Naloxone, Nalmefene, and Naltrexone: Is There a Need for Three Opioid Antagonists?

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Disclosure Information

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  - No Disclosures
- Evan Schwarz, MD – Associate Professor, Emergency Medicine, UCLA
  - No Disclosures
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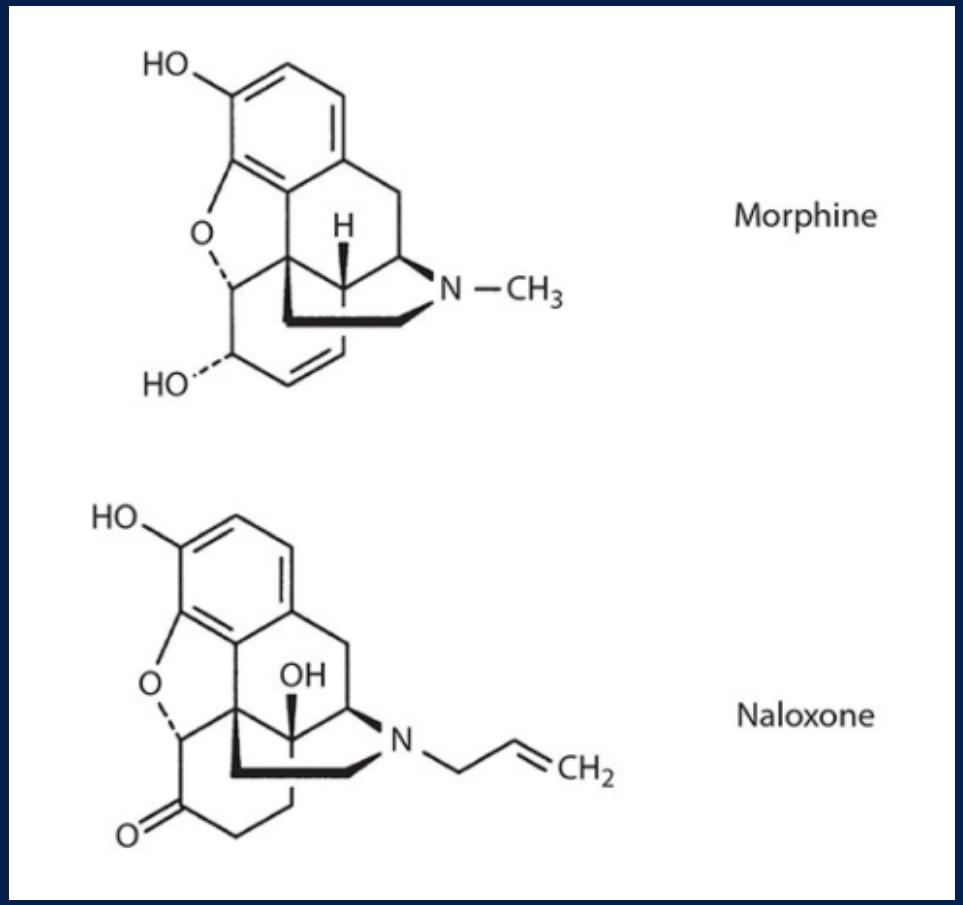
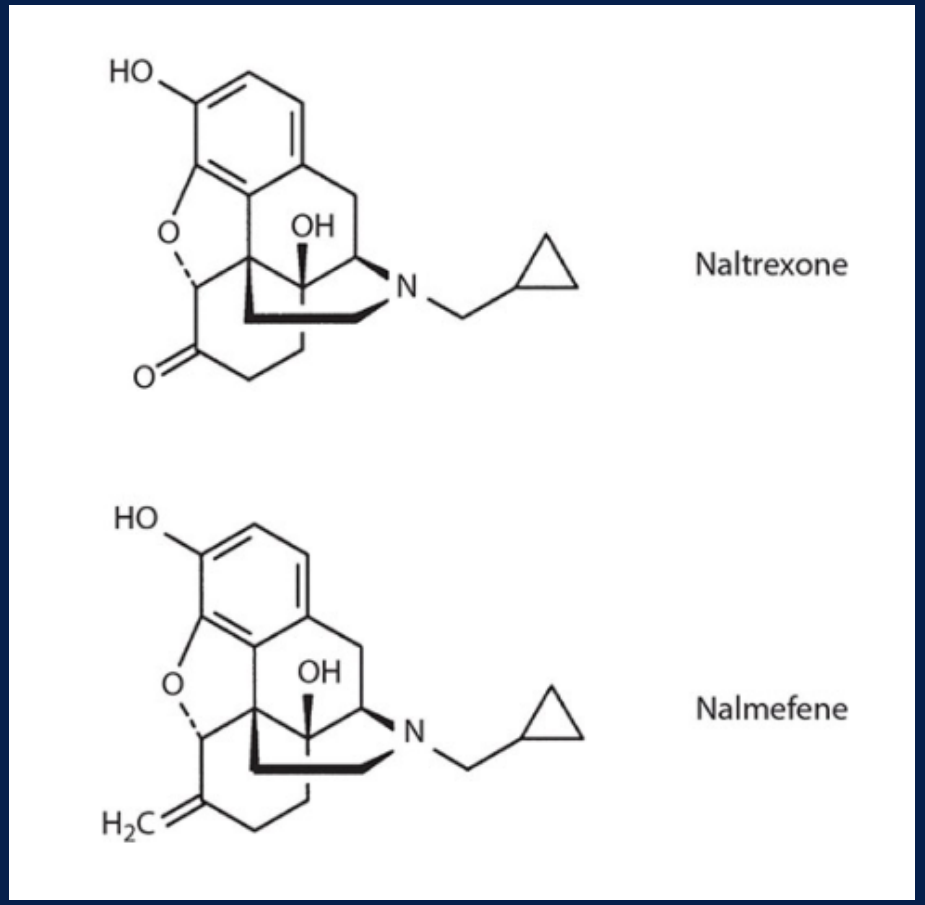
  - No Disclosures
- Robert Cole Pueringer, MD – Medical Toxicologist, Addiction Medicine Specialist, Hospitalist, Medicine, Essentia Health
  - No Disclosures
- Non-presenting: Jeanmarie Perrone, MD – Professor of Emergency Medicine, Director of the Center for Addiction Medicine and Policy, Emergency Medicine, University of Pennsylvania
  - No Disclosures
- Non-presenting: Rachel Wightman, MD, FACMT – Associate Professor, Emergency Medicine and Epidemiology, Alpert Medical School of Brown University
  - No Disclosures

Learning Objectives

- Describe the pharmacology of naloxone, nalmefene, naltrexone, and buprenorphine, including their pharmacokinetic profiles
- Discuss the clinical risks and benefits of the various opioid reversal agents in the management of patients following an opioid overdose, with particular attention to patients using fentanyl and nitazenes
- Explain the risk and treatment of precipitated withdrawal in the acute care setting, including the use of buprenorphine





Nelson et al; 2019

Historical Perspective

- 1915: N-allylnorcodeine - first opioid antagonist synthesized
- 1940s: N-allylnormorphine (nalorphine) was synthesized
- 1954: Nalorphine noted to have agonist and antagonist effects

Campbell et al., 2019; Nelson et al., 2019

History: Naloxone

- 1960: Naloxone synthesized
- 1971: Naloxone approved by FDA for opioid overdose reversal
- 1990s to present: Steady increase in the use of naloxone
- 2015: Naloxone nasal spray first approved
- March, 2023: FDA approves OTC naloxone nasal spray

Campbell et al., 2019

History: Naltrexone

- 1963: Naltrexone synthesized
- 1984: Approved by FDA for OUD
- 1995: Approved by FDA for AUD
- 2006: Depot naltrexone approved by FDA for AUD
- 2010: Depot naltrexone approved by FDA for OUD

Srivastava et al., 2018

History: Nalmefene

- 1995: Approved by FDA for opioid overdose reversal
  - IV, IM, and SC routes
- 2008: Removed from the market for commercial reasons
- 2013: Approved by EU for AUD
  - PO tablets
- May, 2023: FDA approved nalmefene nasal spray for emergency treatment of opioid overdose

Stolbach et al., 2024

Mechanism of Action

- Naloxone and naltrexone (and methylnaltrexone)
  - Competitive opioid antagonists at mu (μ), kappa (κ), and delta (δ) receptors

- Nalmefene
  - Competitive opioid antagonist at the mu (μ) and delta (δ) receptors
  - Partial agonist at the kappa (κ) receptor

Nelson et al., 2019

Comparison: Naloxone & Nalmefene

	Naloxone IN	Naloxone IV	Nalmefene IN
T ½ (h)	2.08	0.5 - 1.5	7.11
T max (h)	0.5	Nearly instantaneous	0.25
Ki (nM)	5.4	5.4	1.0
Wholesale Acquisition Cost ($)	$64.80 - 75/nasal administration [2-pack]	$5.27 - 23.72/mL of 0.4 mg/mL solution	$98 [2-pack]

Table from ACMT and AACT Position Statement: Nalmefene Should Not Replace Naloxone as the Primary Opioid Antidote at This Time

Stolbach et al., 2024

Naloxone Pharmacokinetics

Formulation	Onset	Peak	Half-life	Bioavailability
PO	-	-	-	<2%
SL	~30 sec	-	-	<10%
IV	~1-2 min	~15 min	~60-90 min	
IM	~4-6 min	~15 min	~60-90 min	
IN	~3.4 min (3-17 min)	19-30 min	~120 min	~42-47% (compared to IM)

Stolbach et al., 2024; McDonald et al., 2018; Nelson et al., 2019

Naltrexone Pharmacokinetics

Formulation	Peak	Half-life	Bioavailability
PO	~1 hour	4-10 hours; (4-13 hours)	5-60%
IM	~2 hours (1st); ~2-3 days (2nd)	5-10 days	

Stolbach et al., 2024; McDonald et al., 2018; Nelson et al., 2019

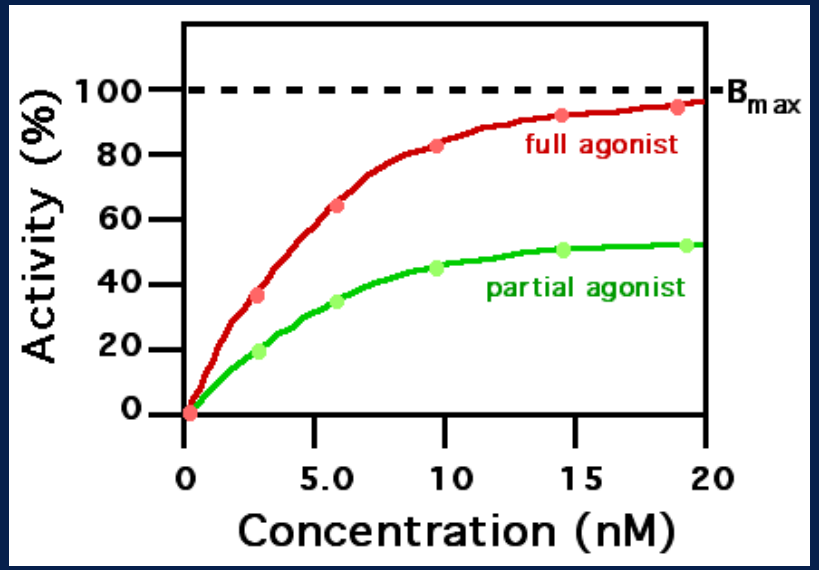
Nalmefene Pharmacokinetics

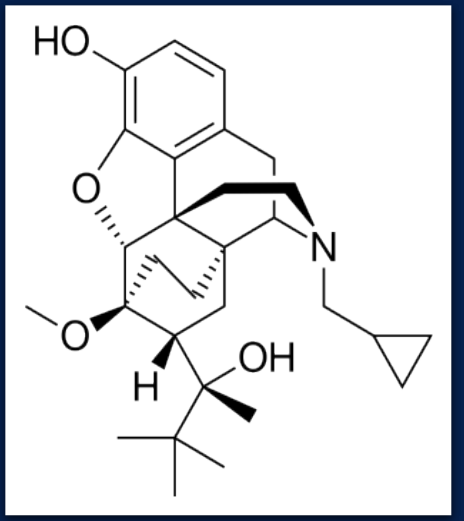
Formulation	Onset	Peak	Half-life	Bioavailability
IV	~2-5 min		~11 hours	
IM	~5-15 min	~2.3 hours	~11 hours	~100%
SC	~5-15 min	~1.5 hours	~11 hours	~100%
IN	~2-5min	~ 15min (10 min - 3 hours)	~11 hours	~80%

Stolbach et al., 2024; Edinhoff et al., 2021

Buprenorphine

- Semisynthetic opioid
- Partial mu (μ) agonist
  - ↓ receptor activation/downstream signaling vs full agonist
    - Withdrawal suppression
    - Less euphoria
    - Less CNS and respiratory depression
    - Retains analgesic properties (like full agonist)
- Other actions
  - Kappa (κ) inverse agonist
  - Delta (δ) antagonist
  - ORL1 agonist





Bart G, 2012

Buprenorphine

- High Potency
  - High affinity
    - low Ki
  - Slow dissociation
    - low Kd
  - High lipophilicity
    - high Log P

Ligand	Ki (~Affinity) (nmol)
Hydrocodone	41.58
Methadone	3.38
Naltrexone	**1.9**
Fentanyl	1.35
Morphine	1.17
Nalmefene	**1.01**
Naloxone	**0.62**
Hydromorphone	0.37
Buprenorphine	**0.22**

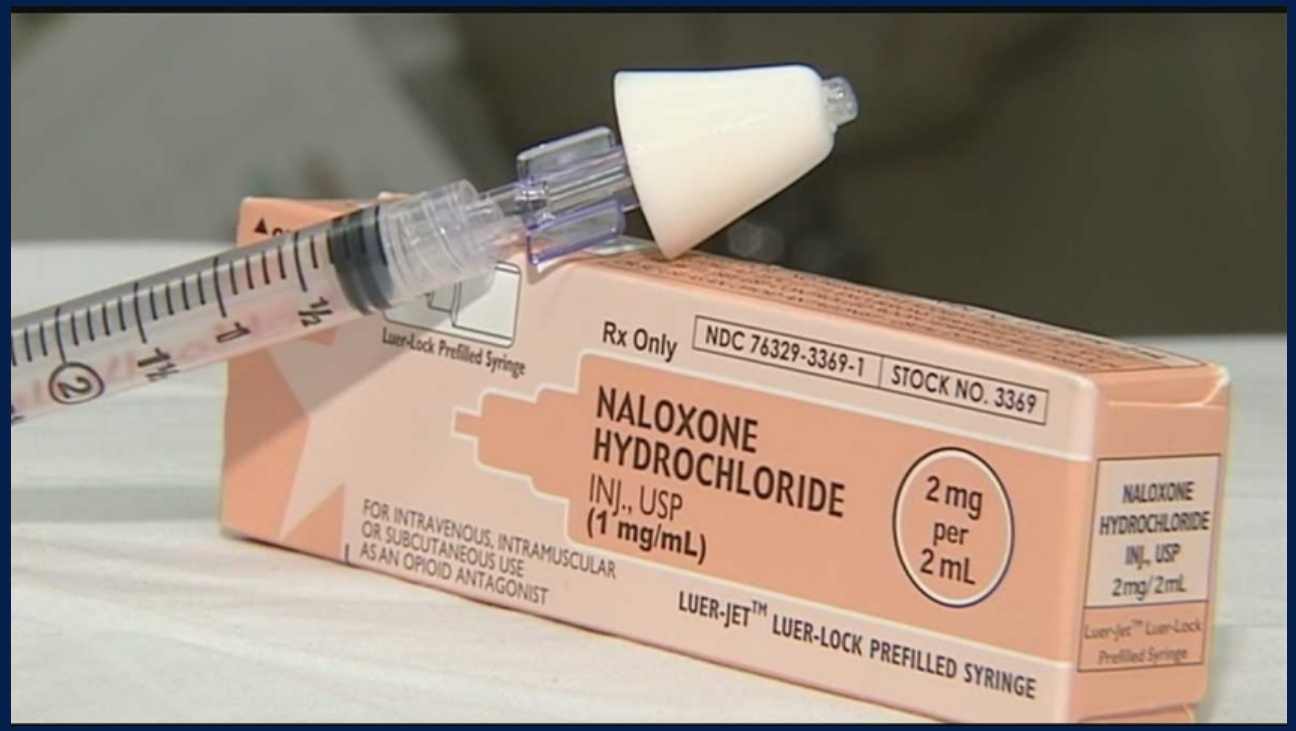
Drug	Log P
Buprenorphine	4.98
Fentanyl	4.28
Methadone	4.77
Nalmefene	**2.7**
Hydromorphone	1.6
Naloxone	**0.69**
Hydrocodone	1.75
Morphine	1.07

Volpe et al., 2011; Stolbach et al., 2024; Greenwald et al., 2022

It Used To Be So Simple!

100% bioavailability
Onset 1-2 min

Goldfrank's Toxicologic Emergencies



All over the place: 10-80%

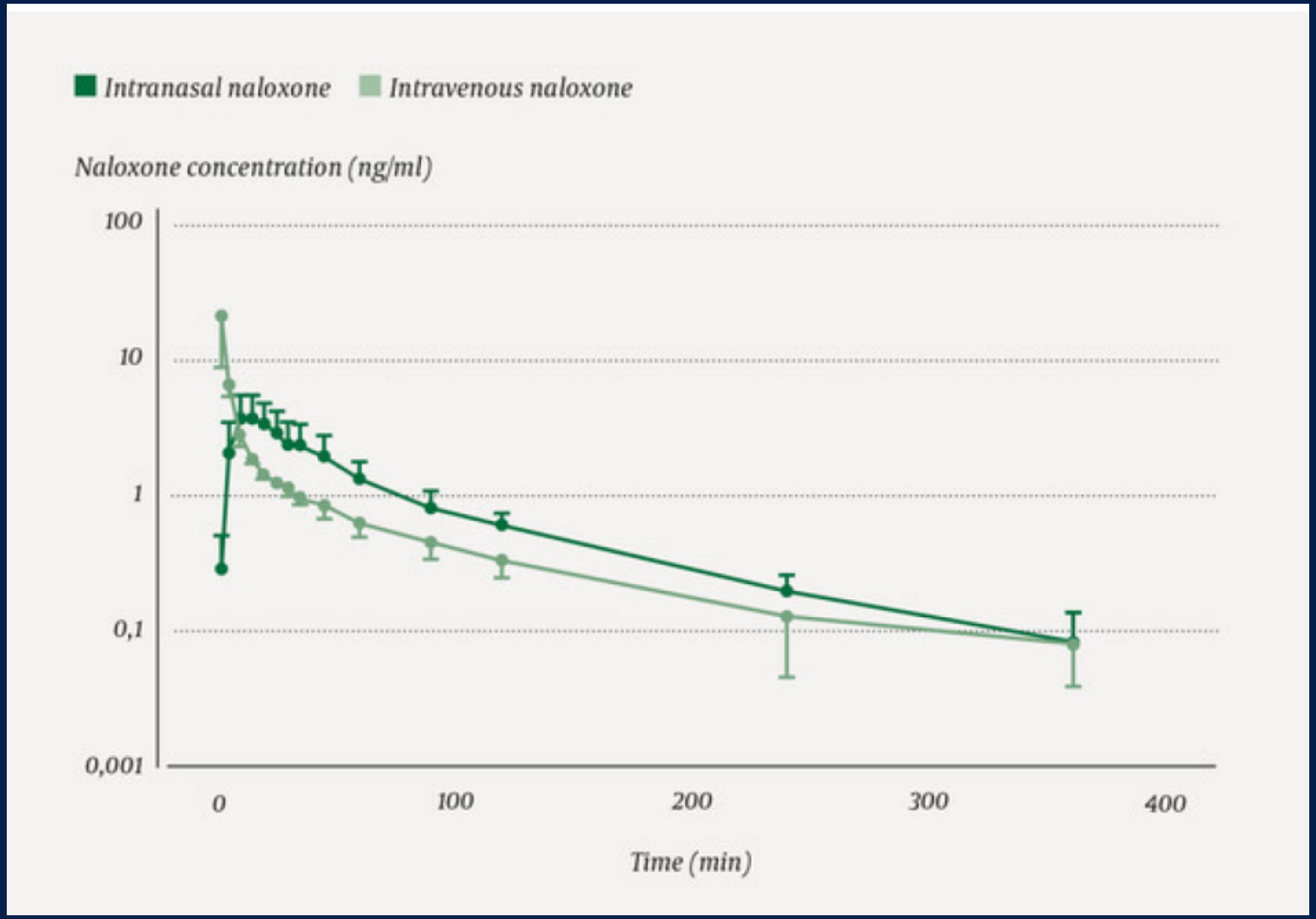
General internet search

Taking a 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



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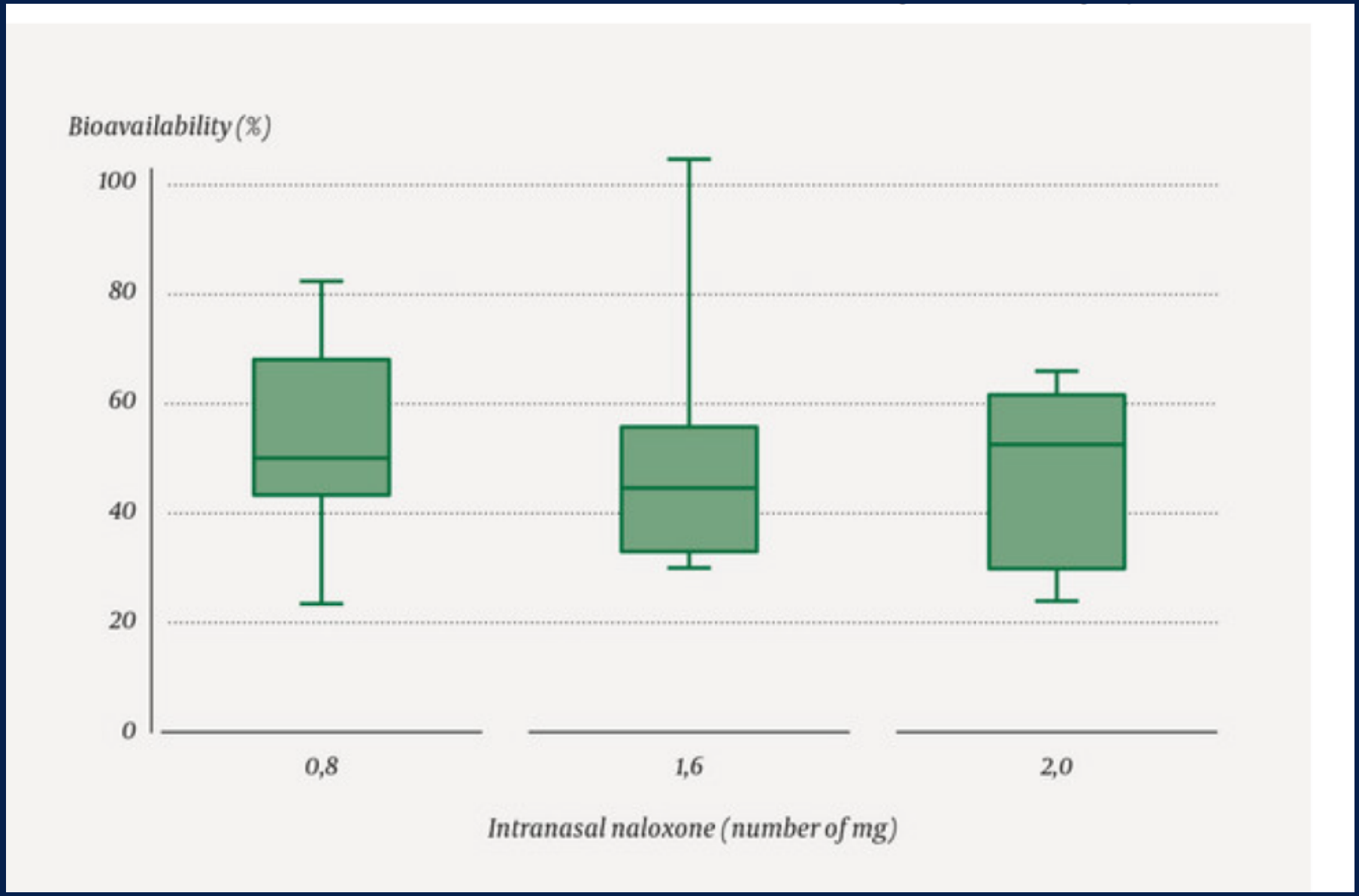

Tylleskar I. Tidsskr Nor Laegeforen 2019

Post-Naloxone Symptoms Among People Administered 8mg vs. 4mg Intranasal Naloxone—New York State (NYS), 2022-23

Data Brief—September 2023 (revised)

The **average number of naloxone doses administered** by law enforcement (LE) responders **was the same regardless of formulation.** There were **no significant differences in hospital transportation or survival** between groups.

	Mean Doses Given	Transported to Hospital	Survived
8mg	1.58 doses	81.0%	99.0%
4mg	1.67 doses	73.4%	99.2%

Data Brief on Post-Naloxone Symptoms Among People Administered 8mg vs. 4mg Intranasal Naloxone - New York State (NYS), 2022-23

Post-Naloxone Symptoms Among People Administered 8mg vs. 4mg Intranasal Naloxone—New York State (NYS), 2022-23

Data Brief—September 2023 (revised)

People administered 8mg naloxone had 2.51 times the likelihood of experiencing opioid withdrawal symptoms including vomiting compared with those administered 4mg naloxone.

Post-Naloxone Symptom	8mg Naloxone % (n)	4mg Naloxone % (n) (Reference)	Relative Risk (95% Confidence Interval)
Opioid withdrawal symptoms including vomiting	37.6% (38)	19.4% (49)	**2.51 (1.51-4.18)***
Disorientation	66.3% (67)	58.5% (148)	1.40 (0.86-2.27)
Lethargy	52.5% (53)	43.5% (110)	1.44 (0.90-2.28)

* Statistical significance at the $p<0.05$ level.

Data Brief on Post-Naloxone Symptoms Among People Administered 8mg vs. 4mg Intranasal Naloxone - New York State (NYS), 2022-23

Case 1

- 41-year-old man BIBFR, found on sidewalk with pinpoint pupils and abrasions to forehead.

- Given 2 mg IV naloxone with improvement but still lethargic when arrives in the ED
  - Given 2 additional doses of naloxone IV (.04 mg) -- no response.
- Head CT/Trauma eval negative
- UDS: cocaine, methamphetamine, opioids

Case 1: Continued

- Hospital Course:
  - Suspected polysubstance use; awakens and spoke to a counselor and discharged with follow-up.
  - Blood sample collected: < 2 h from arrival

Qualitative:

- Fentanyl
- Norfentanyl
- 4-Hydroxy Xylazine
- Metonitazene
- Protonitazene
- Xylazine
- Naloxone
- Oxycodone
- Bromazolam
- Cocaine
- Methamphetamine

Quantitative:

- Fentanyl (14 ng/mL)
- Xylazine (2.4 ng/mL)
- Norfentanyl (4.9 ng/mL)
- Naloxone (2.3 ng/mL)
- Metonitazene (1.0 ng/mL),
- Protonitazene (Positive, <0.5 ng/mL),
- Bromazolam (46 ng/mL)

Case 1: Questions

- What are the proper metrics of successful reversal?
- How is the optimal dose, route of administration, and observation time following reversal determined?
  - Can he self-discharge from the hospital?
- Does naloxone adequately reverse fentanyl or nitazene overdose?
- What does the risk/benefit comparison between nalmefene versus naloxone look like?
- What are the roles of the high-dose naloxone and various nalmefene formulations?

Case 2

- A 56-year-old man presents to the ED after an opioid overdose
- Received naloxone 4 mg IN by EMS in the field
  - Arousable on arrival, able to converse
  - Mild withdrawal present, not treated
  - Vital signs normal
  - Oxygen saturation: 95% RA; End Tidal: 40

Case 2: Continued

- 30 minutes after arrival the patient becomes sedate
  - Oxygen saturation: 95% RA; End Tidal: 55
  - Receives naloxone 0.04 mg intravenously with response
- 45 minutes later the patient resedates
  - Receives escalating naloxone doses of intravenously with response several times over the next two hours with repetitive sedation and hypercapnia

Case 2: Questions

- When should naloxone infusions be used for recrudescent intoxication?
- Is buprenorphine useful to reverse patients with opioid overdose?
- What are the risk/benefits of nalmefene and naltrexone?

Case 3

- A 23-year-old man and daily user of IV heroin/fentanyl arrives at the ED after taking 16mg of SL buprenorphine/naloxone, which he obtained off the street.

- He is irritable with tachycardia (120s), nausea, diaphoresis, piloerection, and diffuse muscle aches. No other drug use.

- COWS 33

Case 3: Continued

- Administered
  - 16mg SL buprenorphine/naloxone (no IV buprenorphine available)
  - 4mg IV ondansetron
- Over the next 1 hour, he reports some improvement but remains anxious/restless with diffuse aches. COWS: 33 → 22

- Administered
  - Additional 16mg SL buprenorphine/naloxone
  - 0.25mg/kg IV ketamine over 1 hour

- After 1 hour, additional improvement, but he remains anxious with nausea and aches. COWS: 12

Case 3: Questions

- What is the best practice in the management of patients with precipitated opioid withdrawal?

- Does the naloxone component of the SL combination product (buprenorphine/naloxone) cause precipitated withdrawal when taken orally? When injected?

Final Takeaways/Summary (Suggested)

- Naloxone and nalmefene are both effective at reversing opioid overdose
- The optimal marker of successful reversal is improved breathing
  - There are several reasons these agents may appear to fail if arousal is used as the endpoint
- The duration of nalmefene is longer, which may lead to prolonged withdrawal
- For repetitive recurrent resedation the use of a naloxone infusion or nalmefene may be helpful
- Precipitated opioid withdrawal management varies based on the precipitating antagonist/partial agonist

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