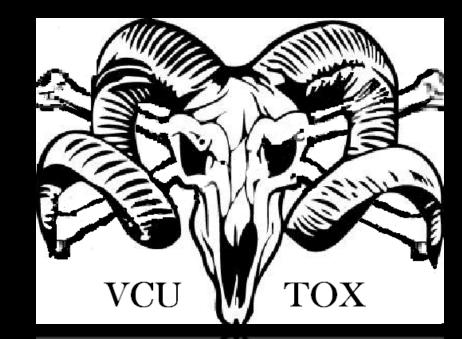
Summary

Higher buprenorphine dosing:

- Evidence is weak...
- May result in lower incidence of P.O.W.
- More rapid & complete termination of W/D
 - Especially for pts with chronic fentanyl use
- May result in improved treatment retention
- No clear signal of harm

COMMENTS? QUESTIONS?





VCU

TOX



Disclosures

Brandon Wills, DO has no financial conflicts of interest to disclose.

There is no commercial or in-kind support for this activity.





Case Presentation #1

PHI

NCU

- 12:35-12:55 [20 min]
 - 5 min: Presentation
 - 2 min: Clarifying questions-Spokes
 - 2 min: Clarifying questions Hub
 - 2 min: Recommendations Spokes
 - 2 min: Recommendations Hub
 - 5 min: Summary Hub

Reminder: Mute and Unmute to talk *6 for phone audio Use chat function for questions

Main Question

Outpatient microinduction for a patient taking methadone

Demographic Information

A 41-year-old female with OUD & cocaine use disorder presents requesting treatment with buprenorphine. Pt currently takes methadone 30 mg daily, states she is not happy with it, continues to use heroin daily despite being compliant with methadone. Pt. has previously had success with buprenorphine and would like to re-start this medication.

Background Information

Denies any past medical or psychiatric history.

Previous Interventions

As above.







Case Studies

- Case studies
 - Submit: <u>www.vcuhealth.org/echo</u>
 - Receive feedback from participants and content experts
 - Earn **\$100** for presenting

Thank You

The success of our telehealth program depends on our participants and those who submit case studies to be discussed during clinics. We recognize the following providers for their contributions:

- · Ademola Adetunji, NP from Fairfax County CSB
- Tara Belfast-Hurd, MBA-PA from Department of Behavioral Health and Developmental Services
- Michael Bohan, MD from Meridian Psychotherapy
- Ramona Boyd, NP from Health Wagon
- Diane Boyer, DNP from Region Ten CSB
- Melissa Bradner, MD from VCU Health
- Kayla Brandt, B.S. from Crossroads Community Service Board
- Candace Fletcher, PharmD Candidate from Hopkins Medical Association
- Susan Cecere, LPN from Hampton Newport News
- Kimberly Dexter, DNP from Hampton Newport News CSB
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- Candace Fletcher, PharmD from Hopkins Medical Association
- Michael Fox, DO from VCU Health
- Shannon Garrett, FNP from West Grace Health Center
- LaShawna Giles, MSW from Hampton Newport News CSB
- Sharon Hardy, BSW, CSAC from Hampton-Newport News CSB
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- Stephanie Osler, LCSW from Children's Hospital of the King's Daughters
- Davina Pavie, QMHP from Hanover County CSB
- Winona Pearson, LMSW from Middle Peninsula Northern Neck CSB
 WORK CSB

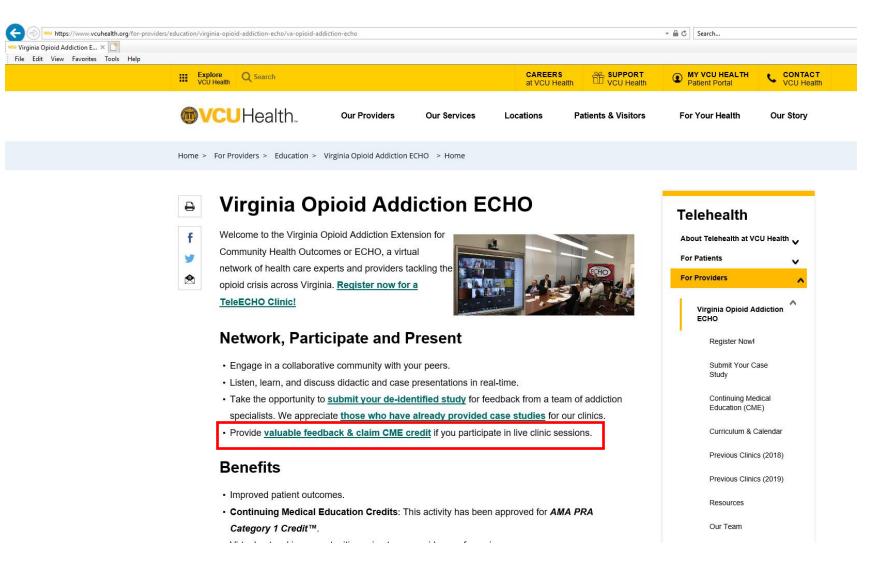
Project ECHO® Virginia Commonwealth University

- Jennifer Phelps, BS, LPN from Horizons Behavioral Health
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- Jashanda Poe, MA from Rappahannock Area CSB
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- Amber Sission, QMHP from Eastern Shore CSB
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- Saba Suhail, MD from Ballad Health
- Michelle Tanner, LPC from Hanover County CSB
- Barbara Trandel, MD from Colonial Behavioral Health
- Bill Trost, MD from Danville-Pittsylvania Community Service
- Art Van Zee, MD from Stone Mountain Health Services
- Ashley Wilson, MD from VCU Health
- Sarah Woodhouse, MD from Chesterfield Mental Health
- Susan Mayorga, BA, CBIS from Community Health Center of the New River Valley
- Jordan Siebert, Peer Recovery Specialist from Daily Planet Health Services

Claim Your CME and Provide Feedback



- <a>www.vcuhealth.org/echo
- To claim CME credit for today's session
- Feedback
 - Overall feedback related to session content and flow?
 - Ideas for guest speakers?







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ile Edit View Favorites Tools Help	Vigini Lonnonwealth			
	Please help us serve you better and learn more about your m Addiction ECHO (Extension of Community I	eeds and the value of the Virginia Opioi lealthcare Outcomes).	4	
	First Name * must provide value			
	Last Name * must provide value			
	Email Address * must provide value			
	I attest that I have successfully attended the ECHO Opioid Addiction Clinic.	Yes		
	* must provide value	No	reset	
	, learn more about Project ECHO Watch video			
	How likely are you to recommend the Virginia Opioid Addiction ECHO by VCU to colleagues?	Very Likely		
		Likely		
		Neutral		
		Unlikely		
		Very Unlikely	reset	
	What opioid-related topics would you like addressed in	the future?		
	What non-opioid related topics would you be interested	in?		



- <u>www.vcuhealth.org/echo</u>
 - To view previously recorded clinics and claim credit

Education	Previous Clinics - 2021
Contact Us	Review topics we covered in previous Virginia Opioid Addiction ECHO clinics.
Diabetes and Hypertension Project ECH0 +	January 15, Buprenorphine Taper Presented by Masaru Nishiaoki, MD
Nursing Home ECHO +	View Presentation View Video
Palliative Care ECHO +	January 29, Panel Discussion: COVID and Chronic Conditions
Virginia Opioid Addiction ECHO –	Panelists: Albert Arias, MD, Alex Krist, MD and Katherine Rose, MD
	View Presentation
Contact Us	View Video
Curriculum Calendar and Registration	February 12, Grief Impacting Recovery Presented by Courtney Holmes, PhD
Our Team	View Presentation
	Video Video
Previous Clinics - 2021	February 26, Virginia Drug Court System
Previous Clinics - 2022	Presented by Melanie Meadows
	View Presentation
Resources	View Video
Thank You	March 12, COVID and Recovery: Panel Discussion
	Presented by Tom Bannard, MBA Omri Morris, CPRS Raymond Barnes, CPRS Erin Trinh, CPRS
Virginia Opioid Addiction ECHO Continuing Medical	View Presentation
Education	View Video
Virginia Opioid Addiction ECHO Evaluation	March 26, Effects of Pharmacology on Cognitive Function
Virginia Sickle Cell Disease ECHO +	Presented by Gerry Moeller, MD
-	View Presentation
Child Abuse Project ECHO +	View Video View Resource
	• View Resource
Early Intervention Project ECH0 +	April 9, PropER Clinic and SUD Virtual Bridge Clinic: Linking Patients from ED to PCP and SUD Care
	Presented by Taruna Aurora, MD and Brandon Wills, MD



OVCU

View Presentation

View Video

VCU Virginia Opioid Addiction TeleECHO Clinics

Bi-Weekly Fridays - 12-1:00 pm

Mark Your Calendar --- Upcoming Sessions

April 15: Harm Reduction and Syringe Exchange

Health Brigade

April 29: Family Dynamics and SUD

William Nicoll, LPC

Please refer and register at vcuhealth.org/echo





THANK YOU!

Reminder: Mute and Unmute to talk *6 for phone audio Use chat function for questions