

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active. Contents lists available at ScienceDirect



International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

# Viewpoint Increasingly powerful opioid antagonists are not necessary



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

#### Background

In the United States (U.S.), drug overdose deaths have increased substantially during the COVID-19 pandemic (Centers for Disease Control and Prevention, 2020). Synthetic opioids are implicated as the primary drivers of this increase. Naloxone, an opioid antagonist which can rapidly reverse opioid-induced respiratory depression, is recommended for use and distribution by health professionals and laypersons to address this crisis. Given the relative potency of many synthetic opioids, it has been theorized that higher doses of naloxone – or even more potent and longer-acting opioid antagonists – may be required to effectively reverse overdoses (Krieter, Gyaw, Crystal, & Skolnick, 2019).

Lucas G. Hill\*, Claire M. Zagorski, Lindsey J. Loera

## **Opioid antagonists**

Prior to 2015, the predominant form of naloxone for first responders was a generic 0.4 mg vial for intravenous (IV) or intramuscular (IM) administration (Lim, Bratberg, Davis, Green, & Walley, 2016). An improvised intranasal (IN) form using a prefilled 2 mg syringe retrofitted with a mucosal atomization device also gained some traction prior to approval of branded 2 mg and 4 mg IN devices in late 2015. Only the 4 mg device has ever been marketed. This was followed by approval of a branded IM device which was initially marketed at a 0.4 mg dose, then later a 2 mg dose, but ultimately discontinued by the manufacturer. In 2021, a branded 8 mg IN device was approved, and development of a branded form of nalmefene is ongoing. Nalmefene is an opioid antagonist with substantially greater mu opioid receptor affinity and a longer elimination half-life compared to naloxone (Krieter et al., 2019).

Pharmacokinetic data for key formulations of each of these opioid antagonists, abstracted from two reports of studies in healthy volunteers, are summarized in Table 1 (Krieter et al., 2016; Krieter et al., 2019). Compared to naloxone 0.4 mg IM, the 4 mg IN and 8 mg IN doses achieve dramatically greater peak concentrations and total drug exposure. Data for naloxone and nalmefene are not directly comparable given differing pharmacodynamic properties, though it is likely that substantially greater mu opioid receptor affinity will translate to a lower concentration achieving a similar physiological effect.

## Considering the evidence

Advocates for more powerful opioid antagonists often cite two retrospective studies which found that emergency medical services (EMS)

\* Corresponding author.

E-mail address: lucas.hill@austin.utexas.edu (L.G. Hill).

https://doi.org/10.1016/j.drugpo.2021.103457

0955-3959/© 2021 Elsevier B.V. All rights reserved.

providers responding to a suspected opioid overdose were more likely to administer multiple doses of naloxone in 2015 (18.2%) compared to 2012 (14.5%) (Faul et al., 2017) and in 2016 (21.4%) compared to 2013 (15.0%) (Geiger, Smart, & Stein, 2020). However, these studies did not describe the route or dose of these administrations. IN naloxone administrations were likely rare as trained clinicians often prefer to carefully titrate IV dosing and may also administer IM. The significance of a modest increase in multiple administrations of unknown IV and IM doses is difficult to ascertain. Given widespread news reports describing the increased prevalence of potent synthetic opioids, often accompanied by alarmist misinformation about passive exposure risk, it is plausible that the increase in multiple naloxone administrations among EMS is an artifact of availability bias with multiple doses of naloxone administered out of an abundance of caution rather than based on clinical signs and symptoms. Patients treated for a suspected opioid overdose may also appear to need more naloxone due to intentional concomitant use of opioids and other sedating drugs (e.g., alcohol, benzodiazepines) and contamination of the illegal opioid supply with non-opioid depressants (e.g., xylazine, barbiturates).

Three other studies, two in emergency departments and one in a syringe services program, provide superior insight regarding the hypothesized need for more powerful opioid antagonists. An analysis of prehospital and emergency department naloxone administration was conducted in Atlanta from 2017 to 2018 (Carpenter et al., 2020). This study included naloxone dosing information and urine drug screen results, and it found that the median dose of naloxone administered in successful reversals did not differ significantly based on the presence or absence of fentanyl (0.8 mg IV vs 0.56 mg IV, p = 0.79). A study conducted in Boston from 2017 to 2018 compared blood fentanyl concentrations to naloxone doses administered among patients experiencing a non-fatal opioid-related overdose (Krotulski et al., 2021). All 20 subjects reported use of heroin, and fentanyl was detected in 19. No relationship between blood fentanyl concentration and naloxone dose administered was identified. Data collected from clients of a syringe services program in Pittsburgh, Pennsylvania from 2013 to 2016 corroborate these results (Bell, Bennett, Jones, Doe-Simkins, & Williams, 2019). While the proportion of opioid overdose deaths testing positive for fentanyl in the county increased from 3.5% to 68.7% during this timeframe, the reported naloxone doses used by clients to effectively reverse opioid overdoses did not change. Notably, the program distributed relatively low-dose 0.4 mg vials for IM administration, and a mean of only 1.56 doses per reversal were required.

#### Table 1

Pharmacokinetics of opioid antagonists in healthy volunteers (Krieter et al., 2016; Krieter et al., 2019).

Drug	Route	Dose	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hours)	AUC (ng·h/mL)
Naloxone	IM	0.4mg	0.9	0.4	1.8
Naloxone	IN	2mg	3.1	0.3	4.7
Naloxone	IN	4mg	5.3	0.5	8.5
Naloxone	IN	8mg	10.3	0.3	15.8
Nalmefene	IN	3mg	4.45	0.25	15.2

Cmax indicates the maximum plasma concentration achieved.

 $t_{\rm max}$  indicates the amount of time elapsed prior to achieving Cmax.

AUC represents the total drug exposure.

#### Unintended consequences

The proliferation of powerful opioid antagonists could have unintended consequences that are counterproductive to efforts to prevent opioid-related overdose deaths. Precipitated opioid withdrawal is a known risk of naloxone for opioid-tolerant individuals, producing symptoms such as hyperalgesia, diarrhea, and vomiting, particularly at higher doses (Purssell et al., 2021). Aversion to being administered naloxone and experiencing opioid withdrawal symptoms was thoroughly documented in an ethnographic study conducted in Scotland from 1997 to 1999 (Neale & Strang, 2015). Nearly all subjects who were familiar with naloxone described it negatively and indicated it should be avoided, and many expressed mistrust of health professionals' judgment regarding when to administer it. Notably, while this study included interviews with 200 people who use opioids, it occurred in an environment of relatively low-dose naloxone administration and poor awareness of naloxone among the subjects. Thus, it is worthwhile to consider the findings of two recent studies describing naloxone wariness among people who use opioids in the U.S.

In one study, 10 adults reporting to an emergency department in Boston with an opioid-related chief complaint were interviewed (Lai et al., 2021). All were familiar with naloxone and had received training in its administration, and they generally reported positive perceptions of it. However, the eight subjects who had previously received naloxone each reported experiencing severe opioid withdrawal symptoms they were eager to avoid in the future. In another study, 20 adults who use opioids in New York were interviewed to identify reasons they do or do not carry naloxone (Bennett, Freeman, Des Jarlais, & Aronson, 2020). A major reported theme from these interviews was a fear of misrecognizing the need for naloxone and inducing or experiencing prolonged opioid withdrawal symptoms. Significantly, an 8 mg naloxone product has not yet been marketed, so these qualitative findings are in the context of 4 mg IN being the highest single-dose naloxone product available. The introduction of an 8 mg IN naloxone product and the potential future introduction of a similarly potent nalmefene product with longer duration of action could plausibly lead some people who use opioids to avoid carrying it.

## Conclusion

The development and marketing of more powerful opioid antagonists should be viewed with great skepticism. Since opioid antagonists are commonly purchased for the public in bulk by state health agencies, a relatively small number of purchasing decisions can impact thousands of individuals. State health agency staff, public health professionals, policymakers, and clinicians should be aware that more potent, longeracting opioid antagonists are not necessary and may have unintended consequences. The input of people who use drugs should be solicited and considered carefully before embracing more powerful opioid antagonists.

## Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## **Declarations of Interest**

Dr. Hill reports serving on a community advisory board for Hikma Specialty Inc. in December 2020. Ms. Zagorski and Dr. Loera report no potential conflicts of interest.

## References

- Bell, A., Bennett, A. S., Jones, T. S., Doe-Simkins, M., & Williams, L. D. (2019). Amount of naloxone used to reverse opioid overdoses outside of medical practice in a city with increasing illicitly manufactured fentanyl in illicit drug supply. *Substance Abuse*, 40(1), 52–55. 10.1080/08897077.2018.1449053.
- Bennett, A. S., Freeman, R., Des Jarlais, D. C., & Aronson, I. D. (2020). Reasons people who use opioids do not accept or carry no-cost naloxone: Qualitative interview study. *JMIR Formative Research*, 4(12), e22411. 10.2196/22411.
- Carpenter, J., Murray, B. P., Atti, S., Moran, T. P., Yancey, A., & Morgan, B. (2020). Naloxone dosing after opioid overdose in the era of illicitly manufactured fentanyl. *Journal* of Medical Toxicology, 16(1), 41–48. 10.1007/s13181-019-00735-w.
- Centers for Disease Control and Prevention. (December 17, 2020). Increase in fatal drug overdoses across the United States driven by synthetic opioids before and during the COVID-19 pandemic. Retrieved May 24 from https://emergency.cdc.gov/ han/2020/han00438.asp.
- Faul, M., Lurie, P., Kinsman, J. M., Dailey, M. W., Crabaugh, C., & Sasser, S. M. (2017). Multiple naloxone administrations among emergency medical service providers is increasing. *Prehospital Emergency Care*, 21(4), 411–419. 10.1080/10903127.2017.1315203.
- Geiger, C., Smart, R., & Stein, B. D. (2020). Who receives naloxone from emergency medical services? Characteristics of calls and recent trends. *Substance Abuse*, 41(3), 400– 407. 10.1080/08897077.2019.1640832.
- Krieter, P., Chiang, N., Gyaw, S., Skolnick, P., Crystal, R., Keegan, F., et al. (2016). Pharmacokinetic properties and human use characteristics of an FDA-approved intranasal naloxone product for the treatment of opioid overdose. *Journal of Clinical Pharmacol*ogy, 56(10), 1243–1253. 10.1002/jcph.759.
- Krieter, P., Gyaw, S., Crystal, R., & Skolnick, P. (2019). Fighting fire with fire: Development of intranasal nalmefene to treat synthetic opioid overdose. *Journal of Pharmacology* and Experimental Therapeutics, 371(2), 409–415. 10.1124/jpet.118.256115.
- Krotulski, A. J., Chapman, B. P., Marks, S. J., Ontiveros, S. T., Devin-Holcombe, K., Fogarty, M. F., et al. (2021). Sentanyl: A comparison of blood fentanyl concentrations and naloxone dosing after non-fatal overdose. *Clinical Toxicology*, 1–8. 10.1080/15563650.2021.1948558.
- Lai, J., Goldfine, C., Chapman, B., Taylor, M., Rosen, R., Carreiro, S., et al. (2021). Nobody wants to be Narcan'd: A pilot qualitative analysis of drug users' perspectives on naloxone. Western Journal of Emergency Medicine, 22(2), 339–345. 10.5811/westjem.2020.10.48768.
- Lim, J. K., Bratberg, J. P., Davis, C. S., Green, T. C., & Walley, A. Y. (2016). Prescribe to prevent: Overdose prevention and naloxone rescue kits for prescribers and pharmacists. *Journal of Addiction Medicine*, 10(5), 300–308. 10.1097/ADM.0000000000223.
- Neale, J., & Strang, J. (2015). Naloxone–does over-antagonism matter? Evidence of iatrogenic harm after emergency treatment of heroin/opioid overdose. *Addiction*, 110(10), 1644–1652. 10.1111/add.13027.
- Purssell, R., Godwin, J., Moe, J., Buxton, J., Crabtree, A., Kestler, A., et al. (2021). Comparison of rates of opioid withdrawal symptoms and reversal of opioid toxicity in patients treated with two naloxone dosing regimens: A retrospective cohort study. *Clinical Toxicology*, 59(1), 38–46. 10.1080/15563650.2020.1758325.