HHS Public Access

Author manuscript

Int J Drug Policy. Author manuscript; available in PMC 2023 August 01.

Published in final edited form as:

Int J Drug Policy. 2022 August ; 106: 103751. doi:10.1016/j.drugpo.2022.103751.

Patient Perceptions of Higher-Dose Naloxone Nasal Spray for Opioid Overdose

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Abstract

Background: Higher-dose formulations of naloxone were recently approved by the FDA for the treatment of opioid overdose. These products were developed based on projected saturation of high-potency fentanyl analogues in the illicit marketplace although the evidence base for their necessity is still under scrutiny. Concern has been raised that unintended reductions in patient acceptance of naloxone may occur due to increased precipitated withdrawal risk associated with higher naloxone doses. A well-founded and time-sensitive call for representation of people who use drugs in this decision-making process has been made. This study provides the first data on patient perceptions of higher-dose formulations to inform this scientific debate and distribution efforts.

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CRediT Author Statement

Justin Strickland: Conceptualization, Methodology, Formal analysis, Writing Original Draft, Supervision; Katherine Marks: Conceptualization, Methodology, Writing Original Draft; Kirsten Smith: Methodology, Writing Original Draft; Jennifer D. Ellis: Formal analysis, Writing Reviewing & Editing; J. Gregory Hobelmann: Writing Reviewing & Editing; Andrew Huhn: Methodology, Writing Reviewing & Editing, Supervision

Conflict of Interest

The authors have no conflicts of interest to disclose.

Ethics

This protocol was reviewed by the Johns Hopkins University Institutional Review Board, who acknowledged that this study did not meet the definition of human subjects research under the DHHS or FDA regulations and was considered to be low/negligible risk because there was no intervention and the study team only received de-identified data.

Methods: Patients (N=1152) entering treatment for opioid use disorder at one of 49 addiction treatment facilities located across the United States completed a preference assessment of naloxone nasal spray formulations. Patients selected a formulation preference across three scenarios (administration for self, administration to others, community responder administration).

Results: A majority of respondents that had been administered naloxone previously reported that their most recent overdose reversal included two or more naloxone administrations (59.9%). Most respondents either had no preference (48.4%) or preferred a higher-dose formulation (35.9%) if personally experiencing an overdose. Similar preference distributions were observed for administration to others and by community responders. Relative to standard-dose preference, respondents preferring higher-dose formulations had a greater odds of recent suspected fentanyl exposure.

Conclusions: These data inform patients, advocates, and policy-makers considering distribution and utilization of naloxone formulations by reporting perspectives of patients with opioid use and overdose experience. Limited evidence for widespread avoidance of higher-dose formulations was found. As real-world evidence of acceptability and effectiveness emerges, either supporting or refuting the widespread need for higher-dose naloxone formulations, it is the responsibility of the scientific and public health community to be responsive to that data.

Keywords

fentanyl; harm reduction; naloxone; opioid; overdose; prevention

Introduction

Naloxone is a lifesaving medication used to rapidly reverse opioid overdose. The United States Food and Drug Administration recently approved two higher-dose formulations of naloxone to include an injectable 5-mg formulation (Zimhi™) and nasal 8-mg formulation (Kloxxado®). The nasal spray formulation became available for distribution in August 2021 and delivers twice the dose of naloxone as the currently distributed nasal spray Narcan® and generic naloxone formulation (i.e., 4-mg) (American Medical Association, 2021). The rationale for the development of higher-dose formulations is based on the projected saturation of high-potency fentanyl and fentanyl analogues in the illicit marketplace (Moss and Carlo, 2019). This new preparation is also a response to calls from the National Institutes of Health for “stronger, longer-acting formulations” (Volkow and Collins, 2017).

A detailed and thoughtful review of the existing literature recently concluded that quality data have not been produced to support the contention that current naloxone products are ineffective to treat fentanyl-related overdose (Britch and Walsh, 2022). In addition, the data on the frequency for which multiple naloxone doses are administered for reversal vary widely and lack critical detail necessary to draw conclusions regarding a hypothesized upward trend in dose due to fentanyl and fentanyl analogues. Caution has been raised that higher-dose approaches to opioid overdose reversal may lead to unintended reductions in patient acceptance of naloxone due to increased risk of precipitated withdrawal (Hill et al., 2022; Zagorski, 2021) and still does not address a significant barrier to saving lives – the limited timeframe during which a fentanyl-related overdose can be treated (Britch

and Walsh, 2022). Providers may also be cautious to distribute these products due to other possible risks such as noncardiogenic pulmonary edema.

As such, a well-founded and time-sensitive call has been made for the voice and representation of stakeholders including people who use drugs in this dialogue in order to inform choice and access to a growing array of opioid overdose reversal products (Hill et al., 2022). Importantly, no data are available on patient perceptions of higher-dose formulations to inform concerns about these products and, in turn, to inform a measured distribution effort. We provide needed data through an observational preference assessment of naloxone nasal spray formulations in a large cohort of patients entering treatment for non-medical opioid use across the United States. We focus on nasal spray given the focus of nasal formulations in harm reduction distribution efforts (e.g., take-home naloxone programs).

Material and Methods

Responses were collected from patients during intake at one of 49 addiction treatment facilities located across the United States via a third-party treatment outcomes platform (Trac9, NLW Partners, LLC, Lubbock, TX, USA). Patients who reported heroin or non-medical prescription opioids as their primary substance at the time of treatment intake were surveyed (N=1152). Original data contained 1178 respondents after removing those under 18 and repeated treatment admissions with the first treatment admission data retained (i.e., to generate a dataset with only unique respondents). Data cleaning identified 26 additional respondents for removal who reported conflicting information about their history of non-medical opioid use. This resulted in a final analytic sample of 1152 respondents. These data cleaning steps were consistent with the preregistered plan. This protocol was reviewed by the Johns Hopkins University Institutional Review Board, who acknowledged that this study did not meet the definition of human subjects research under the DHHS or FDA regulations and was considered to be low/negligible risk because there was no intervention and the study team only received de-identified data. Data were collected from October to December 2021 and analyses were conducted in December 2021 and April 2022.

Survey questions assessed naloxone formulation preferences. Specifically, when presented with survey questions about no-cost formulations of naloxone at various doses, respondents could indicate their preference for free higher-dose naloxone nasal spray, free standard-dose naloxone, either formulation (no preference), or could indicate if they would not want either product formulation. Specific doses and possible side effect profiles were not specified, but respondents were told that the higher-dose formulation was twice as strong (i.e., double the dose) of the standard formulation as would likely be communicated when naloxone is being distributed through harm reduction programs. Respondents were prompted to select their formulation preference across three scenarios: a) if they were experiencing an overdose, b) if they were administrating formulations to someone else experiencing an overdose, and c) for community responders to administer to community members. Additional questions about naloxone and overdose history were also collected (full assessment included in the Supplemental Materials). Data were not collected on availability of or experience with higher-dose formulations. Primary analyses conducted in *R* included estimates of preference with 95% confidence intervals (CI), comparisons

to indifference, and multinomial logistic regression. This study was preregistered at https://osf.io/jr84c with additional data preregistration information in the Supplemental Materials.

Results

Demographic and opioid use characteristics by formulation preferences are in Table 1. The sample was majority male (n=833; 72.3%) and White (n=904; 78.5%). Approximately half of respondents had been administered Narcan® before (n=558; 48.4%). Among those with this history, over half indicated that their most recent administration included 2 or more units of Narcan® (n=334; 59.9%).

Most respondents either had no preference (n=558; 48.4%, 95% CI: 45.5%−51.3%) or preferred a higher-dose formulation (n=413; 35.9%, 95% CI: 33.1%−38.6%) if personally experiencing an overdose. The combined proportion (i.e., either no preference or a higher-dose preference) exceeded 50% according to a one-proportion z-test, $p<.001$. Neither strict preference for standard-dose (n=125; 10.9%, 95% CI: 9.1%−12.6%) or for higher-dose formulation were greater than 50%. Similar preference distributions were observed for administration to others and by community responders (see Supplemental Figure 1 for estimates and 95% CI).

A multivariable multinomial logistic regression indicated that relative to standard-dose preference, respondents who preferred higher-dose formulations had a greater odds of recent suspected fentanyl exposure (Adjusted Odds Ratio [AOR] = 2.11 [95% CI=1.29, 3.44], $p=.003$; table of full model results in Supplemental Materials and descriptives in Table 1). Respondents who had no preference compared to standard-dose preference also had a greater odds of recent suspected fentanyl exposure (AOR = 1.93 [1.19, 3.13], $p=.008$). Relative to standard dose preference, respondents who regularly carried naloxone had a significantly lower odds of reporting indifference (AOR = 0.52 [0.33, 0.82] , $p=.005$), but not high dose preference (AOR = 0.66 [0.42, 1.06] , $p=.09$).

Discussion

This observational preference assessment of higher-dose naloxone nasal spray formulations identified either indifference to product strength or preference for higher-dose formulations in most respondents, while a smaller number (~10%) expressed preference for current-dose formulations. Few systematic differences were observed by preference; however, higher-dose formulations were preferred by patients with suspected recent fentanyl exposure. This is consistent with previous research demonstrating that knowledge of fentanyl exposure risk is associated with safer drug use behaviors (Peiper et al., 2019). Preferences were stable across contexts including administration to self, to others, and by community responders.

We found that over half of respondents with a history of naloxone administration received multiple Narcan® administrations during their most recent overdose reversal. Although it is relevant to consider recall bias or self-report accuracy, these data are consistent with the broader observation that in a proportion of overdose reversals, multiple standard dose naloxone administrations are being administered (Abdelal et al., 2022). It is critical to note that data to assess whether multiple doses were in fact needed to reverse the overdose were

not available in the present study and represents a significant gap in the broader literature. The evidence base for or against higher-dose formulations thus far is mixed and relies on older databases (i.e., 2018 or earlier) and/or those with limited sample sizes (e.g., Bell et al., 2019; Geiger et al., 2020; Krotuski et al., 2021). The current findings, rather, suggest that higher-dose formulations may be acceptable to patients. Modern real-world evidence is required to inform the need for these products and the public health and policy landscape should update according to the results of this work.

The sample was comprised exclusively of patients entering treatment for an opioid use disorder which is both a strength and a limitation of the study. Among this clinical sample, 53.9% had an overdose history and 57.3% reported currently carrying a form of naloxone. Rates of carrying were slightly higher for those with standard-dose preferences, which may reflect a status quo bias, however these rates were only significantly different relative to those with no preference. In addition, 28.9% of the total sample reported experience receiving two or more doses of Narcan®. These patient histories contribute to a diverse sample inclusive of people with lived experience to provide data on patient perceptions of and preferences for standard versus higher-dose naloxone nasal spray formulations, either by virtue of direct or indirect overdose experiences or by virtue of prospection. Although this is also a priority population for naloxone distribution (American Society of Addiction Medicine, 2016), data from a wider array of people who use drugs (e.g., individuals accessing syringe service programs) as well as family and friends and first responders will be important points for future study and dissemination. Exit surveys during discharge, after patients have stabilized, should also be considered as attitudes about and preferences for specific types of intervention may change as a result of treatment. We also did not have access to clinic information, socioeconomic, or geographic data (due to the data deidentification process). It will be important for local distribution efforts to consider how geographic and cultural variations in acceptability likely exist based on factors such as perceived regional risk, access to medical care following reversal, and access to replacement supply of naloxone following use.

It is also critical to contextualize findings by collecting more in-depth retrospective data from people who have experienced or witnessed opioid overdoses and to assess preferences for overdose-reversal products based on knowledge of specific overdose experiences. That the proportion of respondents with overdose histories endorsing no preference was lower and the proportion of respondents with recent fentanyl exposure endorsing preference for standard dose formulations was likewise lower suggests that preferences among people with non-medical opioid use histories are likely shaped by the everyday risk encountered. Likewise, future qualitative and mixed method work may provide rationales for why patients do (and do not) prefer varied formulations offering a nuanced view compared to quantitative reports.

Conclusions

As researchers continue to call for quality data to evaluate existing and emerging pharmacological strategies for the treatment of overdose, it is critical to engage stakeholder communities to inform the development and distribution of this work. These data

inform patients, advocates, clinicians, state health agencies, and policy-makers considering distribution and utilization of naloxone formulations by reporting the perspectives of treatment-seeking patients with opioid use and overdose experience. Minimal evidence for widespread avoidance of higher-dose formulations was observed. Nonetheless, person-centered distribution strategies should be prioritized and paired with overdose education to address barriers to naloxone utilization at any dose (e.g., insufficient training, knowledge about laws and legality; Bennet et al., 2020; Bessen et al., 2019; Dayton et al., 2019). Post-marketing assessments should also monitor utilization and real-world choice for overdose-reversal products following experience with emerging formulations. Continued modern evidence is needed to evaluate the dose-response of naloxone for fentanyl-related overdose reversal. As additional acceptability and effectiveness evidence emerges, either supporting or refuting the widespread need for higher-dose formulations, it is the responsibility of the scientific and public health community to be responsive to that data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Role of Funding Source

Support for Dr Strickland was provided by grant R03DA054098 from the National Institute on Drug Abuse. Support for Dr Smith was provided by that National Institute on Drug Abuse Intramural Research Program. Support for Dr Hobelmann was provided by Ashley Addiction Treatment. Support for Dr Ellis was provided by grant T32DA07209 from the National Institute on Drug Abuse. Support for Dr Huhn was provided by grant UG3DA048734 from the National Institute on Drug Abuse.

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The authors acknowledge that the reported results are, in whole or in part, based on analyses of Trac9.com outcomes research. This manuscript may not represent the opinions of Trac9.com, nor is Trac9.com responsible for its contents or decision to publish these results. No renumeration for the associated work was provided by either Trac9 or Johns Hopkins University.

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Highlights

- Higher-dose formulations of naloxone have recently been approved by the FDA
- Distribution efforts may be impacted by patient concerns of precipitated withdrawal
- Patients entering opioid use treatment reported high-dose formulation perceptions
- Little evidence for widespread avoidance of higher-dose formulations was found
- High-dose preference was related to recent suspected fentanyl exposure

Table 1.

Demographics and Opioid Behaviors by Naloxone Strength Preferences

	Overall (N=1152)	Indifference (n=558; 48.4%)	Prefer High Dose (n=413; 35.9%)	Prefer Standard Dose (n=125; 10.9%)	Neither (n=56; 4.9%)
Age M (SD)	33.6 (10.1)	34.4 (9.9)	32.7 (10.0)	33.0 (10.8)	33.9 (11.5)
Gender %(n)					
Female	27.5% (317)	27.1% (151)	29.1% (120)	24% (30)	28.6% (16)
Male	72.3% (833)	72.9% (407)	70.7% (292)	75.2% (94)	71.4% (40)
Other	0.2% (2)	0% (0)	0.2% (1)	0.8% (1)	0% (0)
Race %(n)					
Black or African American	10.9% (126)	12.4% (69)	9.0% (37)	9.6% (11)	14.3% (8)
Asian	0.8% (9)	0.9% (5)	0.2% (1)	0.8% (1)	3.6% (2)
American Indian or Alaskan Native	1.0% (11)	0.7% (4)	1.5% (6)	0% (0)	1.8% (1)
Native Hawaiian or Pacific Islander	0.2% (2)	0% (0)	0.2% (1)	0% (0)	1.8% (1)
Other	8.7% (100)	9.0% (50)	6.1% (15)	17.6% (22)	5.4% (3)
White	78.5% (904)	77.1% (430)	83.1% (343)	72.0% (90)	73.2% (41)
Ethnicity %(n)					
Non-Hispanic	90.5% (1042)	8.4% (47)	8.0% (33)	17.6% (22)	14.3% (8)
Hispanic	9.5% (110)	91.6% (511)	92.0% (380)	82.4% (103)	85.7% (48)
Level of Care %(n)					
Medically Managed Inpatient	66.3% (764)	75.8% (423)	55.7% (230)	58.4% (73)	67.9% (38)
Residential	27.9% (321)	19.0% (106)	36.3% (150)	38.4% (48)	30.4% (17)
IOP	5.8% (67)	5.2% (29)	8.0% (33)	3.2% (4)	1.8% (1)
Carries Naloxone[a] %(n)	57.3% (660)	55.2% (308)	62.0% (256)	66.4% (83)	23.2% (13)
Narcan	53.6% (618)	53.6% (299)	55.9% (231)	61.6% (77)	19.6% (11)
Naloxone Nasal Spray	4.1% (47)	1.4% (8)	6.3% (26)	9.6% (12)	1.8% (1)
Intramuscular	4.3% (49)	2.2% (12)	7.3% (30)	4.0% (5)	3.6% (2)
Evzio	1.0% (12)	0.2% (1)	2.2% (9)	1.6% (2)	0% (0)
Other	1.6% (18)	0.4% (2)	2.9% (12)	2.4% (3)	1.8% (1)
Overdose History %(n)	53.9% (621)	46.1% (257)	63.9% (264)	64.8% (81)	33.9% (19)
Past Month Suspected Fentanyl Exposure %(n)	72.5% (835)	76.0% (424)	73.6% (304)	64.0% (80)	48.2% (27)
Has Ever Been Administered Naloxone %(n)	48.4% (558)	42.7% (238)	55.2% (228)	59.2% (74)	32.1% (18)
# of Doses of Narcan Administered in Most Recent Reversal[b]					
1 Dose	20.6% (115)	20.2% (48)	18.0% (41)	29.7% (22)	22.2% (4)
2 or More Doses	59.9% (334)	60.9% (145)	59.2% (135)	59.5% (44)	55.6% (10)
Do Not Know	19.5% (109)	18.9% (45)	22.8% (52)	10.8% (8)	22.2% (4)

Note. Presented are percentage (cell sample size) for naloxone strength preferences for administration to self. Mean = M

[a]Carry refers to any product, respondents could endorse more than one.

[b]Responses only for respondents with a history of naloxone administration