Naloxone: What you Need to Know!

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#ASAMAnnual2022

Disclosure Information (Required)

- Dr. JoAn Laes, MD, FASAM – Hennepin County Medical Center
  - No Disclosures
- Dr. Evan Schwarz, MD, FACMT, FASAM – Washington University
  - No Disclosures
- Dr. Lewis Nelson, MD, FACMT, FASAM – Rutgers New Jersey Medical School
  - No Disclosures
- Dr. Robert Cole Pueringer, MD- University of Minnesota and Hennepin County Medical Center
  - No Disclosures

Non-presenting authors

- Timothy J. Wiegand, MD, MD, FACMT, FAACT, DFASAM – University of Rochester Medicine
- Soumya Pandalai, MD, FACP, FASAM – Banner University Medical Center- Phoenix

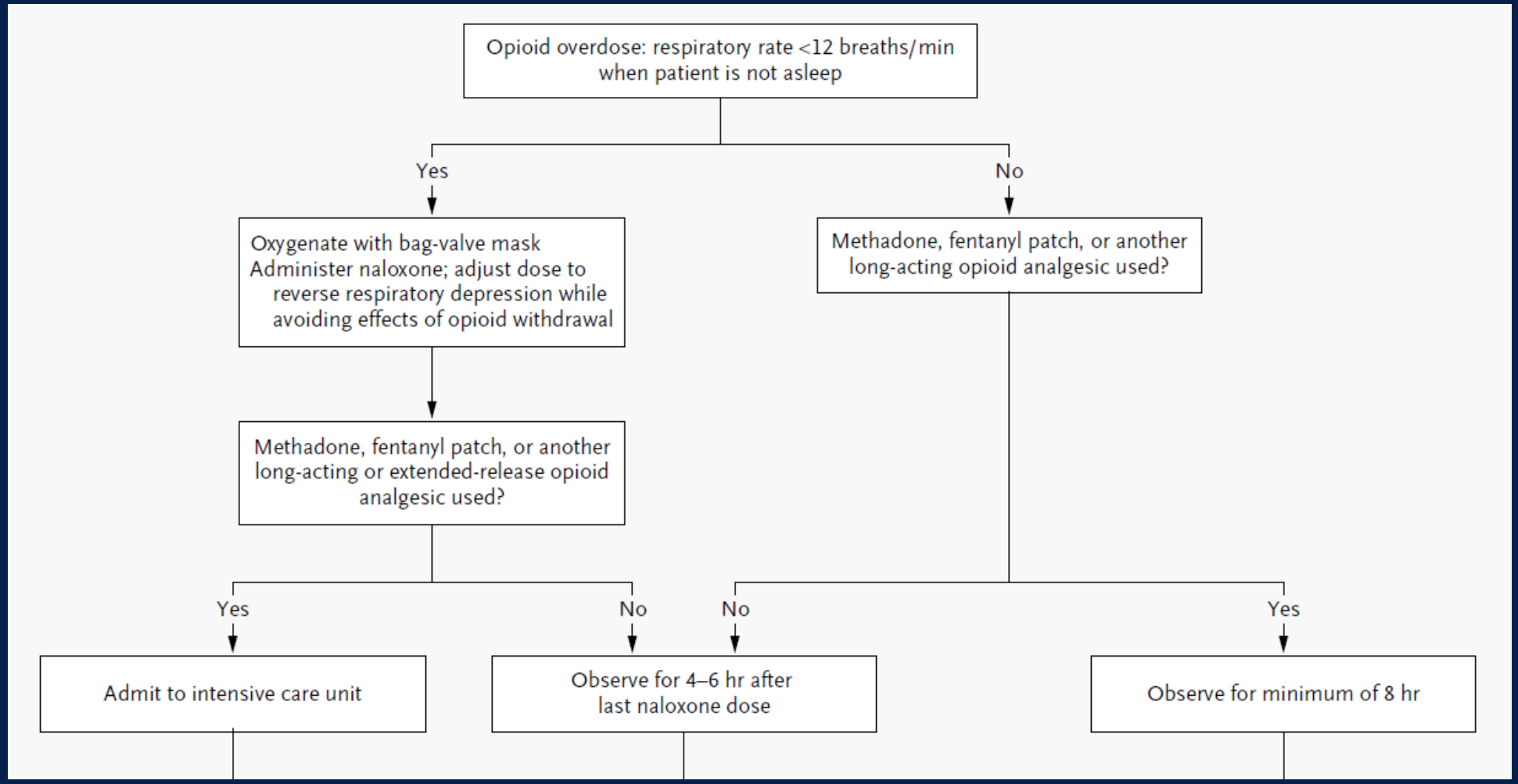
Learning Objectives

- Understand the pharmacology of naloxone and clinical application in the management of opioid overdose
- Review the existing evidence for management of precipitated opioid withdrawal in patients after using full-opioid antagonists
- Describe the use of buprenorphine following overdose reversal by naloxone to increase patient engagement in treatment

Question 1

- A 45 year old receives 1 mg of naloxone IV for a presumed opioid overdose. He is awake and alert but not in withdrawal.
  - How long do you watch him for?
  - Can he self-discharge from the hospital?
  - What about pre-hospital programs that release patients without transporting them?

How Long Do You Watch?



Boyer. N Engl J Med 2012;367:146-55.

Clarke SF. Emerg Med J 2005;22:612-6.

Hendra TJ. BMJ 1996;313:481-2.

Do They Need To Be Watched?

- Retrospective review of encounters in LA from 2011-13
- Subjects received naloxone and RR < 12
- Coroner's records reviewed later (died within 24 hours)
- 205 patients identified ---> 1 death (0.49%)
  - Cause of death: CAD and heroin use
  - No other deaths in 24 hours

Levine. Prehosp Emerg Care 2016;20(5):566-9.

Not The Only One

Clinical paper

Prehospital treatment of opioid overdose in Copenhagen—Is it safe to discharge on-scene?☆

S.S. Rudolph[a,*], G. Jehu[b], S. Louman Nielsen[a], K. Nielsen[a], V. Siersma[c], L.S

[a] The Mobile Emergency Care Unit (MECU), Department of Anaesthesia, Centre of Head and Orthopaedics, Copenhagen Universi
[b] The Department of Forensic Medicine, University of Copenhagen, Denmark
[c] The Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhager

BRIEF REPORTS

Assessment for Deaths in Out-of-hospital Heroin Overdose Patients Treated with Naloxone Who Refuse Transport

Gary M. Vilke, MD, Christian Sloane, MD, Alan M. Smith, MPH, Theodore C. Chan, MD

No Deaths Associated with Patient Refusal of Transport After Naloxone-Reversed Opioid Overdose

David A. Wampler, PhD, D. Kimberley Mc
A. M

Recurrent opioid toxicity after pre-hospital care of presumed heroin overdose patients

J. J. Boyd[1], M. J. Kuisma[1], A. O. Alaspää[1,2], E. Vuori[3], J. V. Repo[1] and T. T. Randell[4]

Are Heroin Overdose Deaths
Prehospital Treatm

Gary M. Vilke, MD, Jean Buchanan, RN, James V. Dunford, MD, Theodore C. Chan, MD

Boyd J. Acta Anaesthesiol Scand 2006;50:1266-70 Wampler DA. Prehosp Emerg Care 2011;15:320-4.
Vilke GM. Acad Emerg Med 2003;10(8):893-7. Vilke GM. Prehosp Emerg Care 1999;3:183-6. Rudolph SS. Resuscitation 2011;82(11):1414-8.

Question 2

- Your state department of mental health reaches out to you. They are considering adding the new naloxone 8 mg IN product to formulary for patients not responding to typical dose of naloxone.
  - Is this a good idea?
  - What could be the complications?
  - Are there reasons that naloxone doesn't appear to work?

SA

[redacted]

Fri 1/21/2022 11:15 AM

To: Schwarz, Evan; Burgess, Douglas M [redacted]

*** External Email - Caution ***

Missouri DHSS is looking at changing our current standing order from Naloxone 4mg intranasal to 8mg intranasal based on pharmacy requests and anecdotal reports of EMS requiring several Naloxone for revival after opioid overdose, as Fentanyl is very prevalent in the State.

Evan, what is your experience in the ER?

Are there any downsides/ cautions to using Naloxone 8mg versus 4mg intranasal?

Thanks!

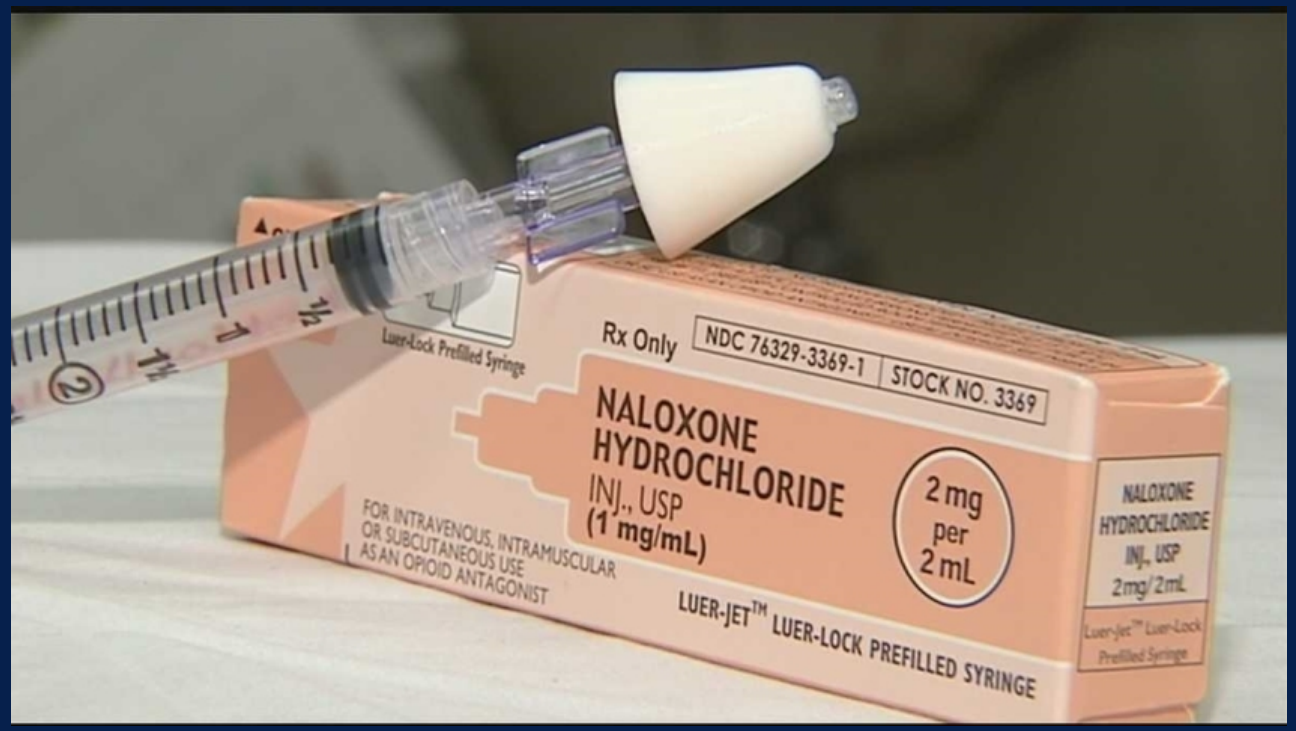
[redacted]

Missouri Department of Mental Health

It Used To Be So Simple!

100% bioavailability
Onset 1-2 min

Goldfrank's Toxicologic Emergencies



All over the place: 10-80%

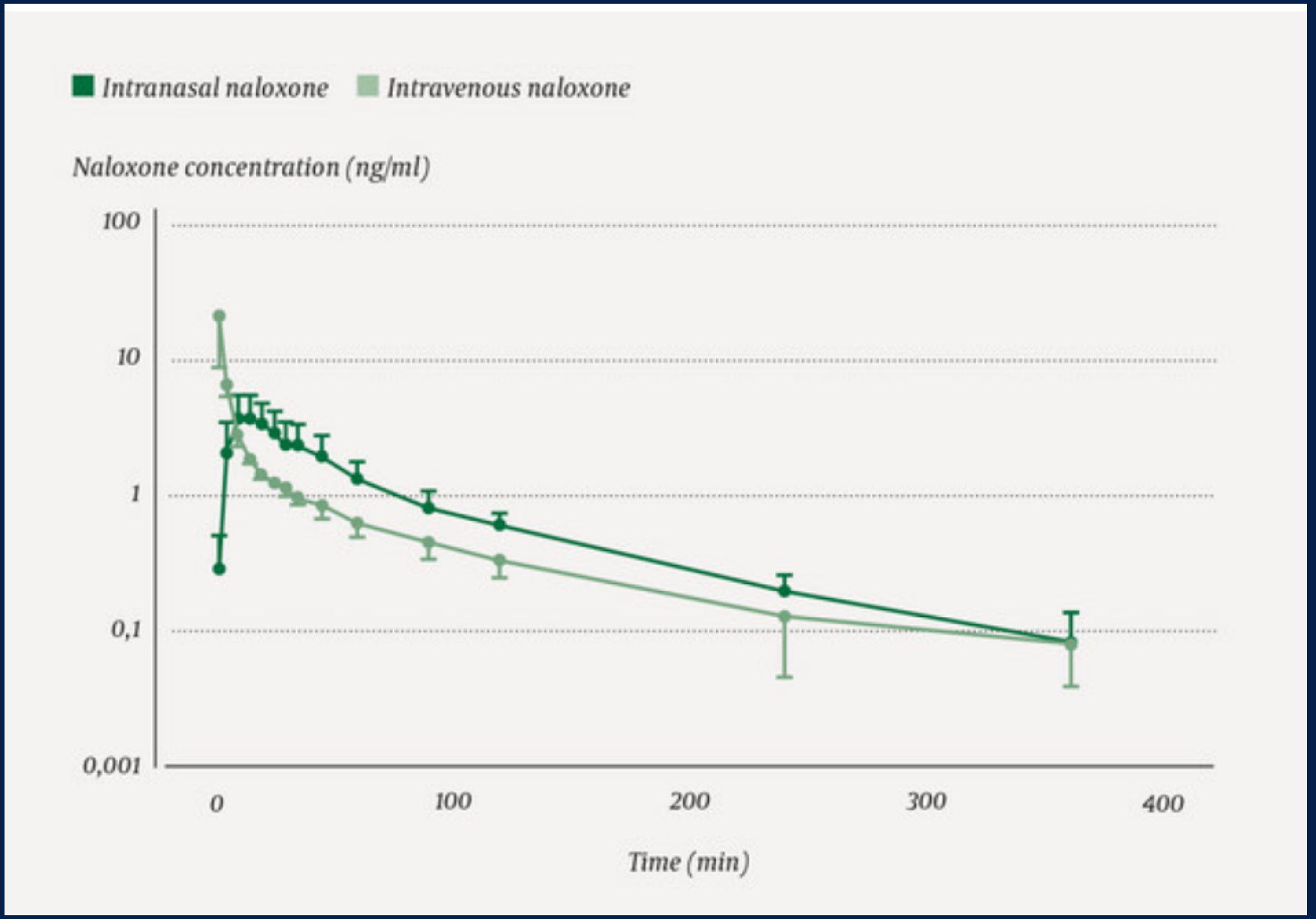
General internet search

Another Look

- Open randomized 2 way phase 1 crossover trial in 5 men
- Naloxone concentration: 20 mg/ml (0.1 ml delivered)
- Compared 2 mg IN v 1 mg IV
- 15 blood samples/patient
- Absolute bioavailability: 47% (24-66%)

Treatment	C_{max} (ng/ml)	T_{max} (min)	AUCo→t (min*ng/ml)	Distribution volume (l)	Clearance (ml/min)	Half-life (min)
2.0 mg intranasal naloxone	4.2 (1.5–7.1)	16 (5–25)	264 (150–408)	430 (172–688)	3 615 (2 198–4 431)	80 (50–132)
1.0 mg intravenous naloxone	22.7 (7.7–49.2)	2.6 (2–5)	282 (211–451)	482 (224–713)	3 656 (2 191–4 623)	90 (66–133)

Tylleskar I. Tidsskr Nor Laegeforen 2019;139(13)



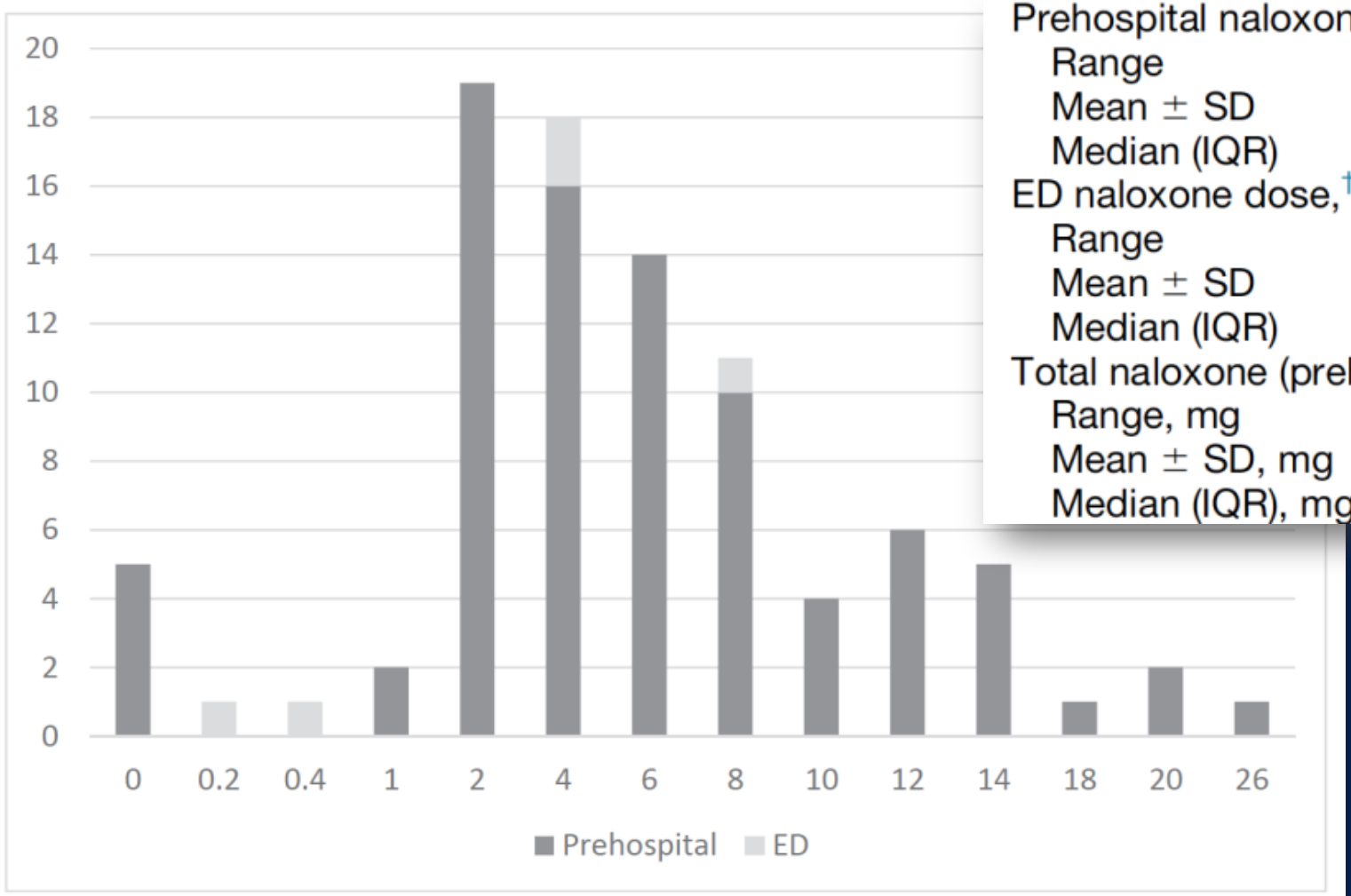
Tylleskar I. Tidsskr Nor Laegeforen 2019;139(13)

Intramuscular Naloxone

- Does intramuscular change anticipated effect and dosing?

Naloxone Resistance?

Higher Doses in the ED?



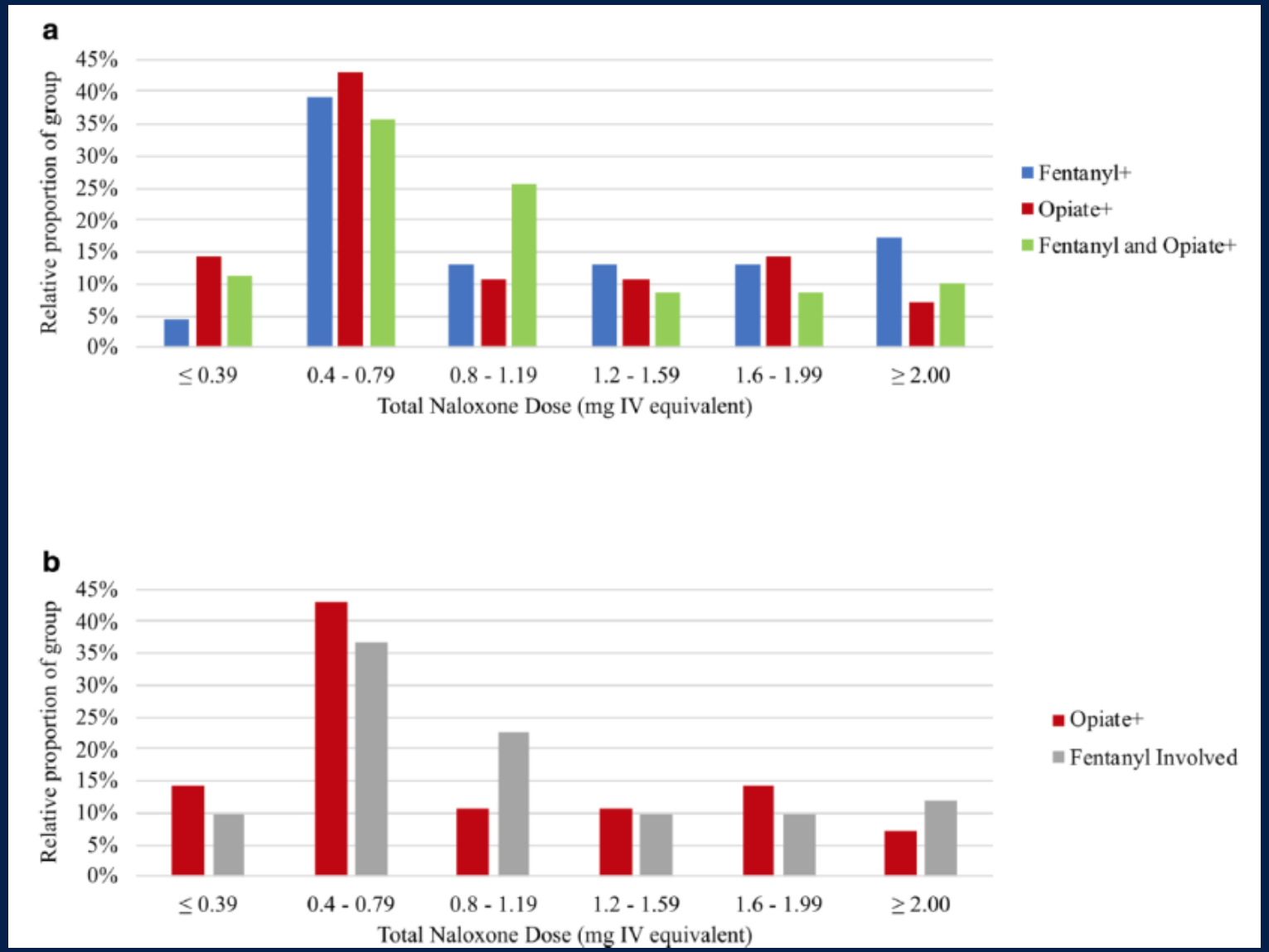
Prehospital naloxone dose,* mg (n = 88)	
Range	0–26
Mean ± SD	5.8 ± 5.0
Median (IQR)	4 (2–8)
ED naloxone dose,† mg (n = 89)	
Range	0–4
Mean ± SD	0.1 ± 0.6
Median (IQR)	0 (0–0)
Total naloxone (prehospital and ED)‡ (n = 88)	
Range, mg	0–26
Mean ± SD, mg	5.9 ± 4.9
Median (IQR), mg	4 (2–8)

Marco CA. J Emerg Med 2018;55(1):64-70

Or Not?

	Any UDS ($n = 121$)	Fentanyl only ($n = 23$)	Opiates only ($n = 28$)	Fentanyl + opiates ($n = 70$)
Prehospital naloxone route, *n* (%)[a]				
Intranasal	46 (38)	5 (22)	12 (43)	29 (41)
Intramuscular	30 (25)	3 (13)	8 (29)	19 (27)
Intraosseus	1 (1)	0 (0)	0 (0)	1 (1)
Intravenous (IV)	75 (62)	19 (83)	14 (50)	42 (60)
Prehospital naloxone dose, median (IQR, range), mg[b]				
Intranasal	0 (0–0.40, 0–4.80)	0 (0–0, 0–4.80)	0 (0–0.40, 0–4.00)	0 (0–0.40, 0–2.00)
Intramuscular	0 (0–0, 0–2.00)	0 (0–0, 0–0.80)	0 (0–0.40, 0–2.00)	0 (0–0.40, 0–2.00)
Intraosseus	0 (0–0, 0–2.00)	0 (0–0, 0–0)	0 (0–0, 0–0)	0 (0–0, 0–2.00)
Intravenous	0.40 (0–0.80, 0–4.0)	0.40 (0.40–1.20, 0–4.00)	0.02 (0–0.40, 0–2.00)	0.40 (0–0.70, 0–2.50)
Total prehospital naloxone, median (IQR), mg IV equivalent	0.58 (0.40–1.16)	0.80 (0.40–1.29)	0.40 (0.36–0.77)	0.72 (0.40–1.00)
ED therapies, *n* (%)				
Naloxone < 1 h after arrival	28 (23)	5 (22)	10 (36)	13 (19)
Naloxone > 1 h after arrival	10 (8)	0 (0)	4 (14)	6 (9)
Naloxone infusion	5 (4)	1 (4)	2 (7)	2 (3)
Intubation	0 (0)	0 (0)	0 (0)	0 (0)
ED IV naloxone < 1 h after arrival, median (IQR, range), mg	0 (0–0, 0–2.00)	0 (0–0, 0–2.00)	0 (0–0.40, 0–1.20)	0 (0–0, 0–2.00)
Total naloxone dose, EMS + ED resuscitation, median (IQR, range), mg IV equivalent	0.80 (0.40–1.38, 0.18–5.20)	0.80 (0.40–1.60, 0.18–5.20)	0.58 (0.40–1.25, 0.18–2.00)	0.80 (0.40–1.38, 0.18–3.60)

Carpenter J. J Med Toxicol 2020;16:41-8.



Naloxone effective in 93% of cases

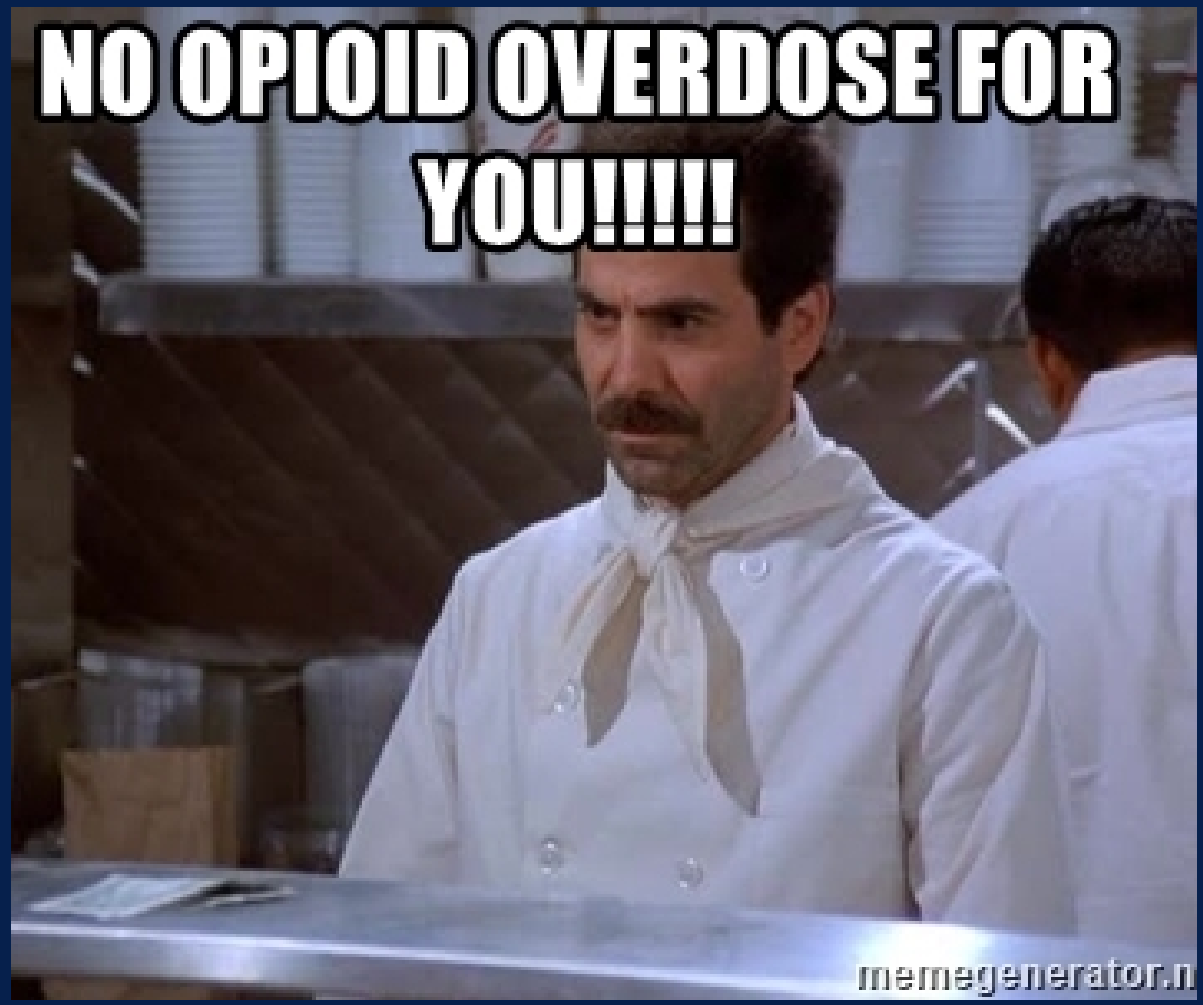
When effective, median IV dose 0.8 mg (IQR 0.4-1.38)

49 (38%) admitted to the hospital for reasons related to the overdose

Carpenter J. J Med Toxicol 2020;16:41-8.

Why Might They Not Have Responded?

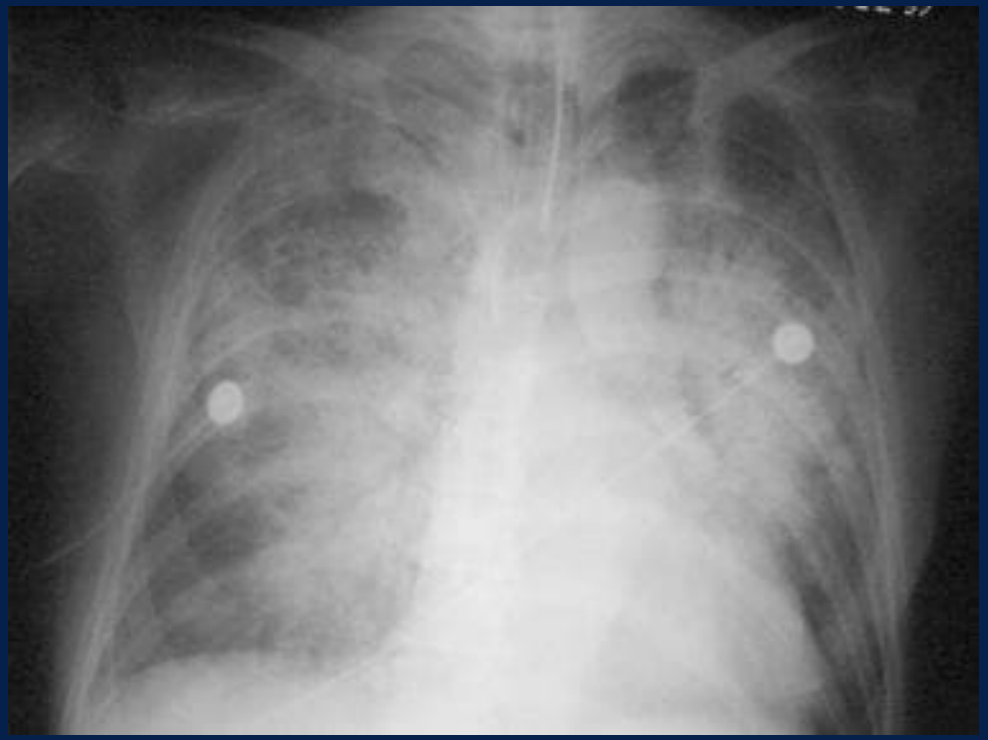
- Timing & Administration (kinetics/dynamics/technique)
- Hypercapnea
- Hypoglycemia
- Opioid mimic
- Polydrug exposure
- Anoxia
- Seizure
- Arrhythmia



For Instance

- 25 y/o with likely opioid overdose
  - Bystanders administer 4 mg IN
  - Receives another 4 mg IN from bystanders prior to EMS arrival
  - EMS bags and intubates him

Significant Labs
VBG: 7.01/>100/32
Cr 2.15 mg/dL



https://emedicine.medscape.com/article/360932-overview

Question 3

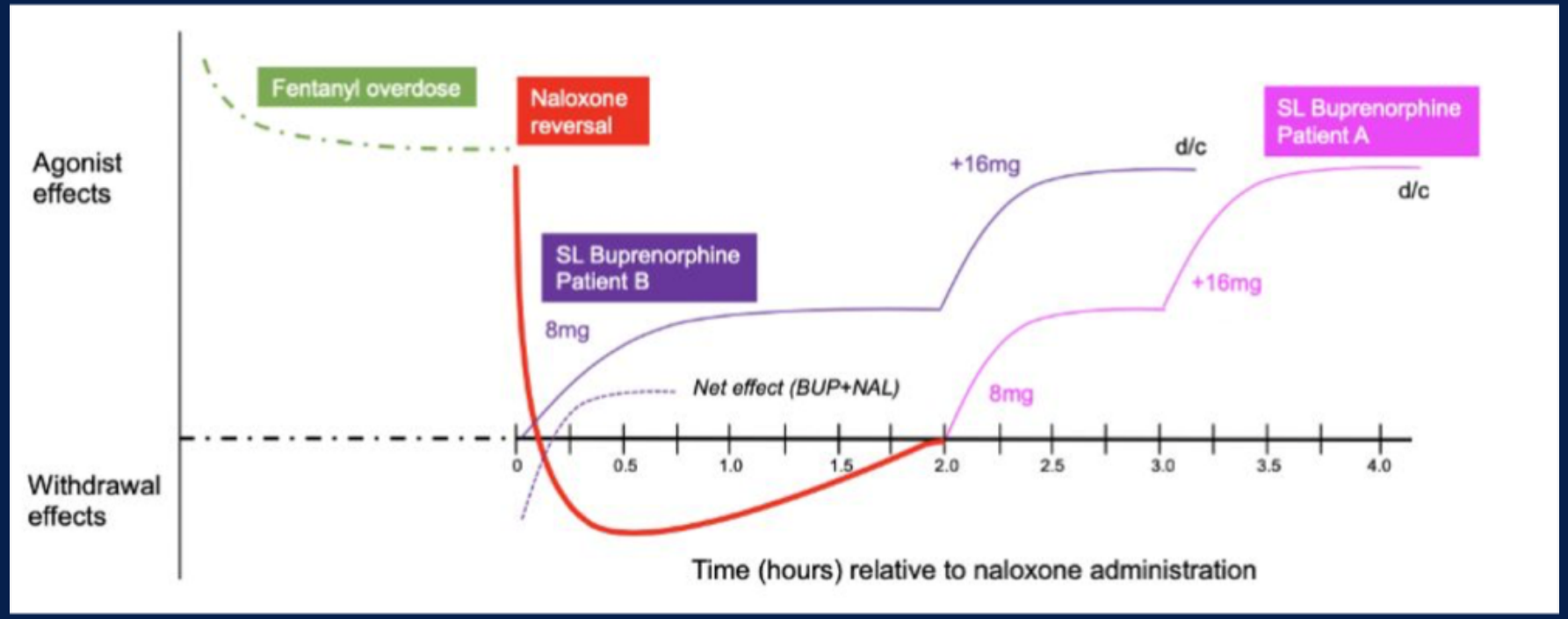
- EMS arrives at the scene and finds a 25 year old apneic patient. They give him 1 mg of naloxone IV and the patient rapidly awakens. However, he begins to vomit and has abdominal pain, is agitated, and appears in opioid withdrawal?
  - How do you best manage this patient if he won't agree to transport?
  - Should a partial agonist such as buprenorphine be administered to certain patients to smooth reversal
  - What are management options for precipitated withdrawal after naloxone?

Precipitated W/D by Precipitant

Precipitant	Class	Route	Onset of withdrawal (minutes)	Duration of Withdrawal
Buprenorphine	Partial agonist	SL, po	10-15	12-24h
Naltrexone	Antagonist	po, IM	15-30	12-72h
Naloxone	Antagonist	IV, IN, IM	1-3	30-60min

Slide from ASAM Precipitated Withdrawal 2021

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.

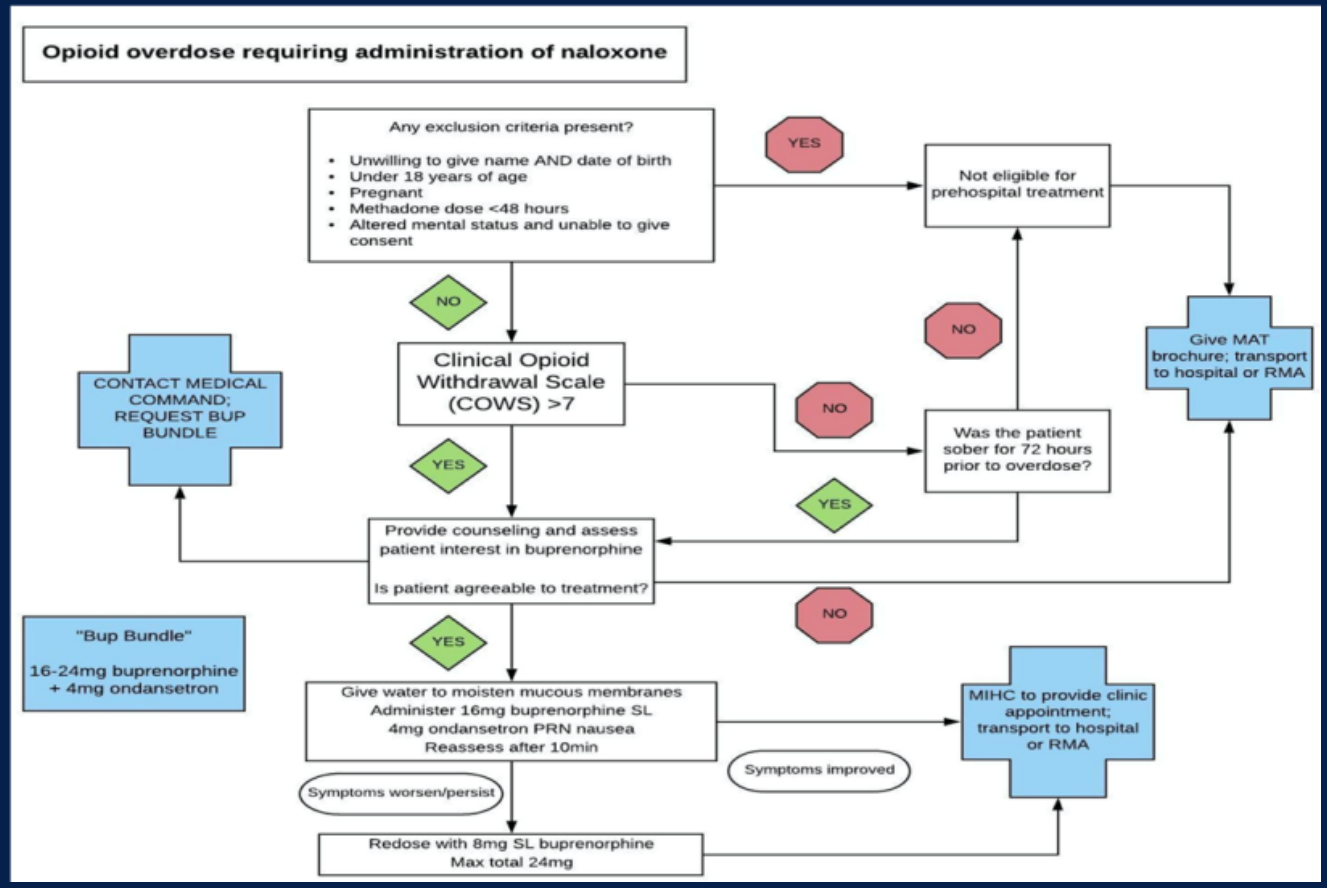
Slide courtesy of Rachel Wightman

#ASAMAnnual2022

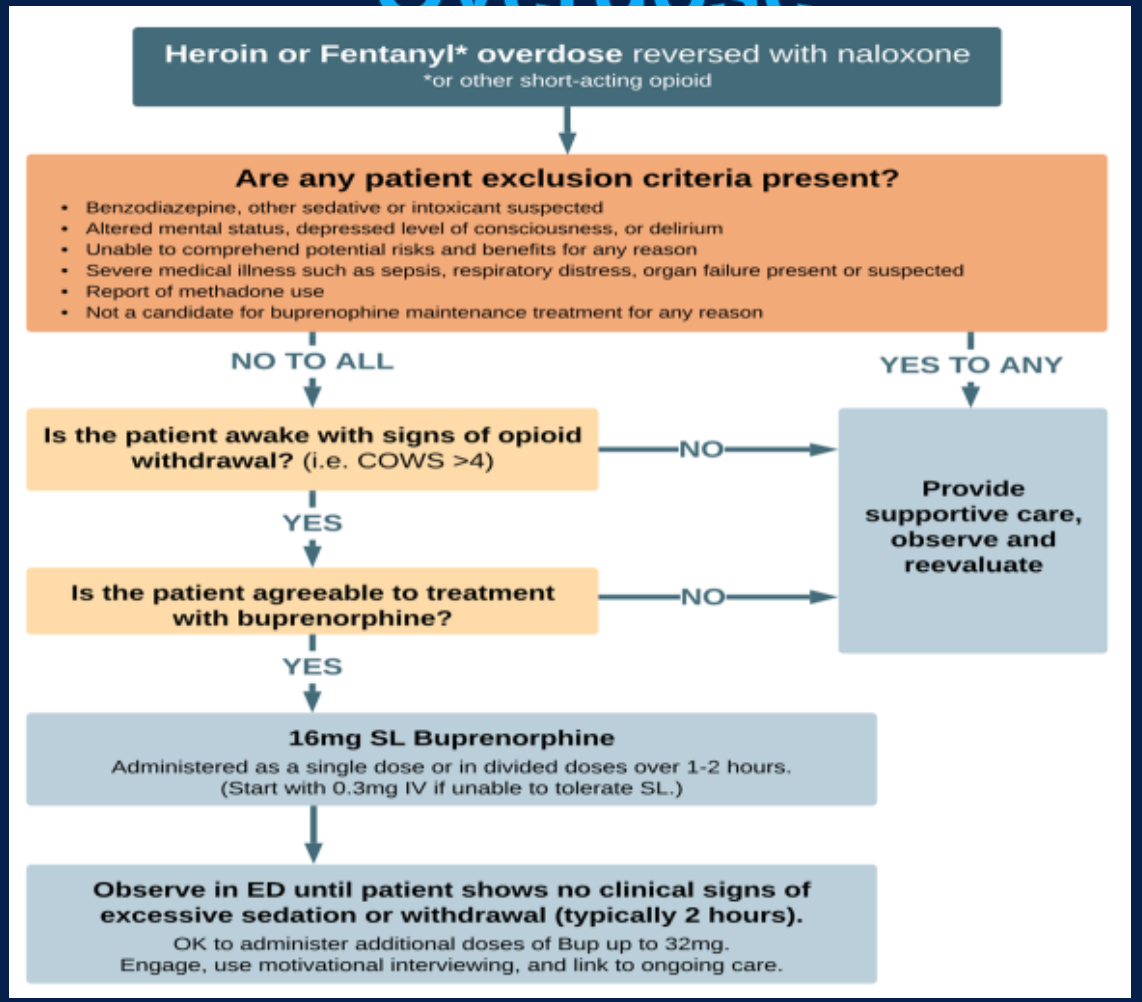
Buprenorphine Field Initiation of ReScue Treatment by Emergency Medical Services (Bupe FIRST EMS): A Case Series

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



Rapid Induction onto Buprenorphine after Overdose



Herring AA, Schultz CW, Yang E, Greenwald MK. Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder. Am J Emerg Med. 2019 Dec;37(12):2259-2262. doi: 10.1016/j.ajem.2019.05.053. Epub 2019 May 29. PMID: 31239086.

Slide courtesy of Rachel Wightman

Connections to Care

- **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
  - PMID: 32208945

- Postoverdose Initiation of Buprenorphine After Naloxone-Precipitated Withdrawal Is Encouraged as a Standard Practice in the California Bridge Network of Hospitals
  - Andrew A. Herring, MD
  - DOI:https://doi.org/10.1016/j.annemergmed.2019.12.015

- **Tele-buprenorphine for emergency department overdose visit follow up and treatment initiation**
  - Rachel S Wightman [1], Brendan Jacka [2], Julia Uber [3], Michelle McKenzie [4], Neha G Reddy [5], Roger Winters [5], Lee Ann Jordison Keeler [6], Elizabeth A Samuels [6]
  - PMID: 34481260

Does Sublingual Naloxone Matter?

Dosage	PK Parameter	Increase in Buprenorphine			PK Parameter	Increase in Naloxone		
		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual
1 x 2 mg/0.5 mg	C_{max}	22%	25%	-	C_{max}	-	-	-
	$AUC_{0\text{-last}}$	-	19%	-	$AUC_{0\text{-last}}$	-	-	-
2 x 2 mg/0.5 mg	C_{max}	-	21%	21%	C_{max}	-	17%	21%
	$AUC_{0\text{-last}}$	-	23%	16%	$AUC_{0\text{-last}}$	-	22%	24%
1 x 8 mg/2 mg	C_{max}	28%	34%	-	C_{max}	41%	54%	-
	$AUC_{0\text{-last}}$	20%	25%	-	$AUC_{0\text{-last}}$	30%	43%	-
1 x 12 mg/3 mg	C_{max}	37%	47%	-	C_{max}	57%	72%	9%
	$AUC_{0\text{-last}}$	21%	29%	-	$AUC_{0\text{-last}}$	45%	57%	-
1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg	C_{max}	-	27%	13%	C_{max}	17%	38%	19%
	$AUC_{0\text{-last}}$	-	23%	-	$AUC_{0\text{-last}}$	-	30%	19%
1 x 16 mg/4 mg film	C_{max}	34%	29%	7%	C_{max}	44%	46%	9%
	$AUC_{0\text{-last}}$	32%	-	-	$AUC_{0\text{-last}}$	49%	36%	3%

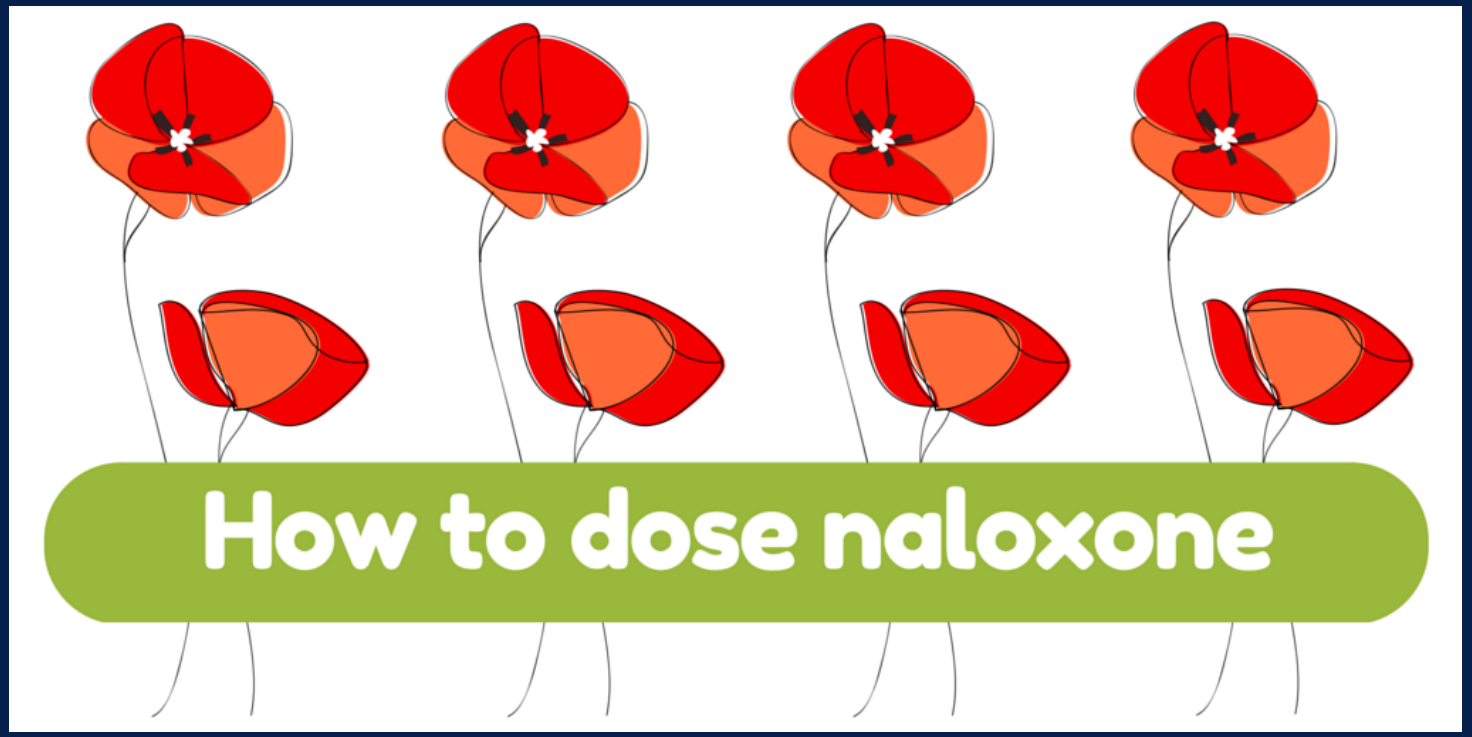
Note: 1. the 16 mg/4 mg strength film is not marketed; it is compositionally proportional to the 8 mg/2 mg strength film and has the same size of 2 x 8 mg/2 mg film. 2. – represents no change when the 90% confidence intervals for the geometric mean ratios of the Cmax and AUC0-last values are within the 80% to 125% limit. 3. There are no data for the 4 mg/1 mg strength film; it is compositionally proportional to 2 mg/0.5 mg strength film and has the same size of 2 x 2 mg/0.5 mg film strength.

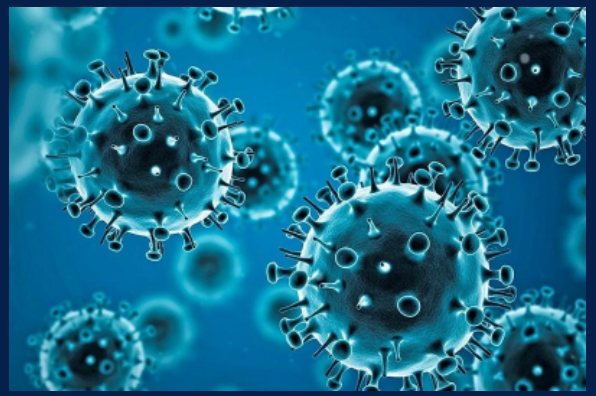
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022410s033,020732s019,020733s023lbl.pdf

Question 4

- A 5 year old is found with respiratory depression and miotic pupils. He receives naloxone and immediately wakes up. Unfortunately, an hour later he has further sedation and respiratory depression requiring further naloxone.
  - Would you start him on a naloxone infusion?
  - Is there something else that you could consider?

Naloxone Infusions





Naltrexone Instead of Naloxone?

Retrospective case series from 2014-2016 in Tehran

Children < 12 with respiratory depression from methadone

Children initially received naloxone

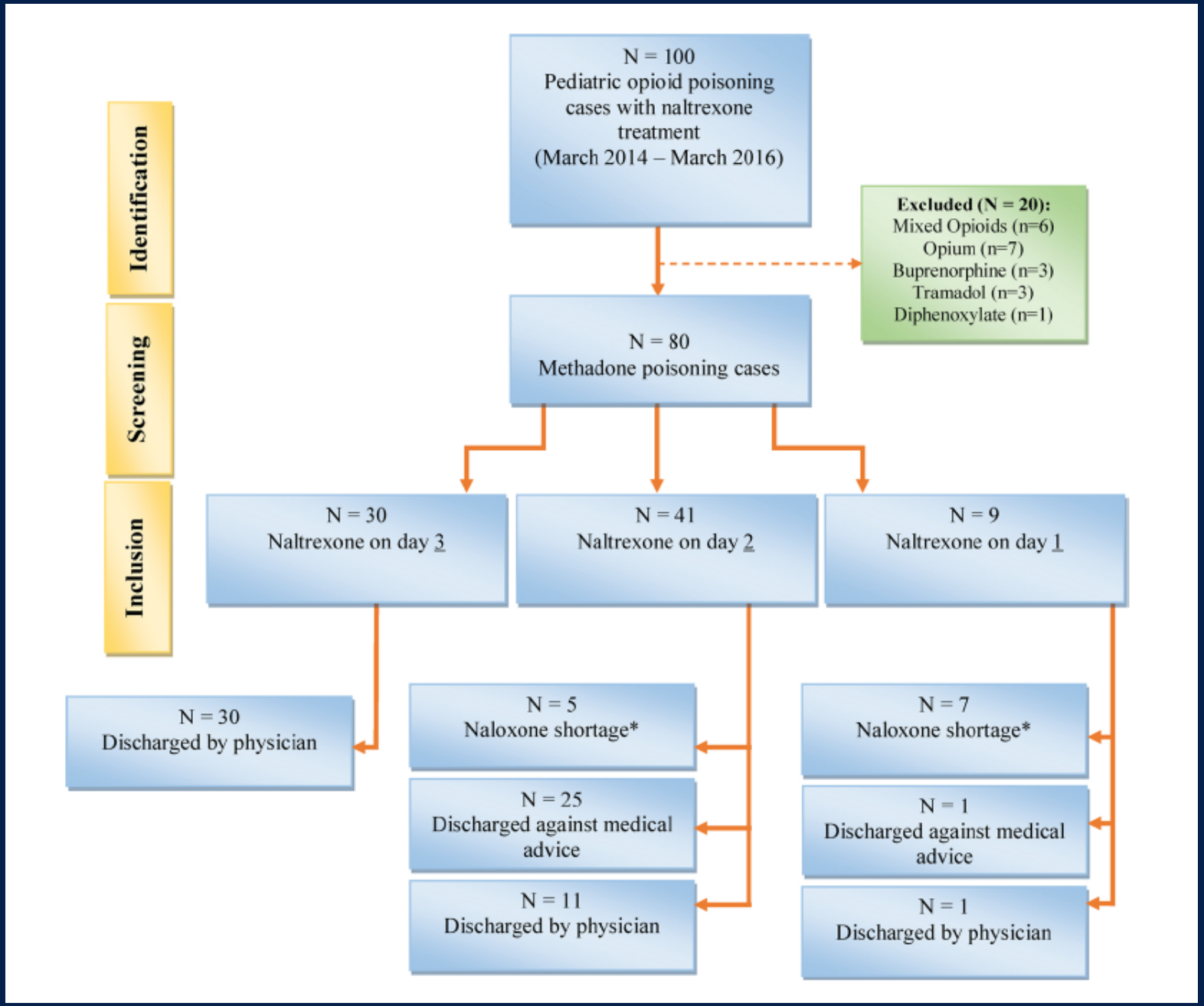
Group 1: Naloxone and daily naltrexone

Groups 2 & 3: Continuous naloxone + naltrexone at discharge

Patients admitted to the floor

Coroner's data obtained

Gholami N. Drug Alcohol Depend 2021;1(219)1-6.



Gholami N. Drug Alcohol Depend 2021;1(219)1-6.

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No 72 hr Readmissions or Deaths Reported

Clinical characteristics by day of naltrexone treatment.

	Day 1 (n = 9)	Day 2 (n = 41)	Day 3 (n = 30)	Total (n = 80)
Methadone: Ingested dose (mg/kg): Median [IQR] (min, max)	0.40 [0.28, 0.90] (0.25, 1.0)	0.50 [0.38, 1.0] (0.20, 1.6)	0.90 [0.48, 1.42] (0.25, 3.3)	0.6 [0.4, 1.1] (0.2, 3.3)
Naloxone: ED dose (mg): Median [IQR] (min, max)	0 [0, 1.4] (0, 2.0)	0.4 [0, 0.8] (0, 8.0)	0 [0, 0.6] (0, 4.0)	0.2 [0, 0.8] (0, 8)
Naloxone: Total cumulative dose[a] (mg): Median [IQR] (min, max)	4.8 [0.8, 18] (0, 36)	18.0 [10.2, 32.6] (2.4, 74.0)	31.2 [18.6, 47.7] (6.0, 86.4)	21.4 [11.3, 36.6] (0, 86.4)
Naloxone: Duration of administration (h): Median [IQR] (min, max)	12 [4, 20] (0, 20)	34 [28, 37] (25, 46)	55 [50, 69] (50, 72)	37 [30, 52] (0, 72)
Naltrexone: Reason for administration				
Shortage of naloxone[b]	7 (78 %)	5 (12 %)	0	12 (15 %)
Discharge against medical advice	1 (11 %)	25 (61 %)	0	26 (33 %)
Discharge by physician	1 (11 %)	11 (27 %)	30 (100 %)	42 (52 %)
Duration of hospitalization: Median [IQR] (min, max)	72 [48, 72] (36, 72)	48 [38, 72] (26, 72)	55 [50, 69] (50, 72)	53 [48, 72] (26, 72)

Gholami N. Drug Alcohol Depend 2021;1(219)1-6.

Final Takeaways/Summary

- Duration of observation after reversal with naloxone should be based on the kinetics of naloxone and not the opioid
- Bioavailability of intranasal naloxone is variable, however, most patients respond to low doses of naloxone
- If patients do not respond to naloxone, it is unlikely from "naloxone resistance" but likely from another cause
- Buprenophine can be used to treat naloxone-precipitated withdrawal

References

1. Boyer et al. Management of opioid analgesic overdose. N Engl J Med 2012;367(2):146-55.
2. Clarke SFJ, et al. Naloxone in opioid poisoning: walking the tightrope. Emerg Med J 2005;22(9):612-6.
3. Hendra TJ, etal. Fatal methadone overdose. BMJ 1996;313(7055):481-2.
4. Zozula A, et al. Non-transport after prehospital naloxone administration is associated with higher risk of subsequent non-fatal overdose. Prehosp Emerg Care 2022;26(2):272-79.
5. Levine M, et al. Assessing the risk of prehospital administration of naloxone with subsequent refusal of care. Prehosp Emerg Care 2016;20(5):566-9.
6. Rudolph SS, et al. Prehospital treatment of opioid overdose in Copenhagen—is it safe to discharge on-scene. Resuscitation 2011;82(11):1414-8.
7. Vilke GM, et al. Assessment for deaths in out-of-hospital heroin overdose patients treated with naloxone who refuse transport. Acad Emerg Med 2003;10(8):893-6.
8. Wampler DA, et al. No deaths associated with patient refusal of transport after naloxone-reversed opioid overdose. Prehosp Emerg Care 2011;15(3):320-4.
9. Boyd JJ, et al. Recurrent opioid toxicity after pre-hospital care of presumed heroin overdose patients. Acta Anaesthesiol Scand 2006;50(10):1266-70.
10. Vilke GM, et al. Are heroin overdose deaths related to patient release after prehospital treatment with naloxone? Prehosp Emerg Care 1999;3(3):183-6.
11. Dowling J, et al. Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. Ther Drug Monit 2008;30(4):490-6.
12. Tylleskar I, et al. Naloxone nasal spray-bioavailability and absorption pattern in a phase 1 study. Tidsskr Nor Laegeforen 2019;139(13).
13. Skulberg AK, et al. Pharmacokinetics of a novel, approved, 1.4 mg intranasal naloxone formulation for reversal of opioid overdose-a randomized controlled trial. Addiction 2019;114(5):859-667.

References

14. Marco CA, et al. Naloxone use among emergency department patients with opioid overdose. J Emerg Med 2018;55(1):64-70.
15. Carpenter J, et al. Naloxone dosing after opioid overdose in the era of illicitly manufactured fentanyl J Med Toxicol 2020;16(1):41-8.
16. 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.
17. Carroll GG, et al. Buprenorphine field initiation of ReScue treatment by emergency medical services (Bupe FIRST EMS): a case series. Prehosp Emerg Care 2021;25(2):289-93.
18. Herring AA, Schultz CW, Yang E, Greenwald MK. Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder. Am J Emerg Med. 2019 Dec;37(12):2259-2262
19. Herring A, et al. Postoverdose initiation of buprenorphine after naloxone-precipitated withdrawal is encouraged as a standard practice in the California bridge network of hospitals. Ann Emerg Med 2020;75(4):552-3.
20. Wightman RS, et al. Tele-buprenorphine for emergency department overdose visit follow up and treatment initiation. Am J Emerg Med 2021;50:409-12.
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022410s033,020732s019,020733s023lbl.pdf
22. Gholami N, et al A study of the effectiveness of naltrexone in preventing recurrence of methadone poisoning in opioid-naïve children. Drug Alcohol Depend 2021;219:108425.
23. Aghabiklooei A, et al. Effectiveness of naltrexone in the prevention of delayed respiratory arrest in opioid-naïve methadone-intoxicated pateints. Biomed Res Int 2013;2013:903172

Photo References

1. How to dose naloxone: https://www.pharmacyjoe.com/how-to-dose-naloxone-for-opioid-reversal/
2. Money: https://abcnews.go.com/US/wireStory/filthy-lucre-paper-money-shunned-fear-virus-spread-69701772
3. IU bed: https://missouriindependent.com/2021/08/28/missouri-icus-filling-as-delta-variant-wave-moves-into-northeast-southeast-regions/
4. COVID: https://www.who.int/health-topics/coronavirus
5. Prehospital ems: https://www.youtube.com/watch?v=VaaW1jCsARQ
6. 8 mg naloxone: https://kloxxado.com/
7. It's not working: https://aftersectionals.com/as-203-so-its-not-working/
8. No overdose for you:https://memegenerator.net/instance/65356266/soup-nazi-no-opioid-overdose-for-you
9. Intravenous naloxone: https://www.networkforphl.org/resources/legality-of-dispensing-and-administering-expired-naloxone-in-illinois/
10. IN naloxone: https://www.wlwt.com/article/kentucky-allows-pharmacies-to-sell-narcan-without-a-prescription/3554381
11. Woke t shirt: https://www.redbubble.com/i/t-shirt/Funny-Nurse-Get-Woke-Narcan-Drug-by-YanShen779/45105291.FB110
12. Mouse: https://theconversation.com/heres-what-that-house-proud-mouse-was-doing-plus-five-other-animals-who-take-cleaning-seriously-114040
13. Brain: https://stock.adobe.com/images/dabbing-cartoon-brain-vector-clip-art-illustration-with-simple-gradients-all-in-a-single-layer/216598336