Precipitated Opioid Withdrawal: When, Where, And What To Do Next

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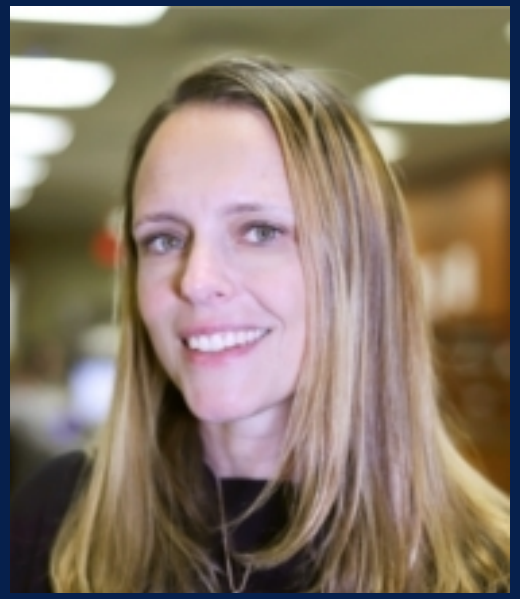

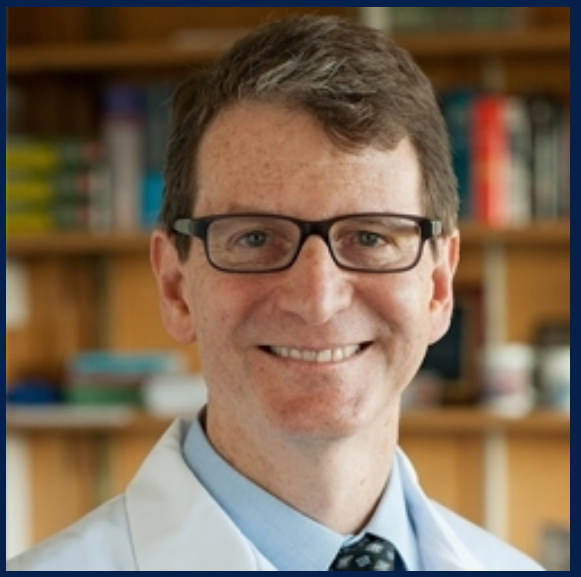

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Disclosure Information

- Rachel S. Wightman, MD
  - No Disclosures
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Learning Objectives

- Understand the pathophysiology of precipitated opioid withdrawal and the associated pharmacodynamics
- Review the existing evidence for management of precipitated opioid withdrawal from partial and full-opioid antagonists
- Address precipitated opioid withdrawal concerns specific to buprenorphine initiation and strategies to reduce risk

Case 1: Low-dose Buprenorphine

38 yo woman w/ OUD.

She has a history of IV heroin use. Reports last use 6 hours prior.

Today in the clinic started a planned buprenorphine initiation at 4mg-1mg buprenorphine-naloxone. 10 minutes after buprenorphine administration developed nausea, vomiting, diarrhea, tachycardia, and hypertension.

Opioid Withdrawal Signs and Sx

Physiologic	Psychological
Restlessness, nausea, vomiting, diarrhea, piloerection, diaphoresis, yawning, mydriasis, and autonomic hyperactivity	Pain, anxiety, stress intolerance, irritability, and drug craving

Discussion Questions

- Is there a difference in patient presentation between precipitated withdrawal and abstinence- related withdrawal?

AUDIENCE POLL 1

How would you treat this patient?

A. 2mg-0.5 mg bup/naloxone
B. 16mg-4mg bup/naloxone
C. Full agonist opioids (e.g., fentanyl or methadone)
D. Treat w clonidine, ondansetron, supportive care

Discussion Questions

- Do you use opioid agonists, opioid partial agonists or non-opioid adjuncts for precipitated withdrawal?

Precipitated W/D Tx

Classes	Treatments
Adjuncts	IVF, loperamide
Sedation	Benzodiazepines, haloperidol, propofol olanzapine
Antiemetics	Ondansetron, metoclopramide, prochlorperazine promethazine
Alpha-2 agonists	Clonidine, dexmedetomidate, lofexidine
Mu opioid full agonist	Fentanyl, methadone
Mu opioid partial agonist	Buprenorphine

Kunzler et al. Precipitated WD Long-acting antagonists . AJEM. 2020.

Precipitated Withdrawal Management

Lower dose buprenorphine

- 2mg/0.5mg buprenorphine-naloxone q1hr for several doses
- Followed by 8mg-2mg for one to two doses

Higher dose buprenorphine

- 16mg buprenorphine x1

  or
- 24mg buprenorphine x1

DISCUSSION

What has been your experience with:

1. Sequential dosing of lower dose buprenorphine

2. Sequential dosing of higher dose buprenorphine

AUDIENCE POLL 2

Does the naloxone portion of buprenorphine-naloxone matter?

A. Yes
B. No
C. I don't know
D. It depends

Pharmacokinetics Sublingual Naloxone

Pharmacokinetic parameters of naloxone — Mean ± SD ($n = 9$)[a]

	Sublingual Bup: 8 mg Nal: 4 mg (B8N4)	Sublingual Bup: 8 mg Nal: 8 mg (B8N8)	Statistical *P* value for treatment effect	Intravenous Bup: 4 mg Nal: 4 mg
Naloxone				
AUC unextrapolated (h*ng/ml)	1.10 ± 0.57	1.75 ± 0.93	0.658	14.97 ± 5.3
AUC extrapolated (h*ng/ml)	1.29 ± 0.66	1.97 ± 1.12	0.549	15.2 ± 5.3
Peak concentration (ng/ml)	0.662 ± 0.529	0.934 ± 0.713	0.176	36.88 ± 24.9
Time of peak (h)[b]	0.928 ± 0.248	1.01 ± 0.31	0.410	–
Elimination rate constant estimate (kd in h^{-1})	0.672 ± 0.335	0.681 ± 0.469	0.621	0.789 ± 0.27
Half-life (h)	1.66 ± 1.83	1.40 ± 0.77	[c]	1.00 ± 0.43

[a] For naloxone AUC extrapolated and unextrapolated, $n = 8$; for naloxone kd $n = 8$ and 7 for doses B8N4 and B8N8, respectively.
[b] Analyzed in linear rather than logarithmic domain. Outcome: bioequivalence not established.
[c] Since half-life is derived from kd, *P* value not calculated.

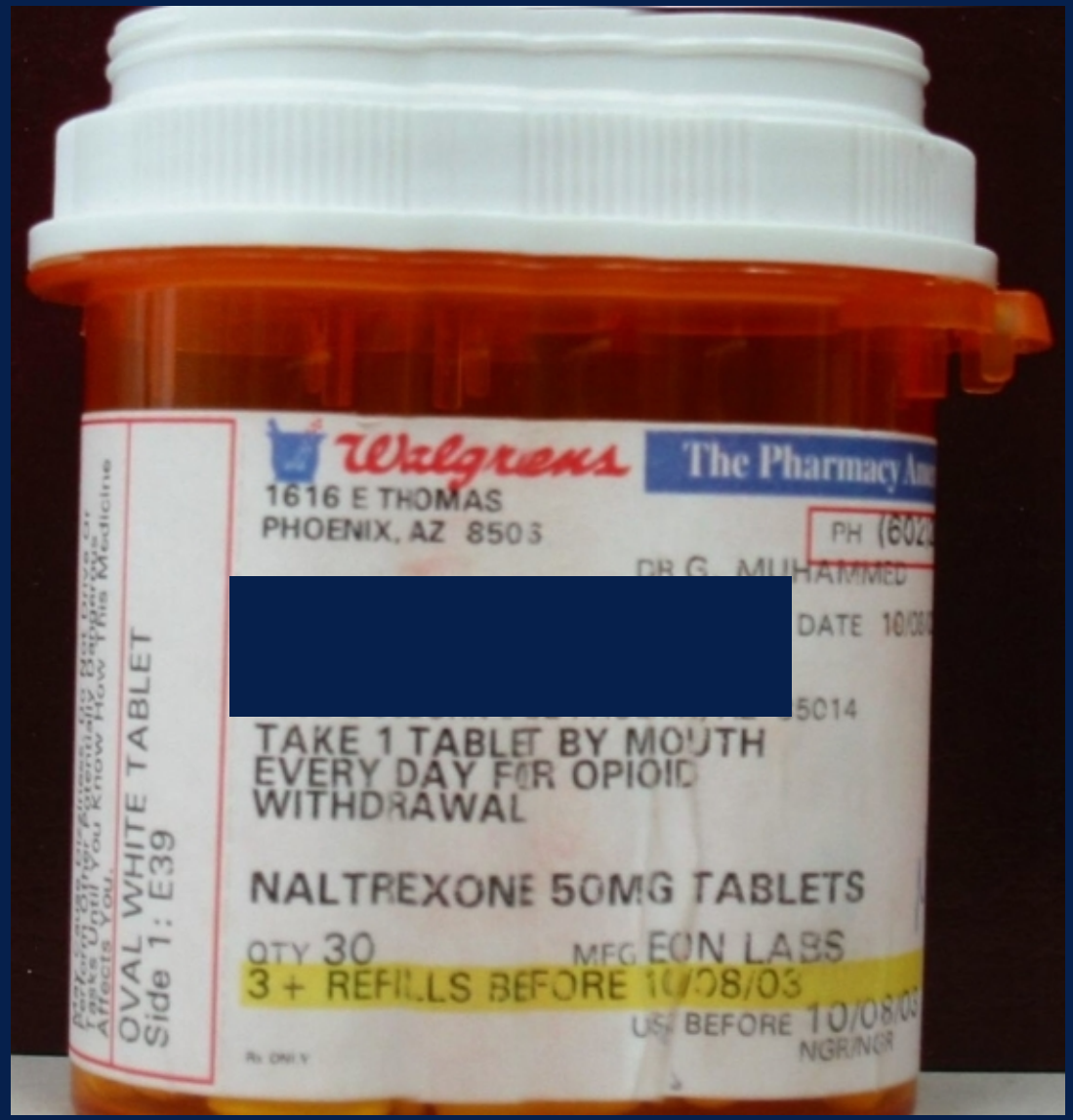
Harris DS. Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. Drug and Alcohol Dependence 2020. 61:85-94.

22 yo man w/ hx of AUD and OUD. Reports 2-3 time daily use of intranasal opioids (oxycodone).

Patient took friend's 50 mg ***naltrexone*** to "withdraw from opioids"

Presents in severe precipitated opioid withdrawal

Case 2: Naltrexone Precipitated WD



Case 2: Naltrexone Precipitated WD

AUDIENCE POLL 3

What would be your first step in management?

A. Clonidine, benzodiazepines, ondansetron, supportive care

B. Buprenorphine

C. Treat w full agonist opioids (e.g, fentanyl, methadone)

Oral Naltrexone Pharmacology

Dose (oral)	Duration of Action
50 mg	24 hours
100 mg	48 hours
150 mg	72 hours

Discussion Questions

- How do you manage precipitated opioid withdrawal from oral naltrexone?

Case 3: Naltrexone ER Precipitated WD

56 yo woman w/ hx opioid dependence previously on extended-release intramuscular naltrexone requesting to restart treatment

20 minutes after extended-release intramuscular naltrexone injection the patient was feeling unwell and was transferred to the ED

VS: BP, 220/110 mmHg; HR, 86/min; RR, 30/min; T, 97.6°F; O2 saturation, 100% on RA

Discussion Questions

- What are your next questions for the patient?

AUDIENCE POLL 4

What would be your first step in management?

A. Clonidine, benzodiazepines, antiemetics supportive care

B. Buprenorphine

C. Full agonist opioids (e.g,methadone, fentanyl)

D. IV Nicardipine

Pharmacology Extended-release Intramuscular Naltrexone

Onset of action is biphasic:

- Transient peak 2 hours after injection
- Second peak occurs 2-3 days later

- Beginning approximately 14 days after injection, concentrations of naltrexone and metabolites slowly decline with detectable concentrations for greater than 1 month

Dunbar JL et al. Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. Alcohol Clin Exp Res 2006;30(3):480-90.

Fishman M. Precipitated withdrawal during maintenance opioid blockade with extended release naltrexone. Addiction 2008;103:1399-1401.

How long should a provider wait before initiating Vivitrol?

- To minimize risk of precipitated opioid withdrawal with Vivitrol, it is recommended that patients should be opioid-free for **7-10 days** prior to initiating therapy.
  - For patients using longer acting opioids or opioids with active metabolites, a longer opioid free period should be observed.
  - However, recent XRNTX clinical trials have shortened the required opioid-free period to **3 days**, recognizing that longer waiting times may reduce rates of treatment initiation.

Rapid Naltrexone Induction

- Day 1 non-agonist adjunct
- Day 2 Buprenorphine-nx 4 mg SL BID
- Day 3 +/- Buprenorphine 4-8 mg SL
- Day 4 Naltrexone 3 mg
- Day 5 Naltrexone 6 mg
- Day 6 Naltrexone 25 mg
- Day 7 Naltrexone 50 mg, followed by 380 mg IM
- Adjuncts: Alpha-2 adrenergic agents (clonidine), benzodiazepines, sleeping agents

Sigmon et al., 2012

Case 4: Patient Using Fentanyl Interested in Buprenorphine

25 yo man w/ hx of IV opioid use

Previously used heroin, but for the past few months has been injecting ***fentanyl*** multiple times per day

Last use yesterday

Interested to start buprenorphine

AUDIENCE POLL 5

Is the risk of precipitated opioid withdrawal higher for patients on fentanyl versus other opioids?

A. Yes

B. No

C. Not sure

PATIENT EXPERIENCE REPORTS – HIGHER RISK PRECIPITATED WD

- " Suboxone does not work with fentanyl…I was almost 72 hours into withdrawal…and I took it [Suboxone] and it made me…I couldn't believe it. Cuz I don't puke or get diarrhea, I don't have that happen ever…But immediately-BAM!"

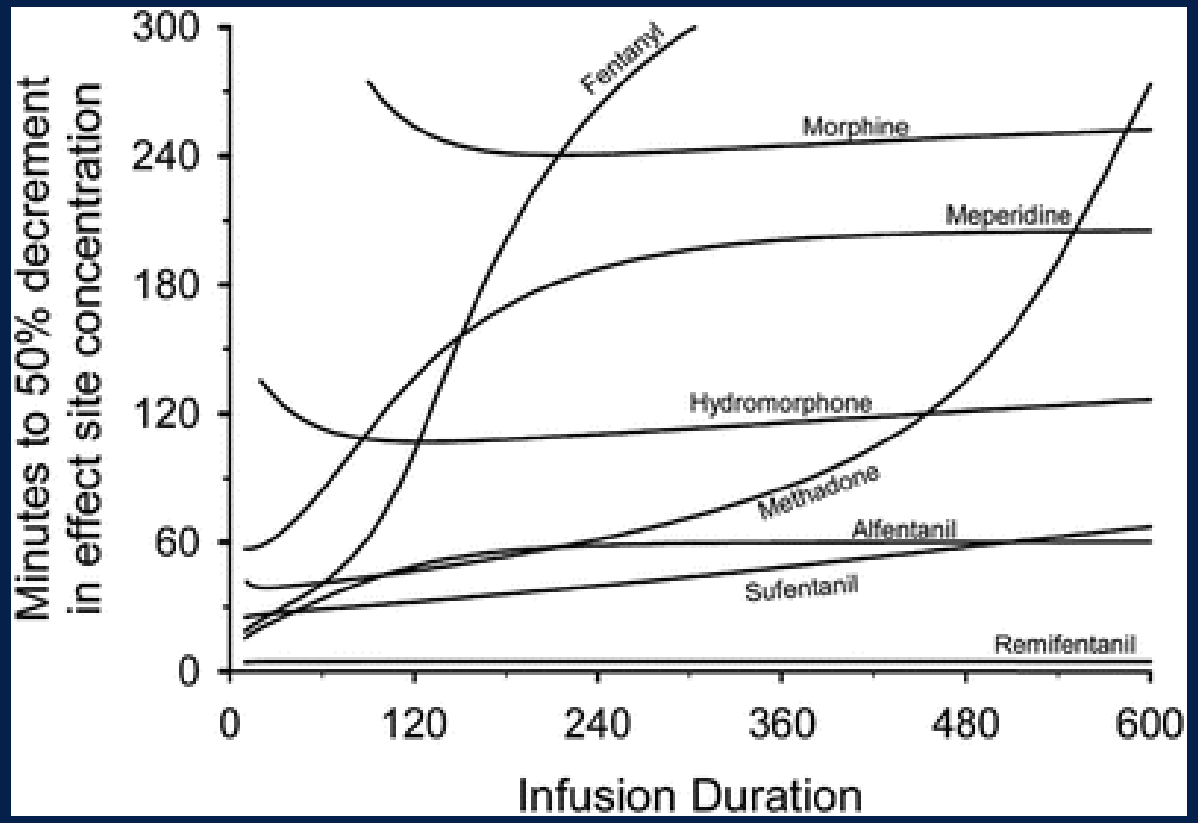
- Yes, for me it sends me into precipitated withdrawals every f*&#ing time that I try to get off of fentanyl."

Silverstein et al. "everything is not right anymore." Int J Drug Policy. 2019. 74:76-73.

Fentanyl Pharmacokinetics

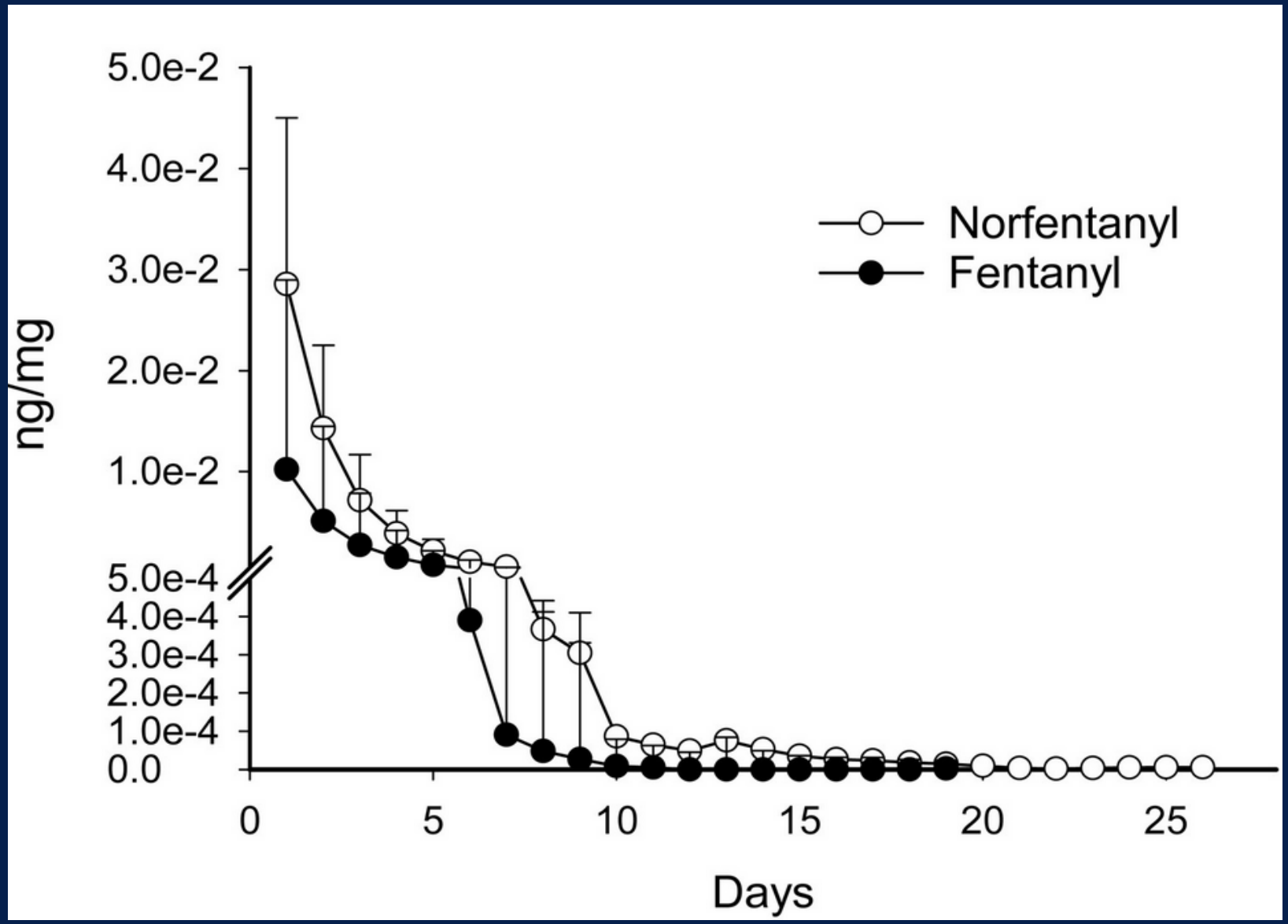
Route	Half-life ($t_{1/2}$)
Single IV bolus	1.5-6 hrs
Continuous IV infusion	8 hrs - $t_{1/2}$ prolongs w/ infusion duration
Intranasal	1.5-7 hrs
Transdermal	20-27 hrs

Fentanyl



Drug	Half life (distrib)	Half life (term)	LogP
Fentanyl	19 min	475 min	4.05
Morphine	68	548	0.89
Hydromorphone	60	1268	1.6
Methadone	120	1377	3.93

FENTANYL NORFENTANYL ELIMINATION IN URINE



Huhn SA et al. Protracted renal clearance of fentanyl in persons with opioid use disorder. Drug Alcohol Depen. 2021

Discussion: Provider Strategies

- Longer Washout/Higher COWS
- Starting Low – Doses <1 mg (Microdosing)
- Giving Bigger Doses Up Front (Macrodosing)

AUDIENCE POLL 6

How long do you have to wait since last fentanyl use before starting buprenorphine?

A. 6 hours
B. 12-24 hours
C. >48 hours
D. It doesn't matter, look at the COWS

AUDIENCE POLL 7

In your practice what strategies/precautions do you use when initiating buprenorphine for patients using fentanyl?

A. Microdosing

B. Use Higher COWS

C. Wait Longer

D. Macrodosing

E. No Change

Case 5: Naloxone to Bup Transition

24 yo man w/ hx of OUD. Has been using IV heroin/fentanyl daily.

Reports he doesn’t want to wait for withdrawal to start buprenorphine. He is afraid he will return to use during abstinent period.

AUDIENCE POLL 8

Is use of naloxone in the ED to induce withdrawal in order to start buprenorphine beneficial?

A. Yes

B. No

Discussion Question: Naloxone to Buprenorphine

- What are the ethics of this practice?
- How do you obtain informed consent?
- What is the evidence of safety/efficacy?

Case 6: Patient on Methadone

42 yo woman w/ hx of OUD on methadone presents in opioid withdrawal

Missed her methadone dose this morning

Took a friends buprenorphine-naloxone 8 mg-2 mg sublingual tablet to treat
withdrawal symptoms

Is in severe precipitated opioid withdrawal

AUDIENCE POLL 9

How would you treat this patient?

A. Give more buprenorphine
B. Treat with methadone
C. Treat with high dose fentanyl
D. Treat with clonidine, zofran, acetaminophen- supportive measures

Discussion

- Does the *dose* of last methadone matter?
- Does the *time* of the last methadone dose matter?
- If Tx w Buprenorphine- What dose?
- If Tx w Methadone- What dose?

Final Takeaways

- Understand the complex pharmacology and range of clinical scenarios of precipitated withdrawal
- Management options for precipitated withdrawal from partial versus full antagonists
- Address precipitated withdrawal concerns specific to buprenorphine initiation and strategies to reduce risk

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Appendix

Precipitated Withdrawal = Higher Risk

Withdrawal Precipitated by Opioid Antagonist/Partial Agonist	Opioid Withdrawal due to Opioid Cessation
Catecholamine surge can lead to hyperventilation, tachycardia, and hypertension.	Psychological and physical craving Muscle aches, diffuse body pain, cramping, sweating, insomnia, diarrhea.
Rare reports of arrhythmia, agitated delirium, autonomic instability, rhabdomyolysis, aspiration pneumonia, pulmonary edema, seizures, and death.[1,2,3,4]	Not acutely life threatening.

1.Wightman RS, Nelson LS, Lee JD, Fox LM, Smith SW. Severe opioid withdrawal precipitated by Vivitrol!. Am J Emerg Med 2018;36:1128.e1–2.
2. Quigley MA, Boyce SH. Unintentional rapid opioid detoxification. Emerg Med J 2001;18:494–5.
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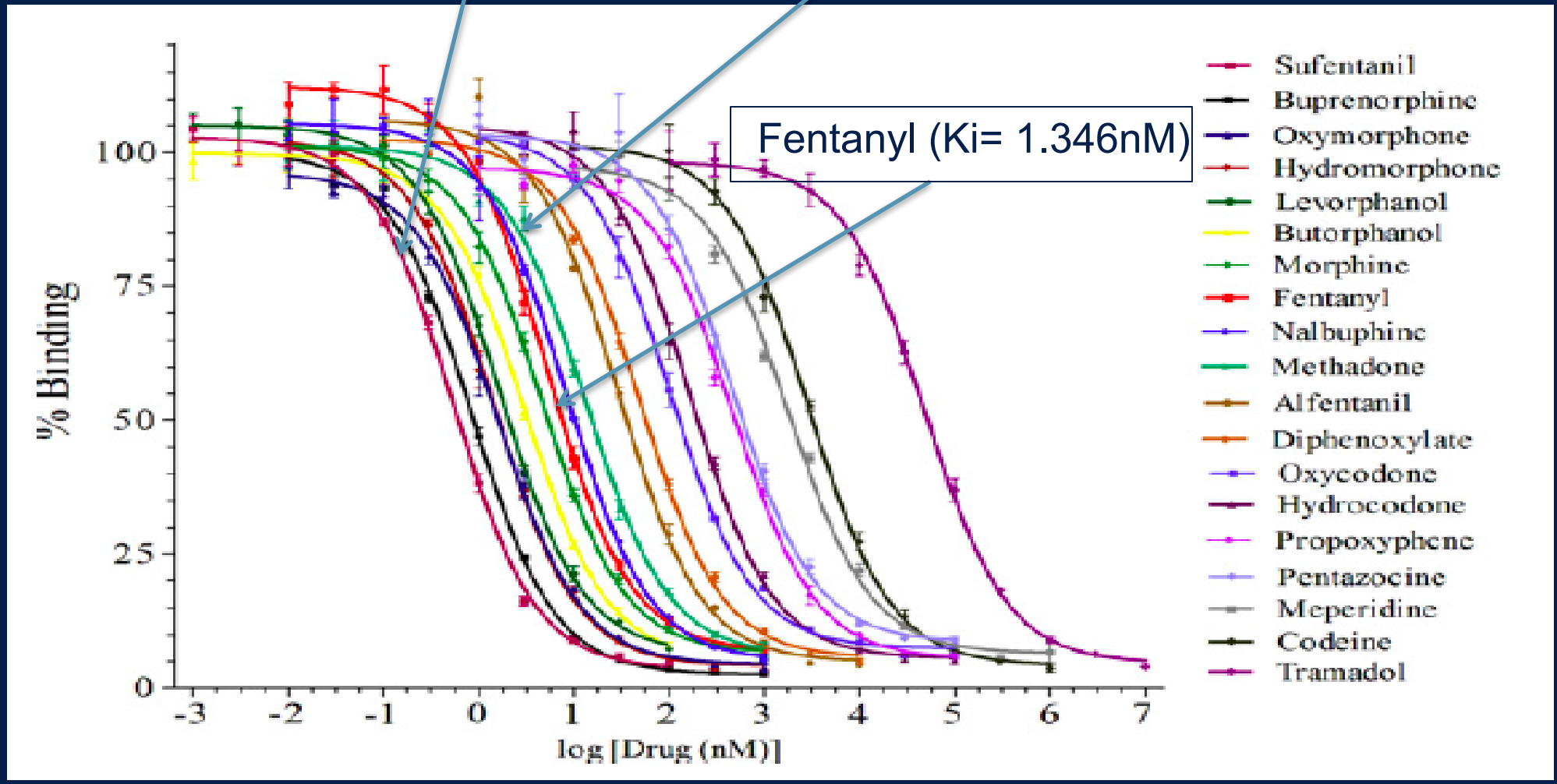
OPIOID RECEPTOR BINDING AFFINITY

Buprenorphine (Ki=0.216 nM)

Methadone (Ki=3.378nM)

Naloxone Ki= 1.52 nM,
Naltrexone Ki= 1.55 nM

Fentanyl (Ki= 1.346nM)



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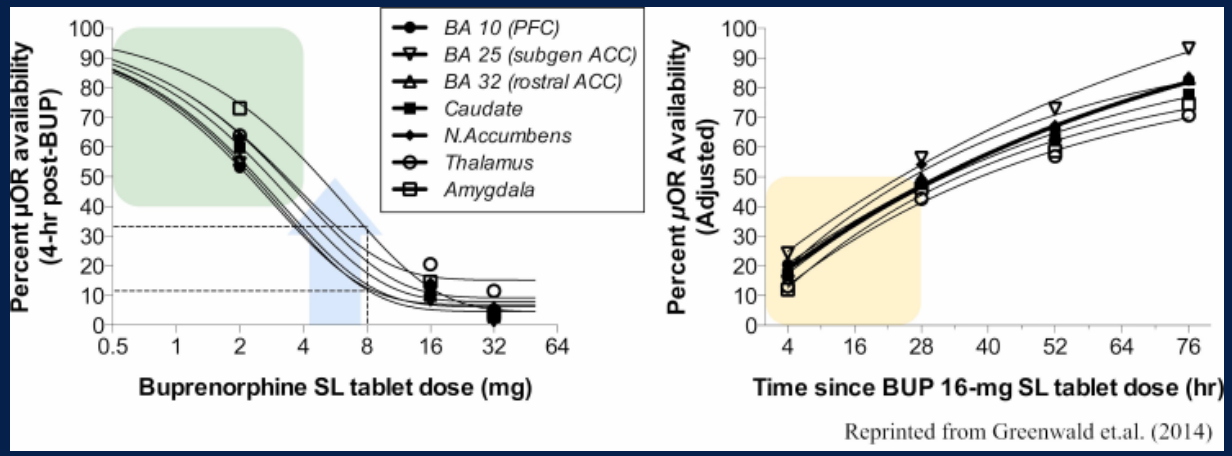
Volpe D, et al 2011

- most ligands repeatedly associate and dissociate from receptors; two affinity values Ki and Kd, respectively, reflect this variable state of affairs



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Case Report

Severe opioid withdrawal precipitated by Vivitrol®

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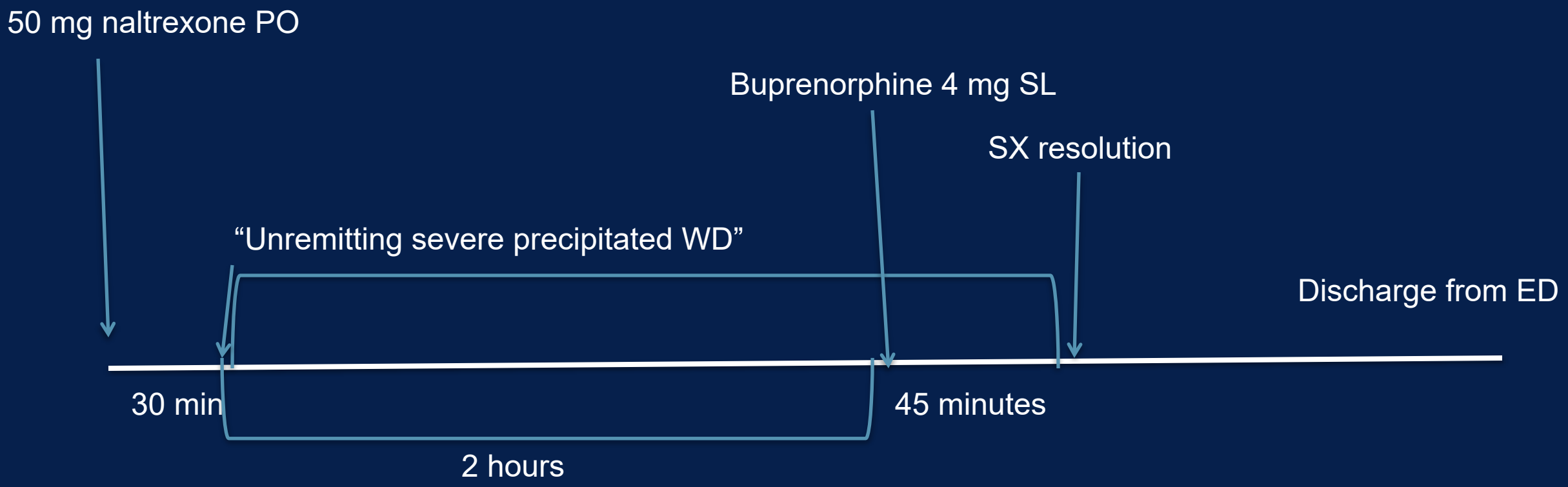
BUPRENORPHINE REVERSAL OF UNINTENTIONAL NALTREXONE PRECIPITATED OPIOID WD



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[CASE SERIES]

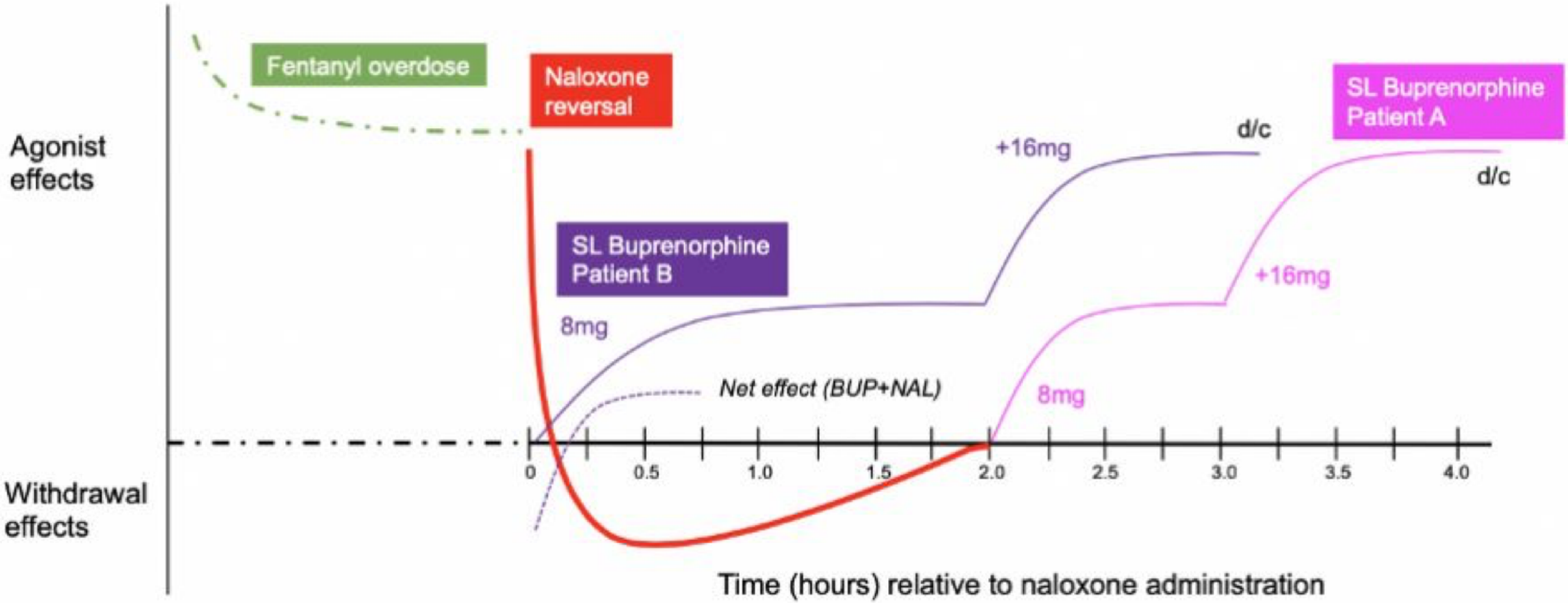
Buprenorphine Rescue from Naltrexone-Induced Opioid Withdrawal During Relatively Rapid Detoxification from High-Dose Methadone: A Novel Approach

by VANESSA URBAN, MD; and ROLLY SULLIVAN, MD

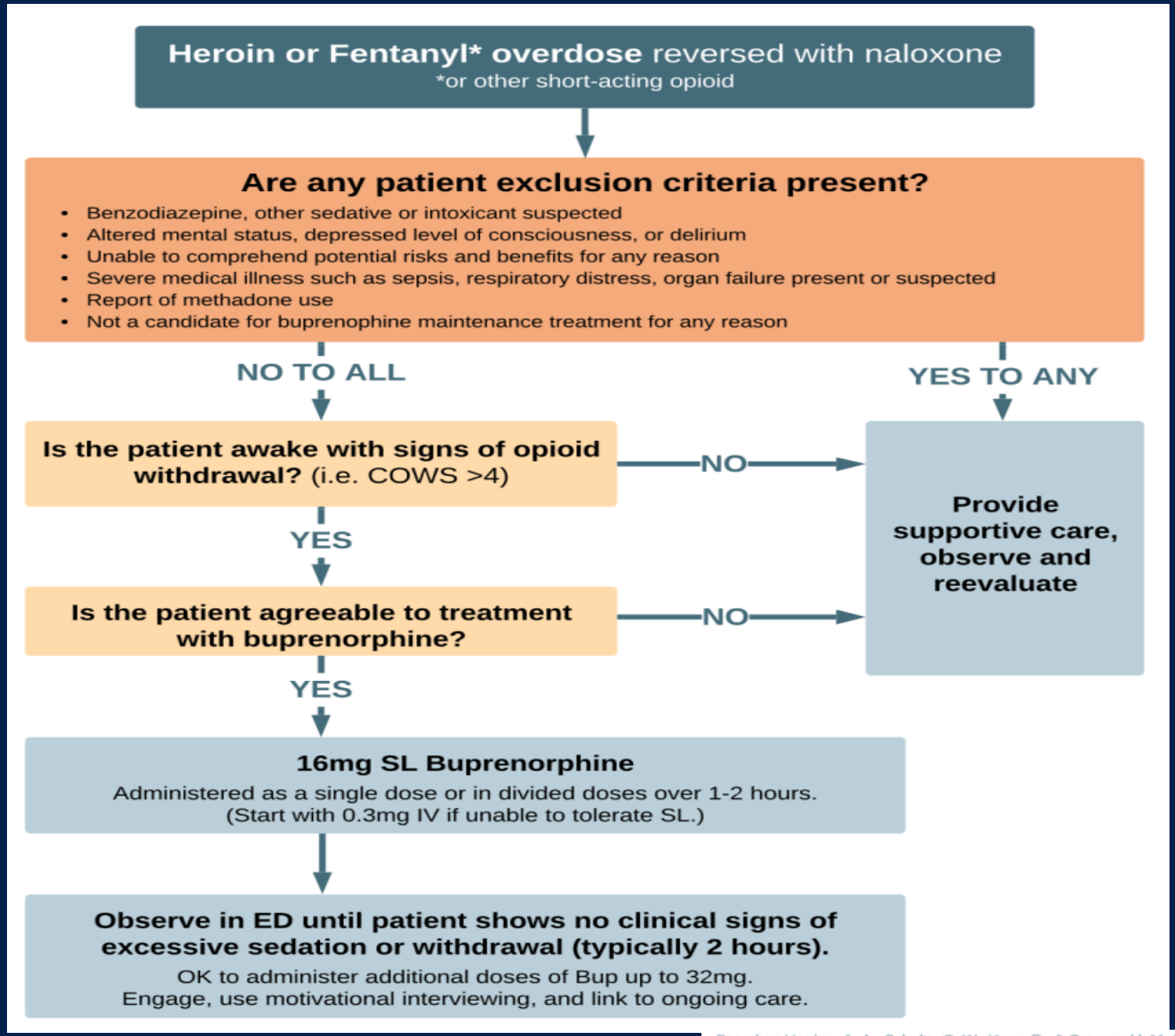
AUTHOR AFFILIATIONS: Dr. Urban is Clinical Instructor and Dr. Sullivan is Professor, Department of Behavioral Health and Psychiatry, West Virginia University of Medicine, Morgantown, Virginia.

Urban V, Sullivan R. Buprenorphine rescue from naltrexone-induced opioid withdrawal during relatively rapid detoxification from high-dose methadone: a novel approach. Psychiatry (Edgmont). 2008 Apr;5(4):56-8.

BUPRENORPHINE AFTER NALOXONE



Herring A et al. Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder. AJEM. 2019.37:2259-2262.

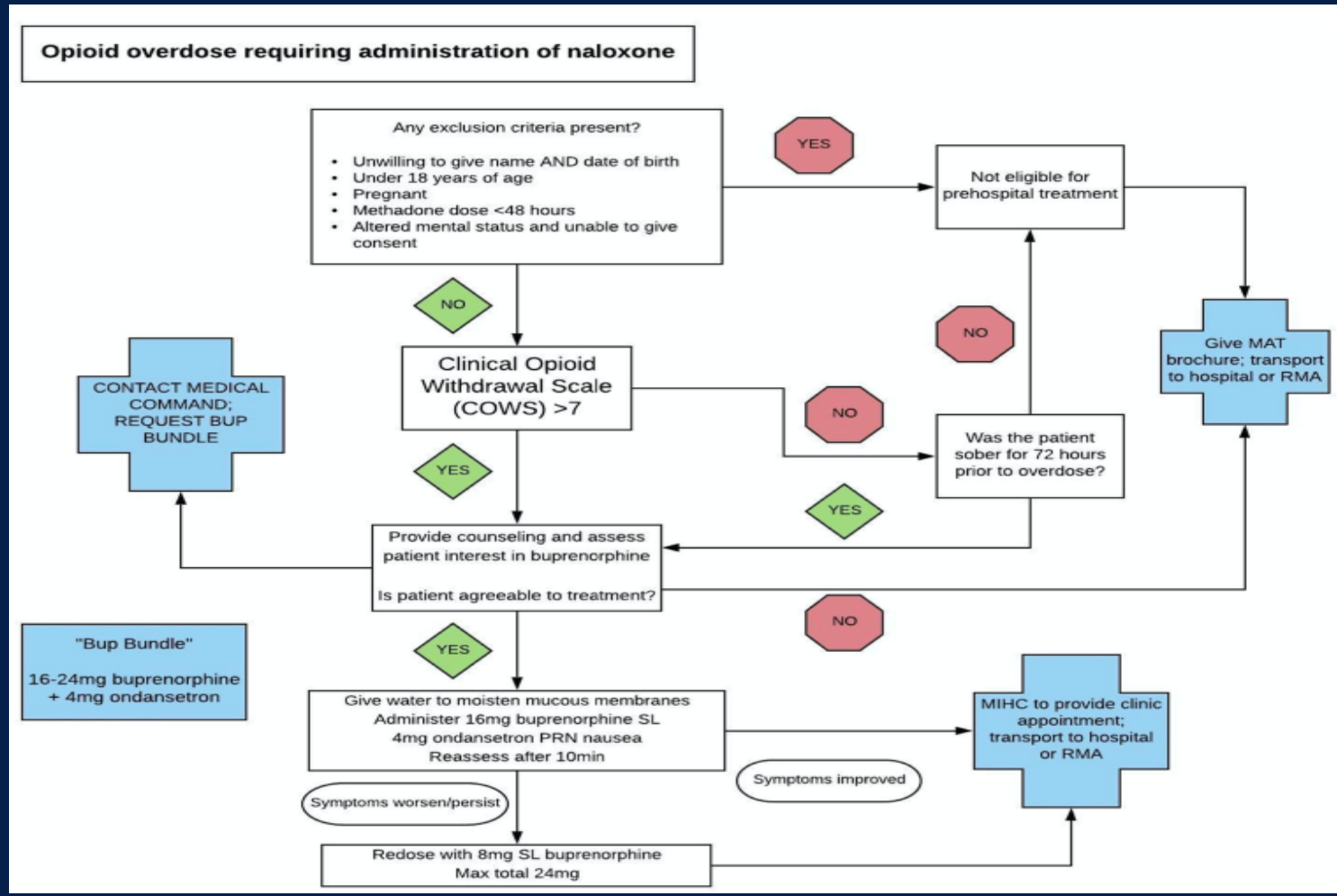


Based on Herring, A. A., Schultz, C. W., Yang, E., & Greenwald, M. (2019). Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder. *The American journal of emergency medicine*.

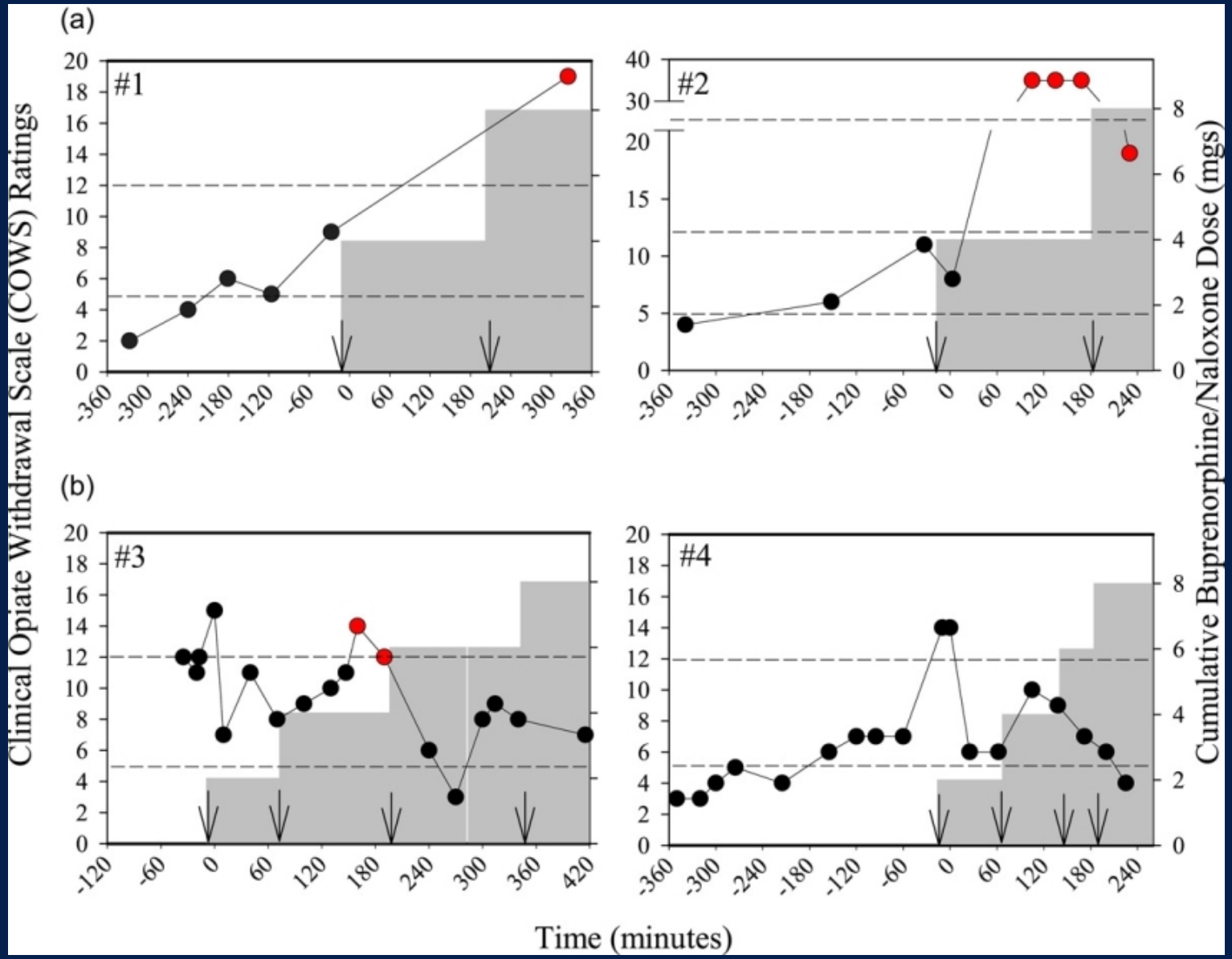
Buprenorphine Field Initiation of ReScue Treatment by Emergency Medical Services (Bupe FIRST EMS): A Case Series

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

EMS delivered buprenorphine after an opioid overdose



CASE SERIES: 4 PATIENTS BUPRENORPHINE INITIATION AND COWS



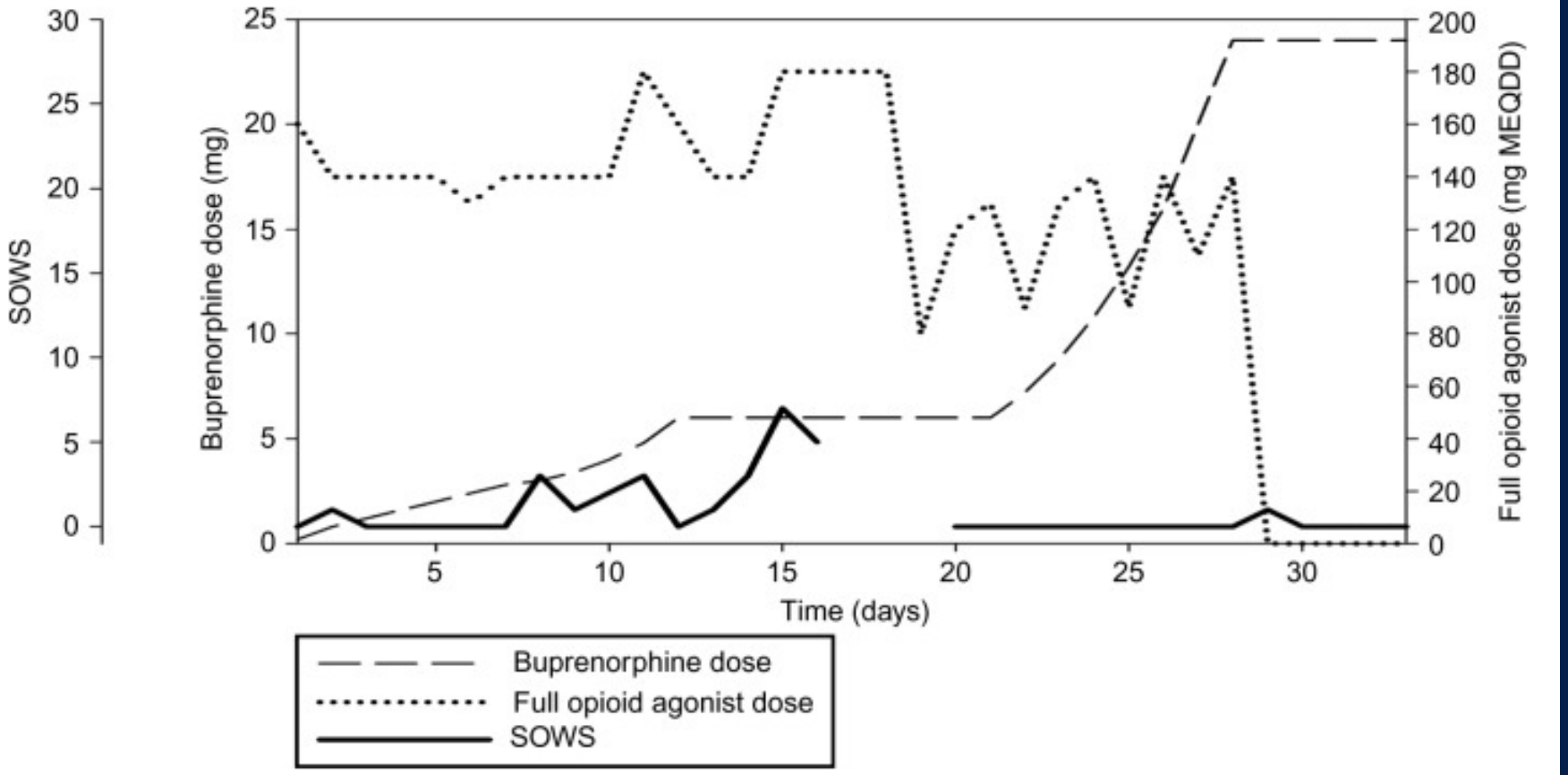
Antoine et al. Method for Successfully Inducting Individual Who Use Illicit Fentanyl Onto Buprenorphine/naloxone. The American Journal of Addicitons. 2021.30: 83-87.

GUIDANCE FOR BUPRENORPHINE INITIATION IN PATIENTS USING FENTANYL

- Instruct the patient to abstain from any opioid use for a minimum of:
  - 12-16 hours for short-acting opioids
  - 24 hours for sustained-release opioid medications
  - 36 hours for methadone

- Observe and document Mild vs. Moderate withdrawal:
  - ***NOTE: Be aware of Fentanyl; do not induce unless moderate withdrawal (COWS 13 to 15) is observed***

MICRODOSING PROTOCOL



H€ammig R, Kemter A, Strasser J, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: The Bernese method. *Subst Abuse Rehabil.* 2016;7:99.

Klaire et al. Rapid micro-linduction of buprenorphine/naloxone for opioid use disorder in an inpatient setting: a case series. *The American Journal on Addictions.* 2019.28:262-265.

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		1-4 mg IV q4h PRN	3 mg
Day 1	0.25g SL q4h	1 mg	1-4 mg IV q4h PRN	11 mg
Day 2	0.5 mg SL q4h	2.5 mg	1-4 mg IV q4h PRN	15 mg
Day 3	1 mg SL q4h	5 mg	1-4 mg IV q4h PRN	15 mg
Day 4	2 mg SL q4h	8 mg	1-4 mg IV q4h PRN	4 mg
Day 5	16 mg SL daily	16 mg	Discontinued	

Original Investigation

April 28, 2015

Emergency Department-Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence

A Randomized Clinical Trial

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