

Selection of RiVive's 3.0 mg Naloxone Dose

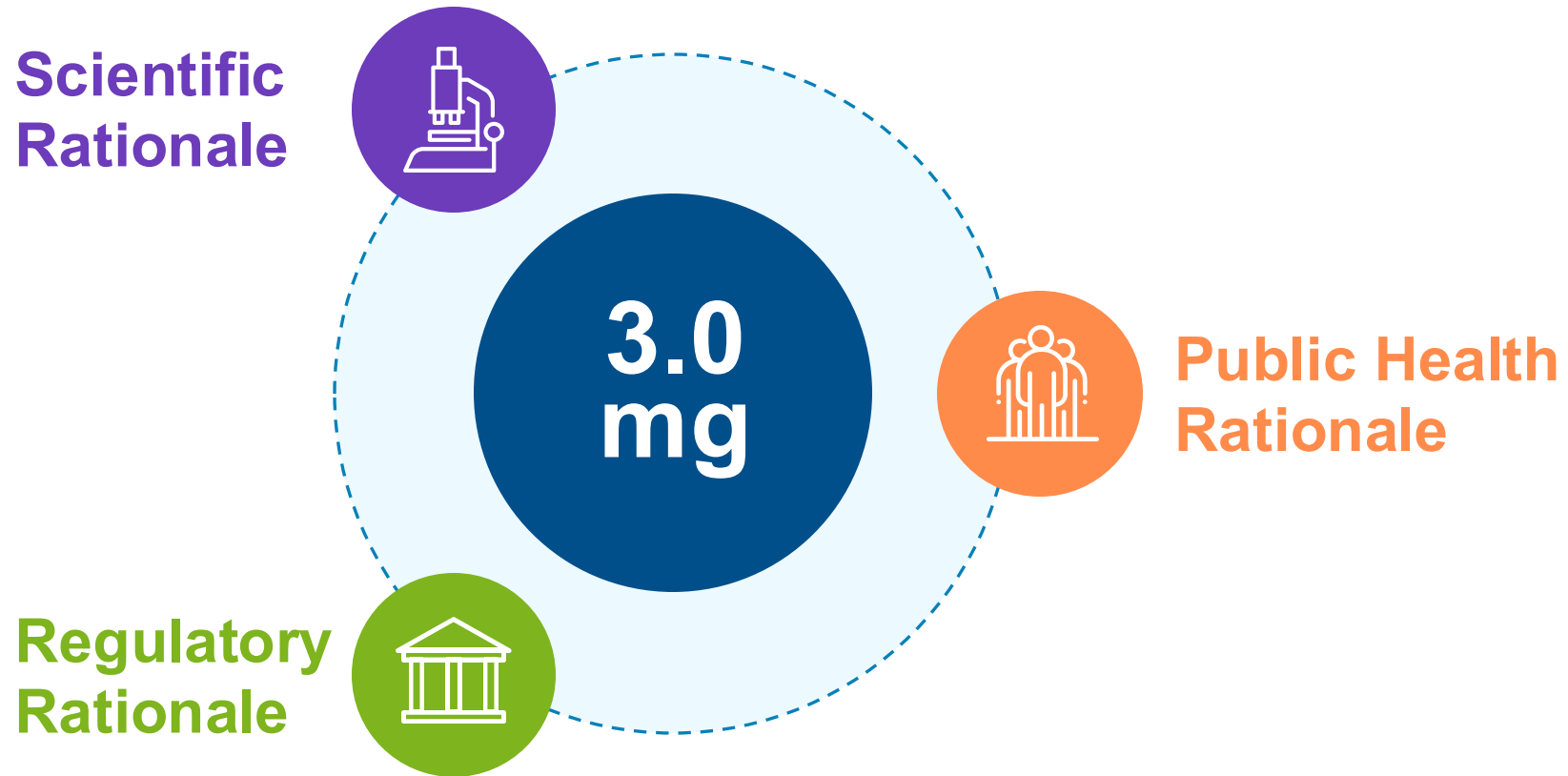
Michael R. Hufford, PhD

Co-Founder and Chief Executive Officer

Harm Reduction Therapeutics



RiVive's 3 mg Dose Rationale



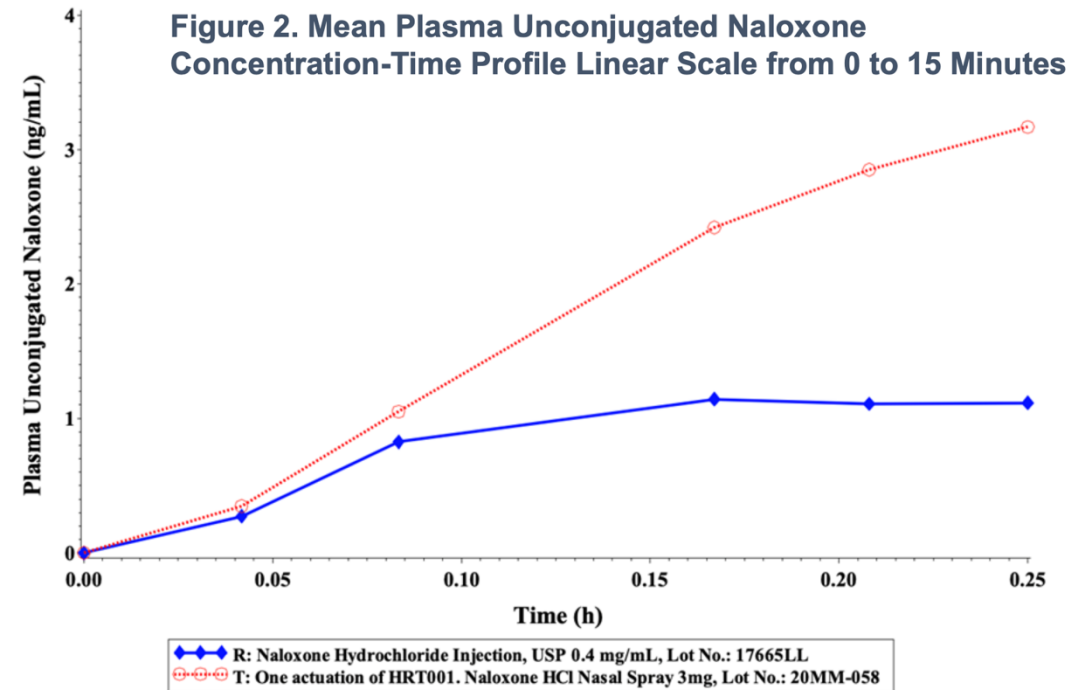
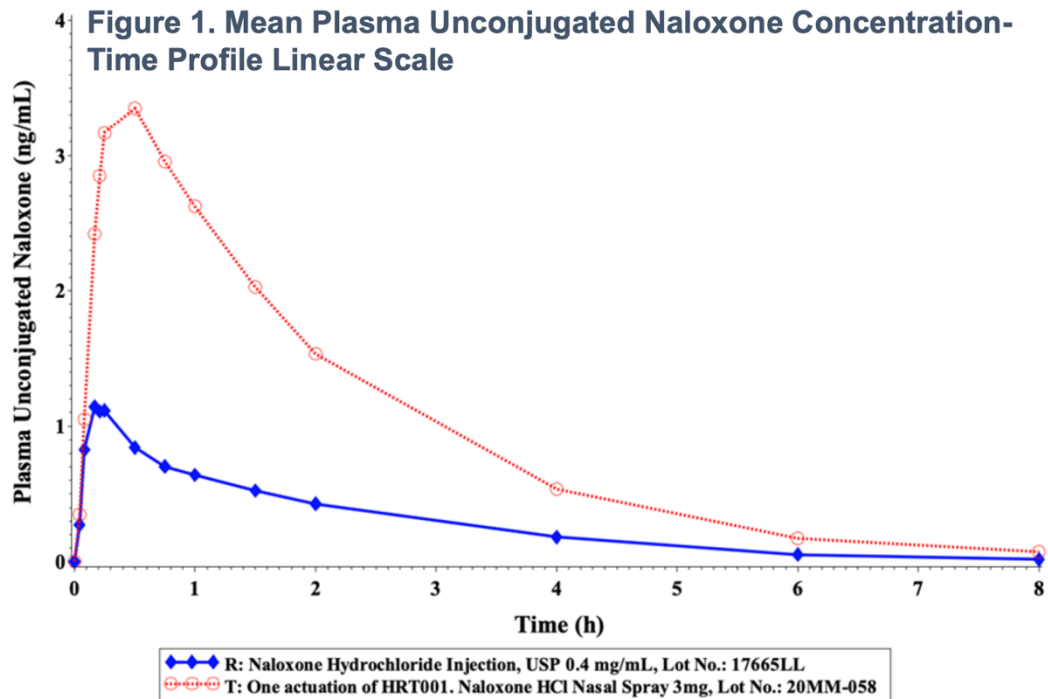
RiVive's 3 mg Dose: Scientific Rationale



RiVive® FDA Approval Data: Identical 0.4mg IM Comparator Used to Approve Narcan

RESULTS

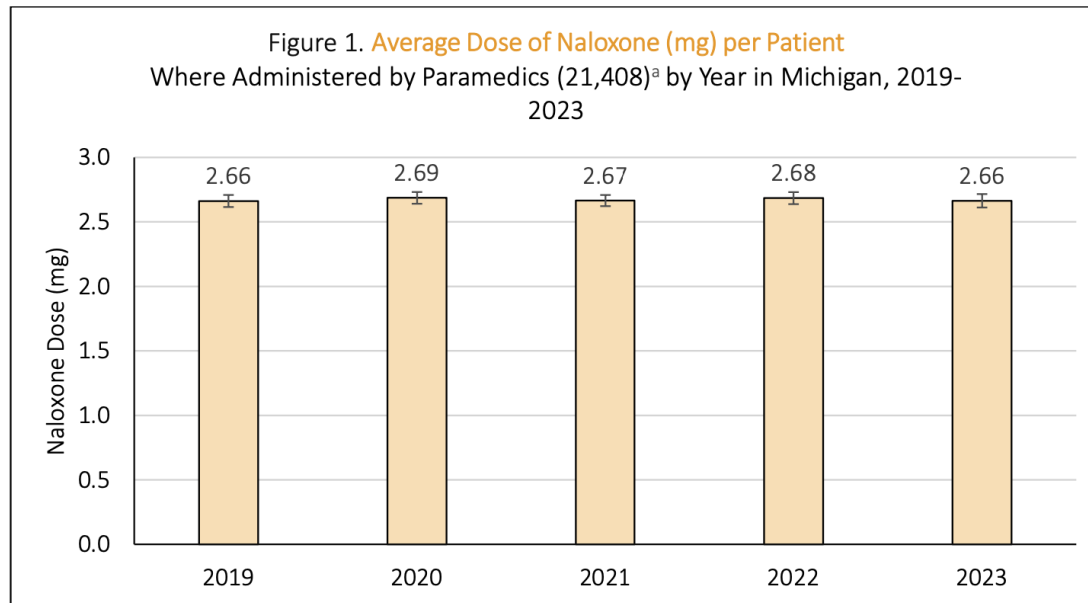
Concentration-time profiles for the entire time course and 0 to 15 min are shown in Figure 1 and Figure 2, respectively.



Ashworth et al., CPDD, 2023

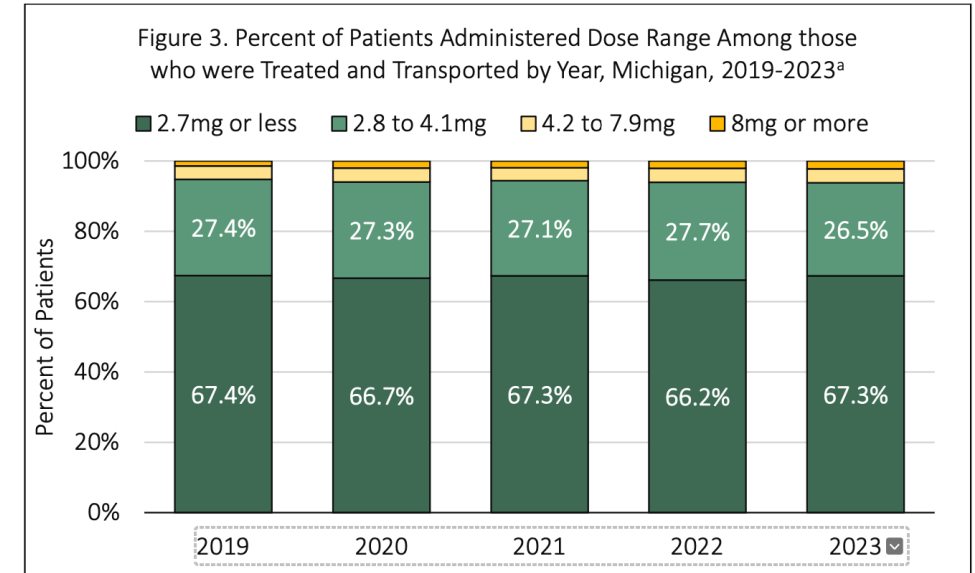
No Increase in Naloxone Dose Required for Reversals: 2019-2023

Trends in Paramedic Naloxone Administration and Patient Outcomes Throughout Increased Fentanyl Use



Source: Michigan Emergency Medical Services Information System (MiEMSIS), Bureau of Bureau of Emergency Preparedness, EMS and Systems of Care (BEPESOC).

^an = number of total EMS responses to probable opioid overdose and excludes responses where naloxone was given by role other than paramedic (n=18,325), responses where naloxone dosage was not recorded (n=13,333), responses where naloxone was not administered (n=6,263), responses where more than one type of role gave naloxone to one patient (n=3,305) and responses with suspected erroneous values (see data notes for detail) for mg of naloxone (n=1,361).



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Naloxone Dosing After Opioid Overdose in the Era of Illicitly Manufactured Fentanyl

J. Med. Toxicol. (2020) 16:41–48

47

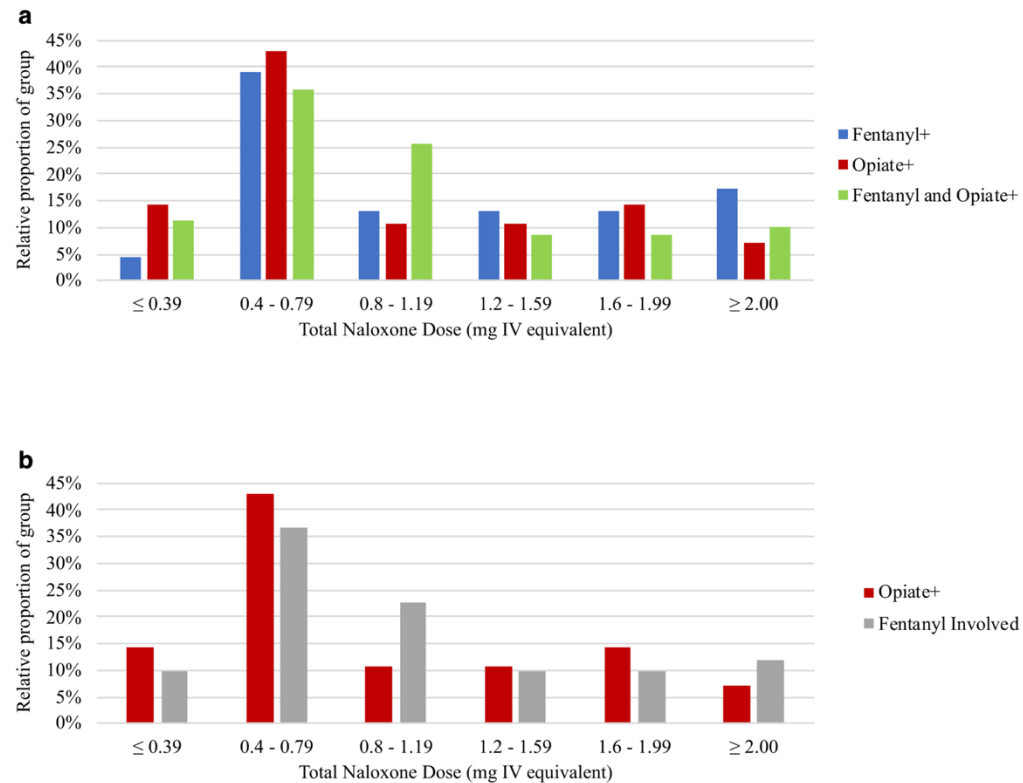


Fig. 2 Distribution of naloxone dosing by UDS results. **a** Comparing fentanyl+, opiate+ and fentanyl and opiate+ cases. **b** Fentanyl+ and fentanyl and opiate+ groups are combined to form the fentanyl-involved group

Conclusion Our findings refute the notion that high potency synthetic opioids like illicitly manufactured fentanyl require increased doses of naloxone to successfully treat an overdose. There were no significant differences in the dose of naloxone required to treat opioid overdose patients with UDS evidence of exposure to fentanyl, opiates, or both. Further evaluation of naloxone stocking and dosing protocols is needed.

From: **Intranasal Naloxone Repeat Dosing Strategies and Fentanyl Overdose: A Simulation-Based Randomized Clinical Trial**

JAMA Netw Open. 2024;7(1):e2351839.
doi:10.1001/jamanetworkopen.2023.51839

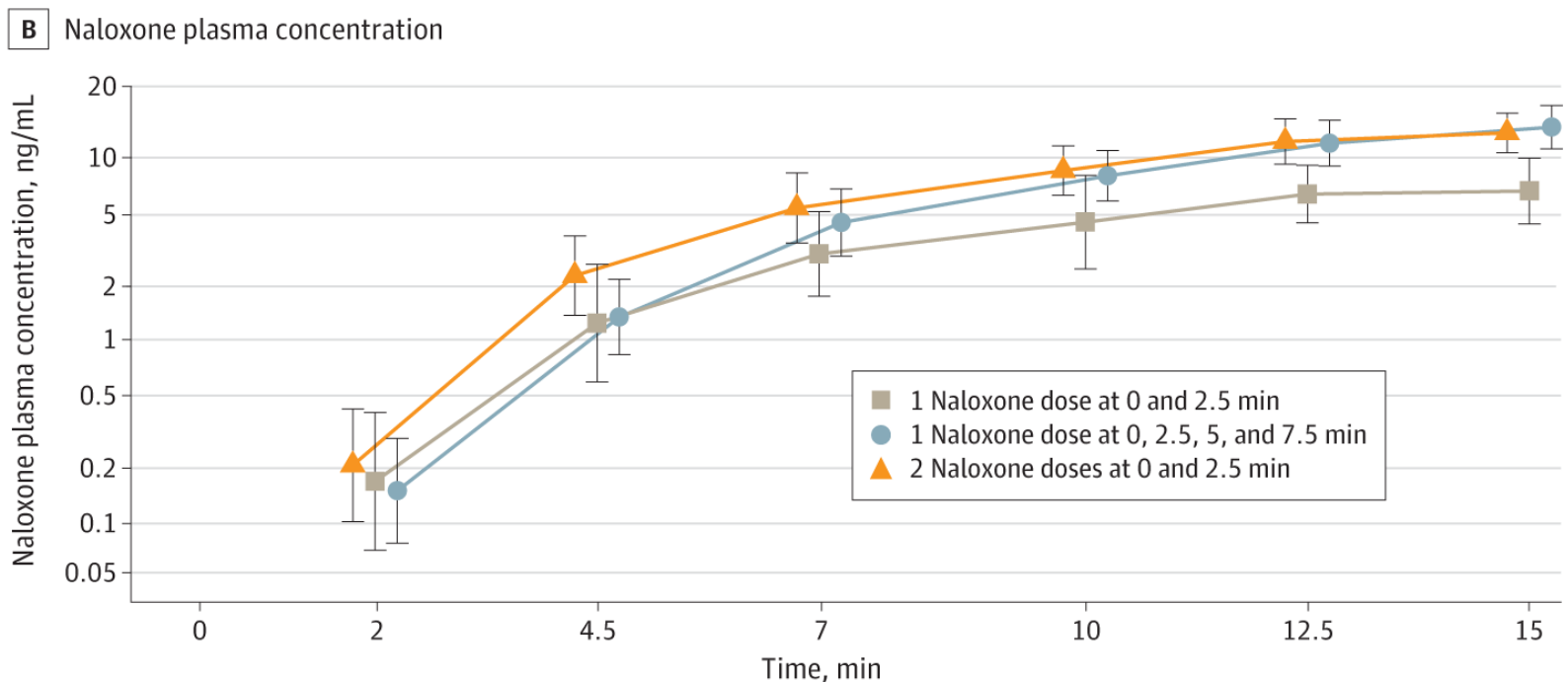


Figure Legend:

Naloxone Plasma Concentration and Comparisons Between Treatment Groups A, Individual participant observed data and box-and-whisker plot summaries for naloxone plasma concentration. The line through each box represents the median. The lower and upper borders of the box represent the 25th and 75th percentiles, respectively. The whisker extends from the box border to the last observation within 1.5 times the IQR. B, Naloxone plasma concentration. Error bars represent 2-sided 95% CIs. C, Comparison of naloxone plasma concentration between dosing strategies. Error bars represent 1-sided 97.8% CIs. The prespecified times for comparison of 1 dose at 0, 2.5, 5, and 7.5 minutes vs 1 dose at 0 and 2.5 minutes were 10, 12.5, and 15 minutes. The prespecified times for comparison of 2 doses at 0 and 2.5 minutes vs 1 dose at 0 and 2.5 minutes were 4.5, 7, and 10 minutes. eTable 3 in Supplement 2 contains the number of participant samples included at each time for each dosing group.

Increasing naloxone dose yields more withdrawal, identical survival rates

Timeline: March 26, 2022 to August 16, 2023

Setting: NYS

Participants: NYSP (3 of 11 troops received 8mg, others continued to receive 4mg)

Number of Administrations: 8mg: 101 4mg: 253

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%

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.



Viewpoint

Increasingly powerful opioid antagonists are not necessary

Lucas G. Hill^a, Claire M. Zagorski, Lindsey J. Loera

College of Pharmacy, The University of Texas at Austin, 2409 University Avenue, A1910, PHR 2.222G, Austin, TX 78712, United States



Essay

A call for compassionate opioid overdose response

Erin Russell^{a,*}, Mary Hawk^b, Joanne Neale^c, Alex Bennett^d, Corey Davis^e, Lucas G. Hill^f, Rachel Winograd^g, Lauren Kestner^h, Amy Lieberman^e, Alice Bellⁱ, Tim Santamour^j, Stephen Murray^k, Kristin E. Schneider^l, Alexander Y. Walley^m, T. Stephen Jonesⁿ



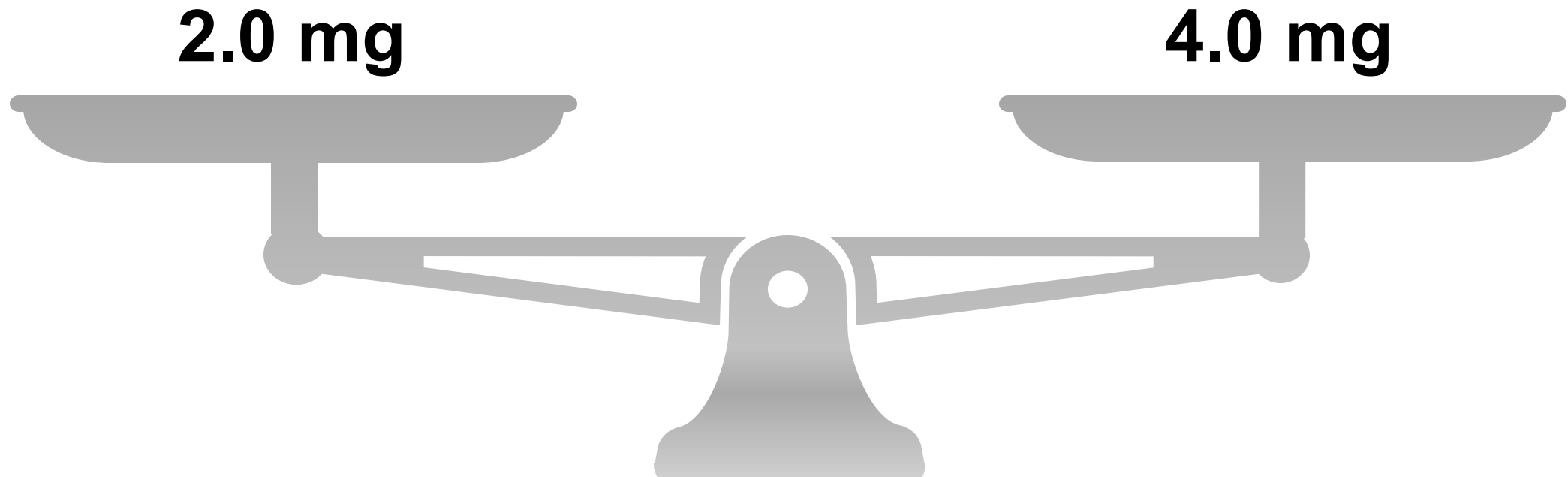
RiVive's 3 mg Dose: Regulatory Rationale



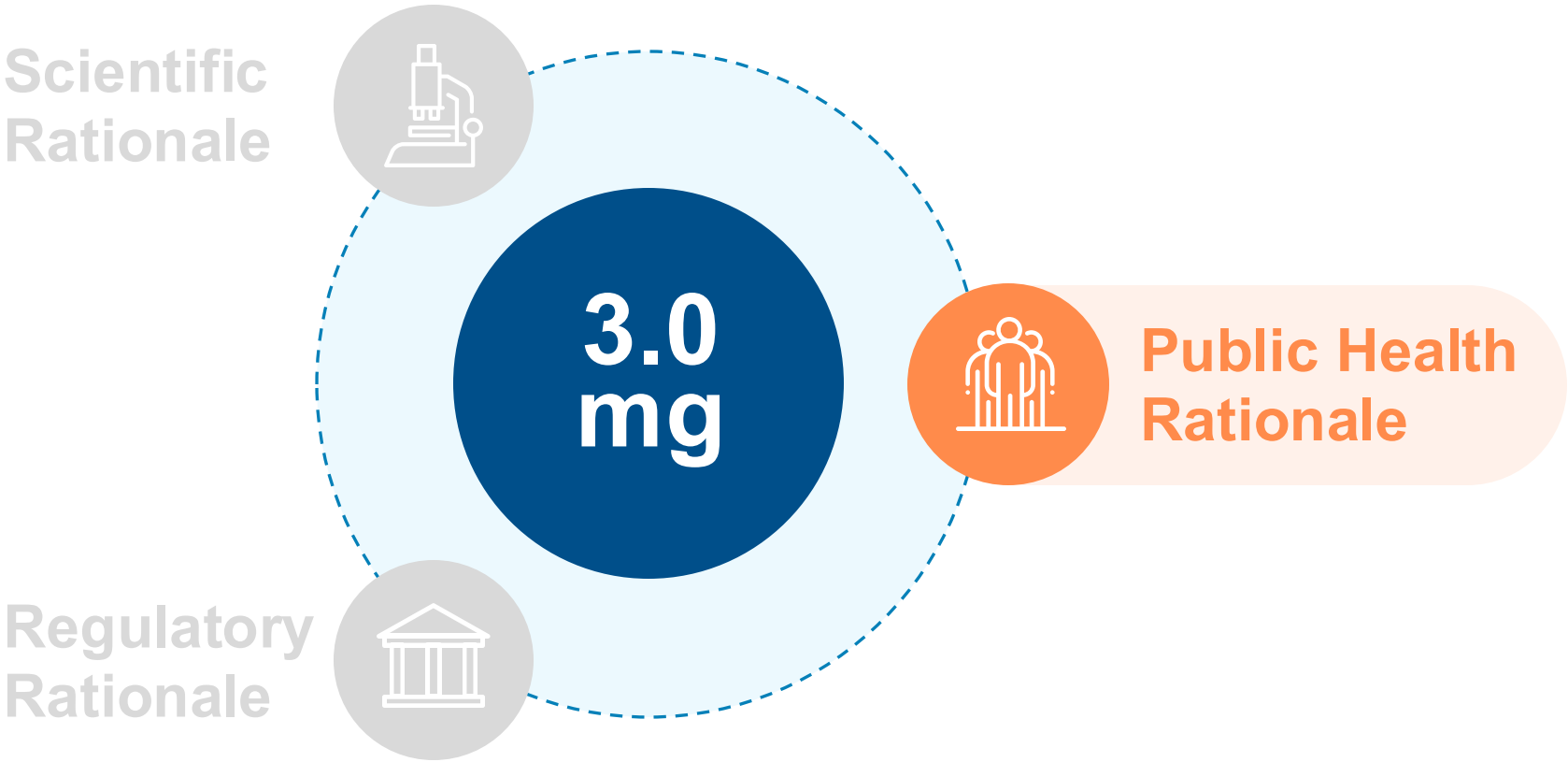
FDA's Feedback to Mundipharma on 2 mg Dose

“Given that the 2 mg dose of your drug product appears to generate lower systemic naloxone exposure at the early time points post-administration compared with the intramuscular administration of the EU naloxone product, and if your product also has lower exposure when compared to a product approved in the US, **it may be worthwhile to consider developing and testing a higher strength of your drug product, such as 2.5 or 3.0 mg.** This would provide more assurance that your drug product would be similarly efficacious to approved naloxone.” (emphasis added)

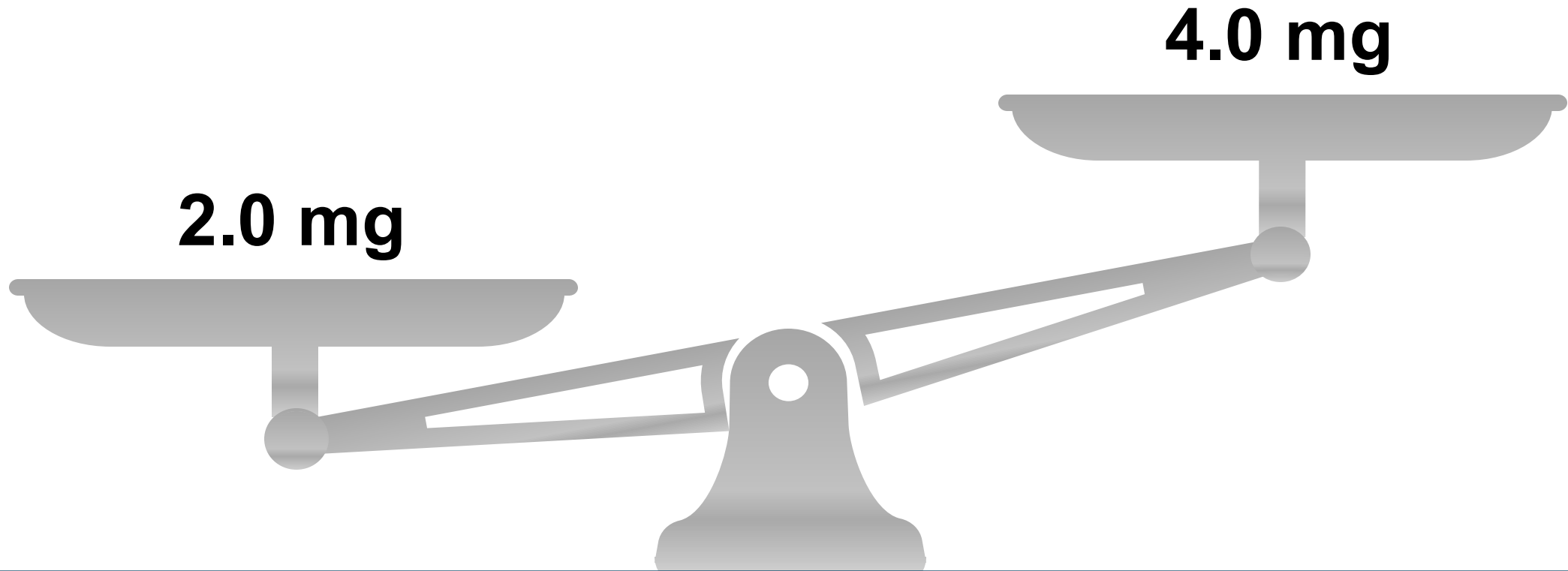
The FDA viewed any 2-4mg IN naloxone product as eligible for OTC status



RiVive's 3 mg Dose: Public Health Rationale



Harm Reduction experts uniformly urged us to develop a 3mg product



The Tragic Equation of Opioid Overdose

LIFE or DEATH =



VARIABILITY
in the amount
of opioids
consumed

VARIABILITY
in the potency
of the opioid
consumed

EXPOSURE
to other
drugs

TIME
since OD
occurred

COMORBID
health
conditions

Economic Drivers Have Limited Access to Naloxone, Costing Lives



The NEW ENGLAND JOURNAL of MEDICINE

Perspective
DECEMBER 8, 2016

The Rising Price of Naloxone — Risks to Efforts to Stem Overdose Deaths

Ravi Gupta, B.S., Nilay D. Shah, Ph.D., and Joseph S. Ross, M.D., M.H.S.

Recent and Current Prices for Naloxone.*

Naloxone Product	Manufacturer	Previous Available Price (yr)	Current Price (2016)
Injectable or intranasal, 1 mg-per-milliliter vial (2 ml) (mucosal atomizer device separate)	Amphastar	\$20.34 (2009)	\$39.60
Injectable			
0.4 mg-per-milliliter vial (10 ml)	Hospira	\$62.29 (2012)	\$142.49
0.4 mg-per-milliliter vial (1 ml)	Mylan	\$23.72 (2014)	\$23.72
0.4 mg-per-milliliter vial (1 ml)	West-Ward	\$20.40 (2015)	\$20.40
Auto-injector, two-pack of single-use prefilled auto-injectors (Evzio)	Kaleo (approved 2014)	\$690.00 (2014)	\$4,500.00
Nasal spray, two-pack of single-use intranasal devices (Narcan)	Adapt (approved 2015)	\$150.00 (2015)	\$150.00

* Price information was obtained from Medi-Span Price Rx (Wolters Kluwer Clinical Drug Information).

FIRST OPINION

STAT

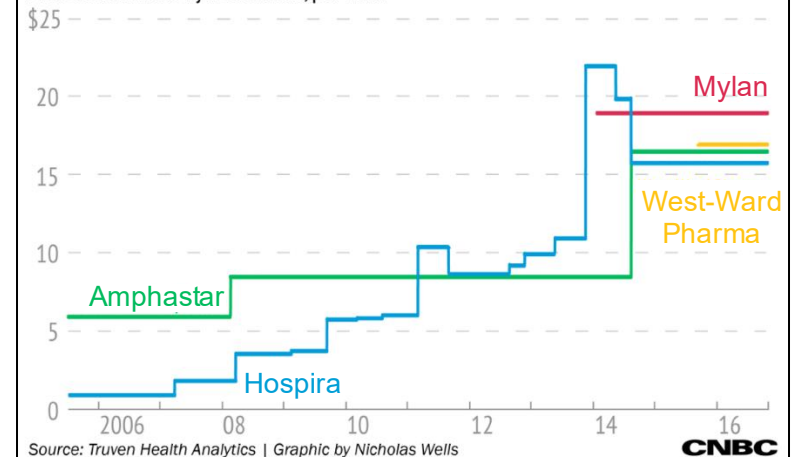
The costs of heroin and naloxone: a tragic snapshot of the opioid crisis

By Michael Hufford and Donald S. Burke Nov. 8, 2018

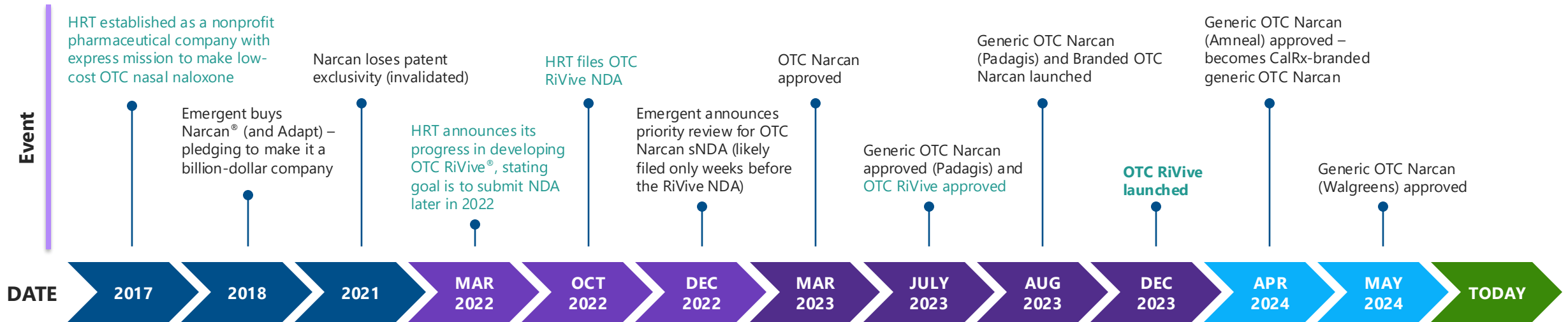
Reprints

The cost to reverse an overdose

Price of naloxone hydrochloride, per 1 ml



HRT Pioneered OTC Naloxone, Forcing the Market OTC and Lowering Prices



Rx Only

\$140+ Narcan retail

\$50-75 Narcan Public Interest Pricing (PIP)*

OTC

\$45
Narcan & Generic retail

\$41
Narcan PIP

\$36
RiVive

\$24
(CalRX, specific buyers in CA only)

\$45
Narcan retail

\$35
Generic Narcan retail

mid-\$30s
RiVive (\$33), Generic retail, and Narcan PIP

*Special pricing for qualified buyers of Narcan (e.g., First Responder, State or Local Government Agency, School, Community-based organization, harm reduction)