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Naloxone Formulation For Overdose Reversal Preference Among Patients Receiving Opioids for Pain Management

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Abstract

Background—Opioid-related overdose has increased 137% in the past decade. Training nonmedical bystanders to administer naloxone (NarcanTM) is a widely-researched intervention that has been associated with decreases in overdose rates in the communities in which it has been implemented. A recent review advocated for noninjectable formulations of naloxone, however patient preference for naloxone formulations has not yet been examined (Strang et al., 2016).

Methods—Two cohorts of respondents (N1=501, N2=172) who reported currently being prescribed an opioid for pain management were recruited through the crowd-sourcing program Amazon Mechanical Turk (MTurk) to assess their preference for naloxone formulations. All respondents were provided a description of different formulations and asked to indicate all formulations they would be willing to administer for overdose reversal and to then rank formulations in order of preference.

Results—Results were remarkably similar across both cohorts. Specifically, respondents preferred noninjectable formulations (intranasal, sublingual, buccal) over injectable (intravenous, intramuscular) formulations. A small percent (8.9 – 9.8%) said they would never be willing to administer naloxone. An identical percent of respondents in both cohorts (44.9 %) rated intranasal as their most preferred formulation.

Conclusions—Two independent cohorts of respondents who were receiving opioid medications for pain management reported a preference for noninjectable over injectable formulations of naloxone to reverse an opioid overdose. Though initial preference is only one of many factors that impacts ultimate public acceptance and uptake of a new product, these results support the additional research and development of noninjectable naloxone formulations.

Keywords

naloxone; opioid; overdose; opioid use disorder; narcan

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1. Introduction

In the United States, the rate of overdoses related to opioids has increased more than 137% over the past decade (Rudd et al., 2016) and unintentional poisonings (which are driven by opioid-related overdoses) are now the leading cause of accidental death in adults aged 25–64 (Centers for Disease Control and Prevention (CDC) and Wonder Database, 2015). Naloxone (Narcan™) is a fast-acting opioid antagonist that can be used to reverse the agonist effects of opioids to stop an overdose. In the past decade, there have been increasing efforts to equip non-medical persons with naloxone and train them in its administration to reverse an opioid overdose (Wheeler et al., 2015). These efforts have been associated with significant reductions in overdose rates in communities in which they have been implemented (Walley et al., 2013). The United States has recently declared the opioid epidemic to be a national emergency (McCarthy, 2017), and numerous federal, state, and organizational-level efforts are being made to expand access to naloxone. This is somewhat complicated by the fact that naloxone is currently only available by prescription, though efforts to circumvent this barrier, such as formalizing standing orders at pharmacies to allow individuals to purchase naloxone more easily (Davis and Carr, 2017; Morton et al., 2017) and training physicians to prescribe naloxone to patients receiving opioids for pain management (Madras, 2017), appear to be working. There is significant interest in making an over-the-counter version of naloxone available as well.

Because naloxone was developed for medical personnel to use in hospital settings, it has traditionally been available only as an injectable product (generally intravenous or intramuscular). With the onset of nonmedical bystander training programs, there has been interest in developing additional naloxone formulations that may be easier for individuals who have no medical training to use in opioid overdose situations. Ease of use is an important consideration as overdose situations are often chaotic and stressful, so products that do not require much technical skill and have reduced risk of collateral problems (e.g., accidental needle stick) are likely to be more widely utilized.

The most prominent example of a noninjectable formulation is intranasal naloxone. The first intranasal product was an aftermarket atomizer that was added to the standard naloxone injection ampule, which allowed the user to spray naloxone into nasal passageways (Doe-Simkins et al., 2009). Intranasal naloxone has now been formally developed into a recently FDA-approved product (Krieter et al., 2016). Possibilities for developing transmucosal formulations, such as sublingual or buccal products, are also being explored. Although the bioavailability of these formulations is significantly lower than an injectable formulation (Rosado et al., 2007), pharmacological studies have reported approximately 10–25% of naloxone administered transmucosally is absorbed and that high doses are able to reverse opioid-agonist effects in humans (Weinberg et al., 1988; Preston et al., 1990; Harris et al., 2000). Mucodel Pharma is currently developing a buccal formulation of naloxone. This reflects a growing interest in the evaluation of additional noninjection formulations of naloxone for bystander use. For instance, a systematic review recently discussed the value of additional noninjectable methods for delivering naloxone, and advocated for further research and development of intranasal, sublingual, and buccal formulations (Strang et al., 2016).

What is not yet known is what naloxone formulation type(s) nonmedical persons would prefer. This is a critical issue because reticence to administer a specific naloxone formulation may impede any public health impact that increasing access to naloxone could have on reducing fatal overdoses. Information on administration preference is also important for companies developing new formulations of naloxone, and could help inform the development of package inserts and instructional guidance regarding the utilization of these new products. This manuscript describes the outcomes of two independent surveys of individuals who are receiving opioids for pain management and were asked about their preference for administering different formulations of naloxone for opioid overdose reversal.

2. Methods

2.1 Respondents

Respondents were recruited in two independent cohorts. Both cohorts had to report currently taking a prescribed opioid for their pain and being 18 or older to be eligible for the study; cohort 1 also had to report experiencing pain for three months or more. Cohort 1 was recruited in 3/2015 and Cohort 2 was recruited between 4/2017 – 8/2017. Both cohorts were recruited from the online crowd-sourcing program Amazon Mechanical Turk (MTurk) (Buhrmester et al., 2011). Interested individuals (“workers”) responded to a human intelligence task (“HIT”) request to participate in a survey on “health behaviors”. The survey was restricted to individuals who lived within the United States and who had 80% approval ratings from their previous completion of HITs. The specific nature of the survey and its eligibility criteria were concealed to prevent individuals from misrepresenting themselves to gain entry into the survey. Respondents (N=4,639) completed an eligibility survey (N=3,157 in Cohort 1; N=1,482 in Cohort 2) and those who met criteria (Total N=673; N=501 in Cohort 1, N=172 in Cohort 2; 14.5% of those completing eligibility survey) were advanced to the primary survey. Respondents were compensated up to \$5.00 for primary survey completion. Respondents provided responses anonymously and were instructed that their completion of the survey items served as their consent to participate in the study. The Johns Hopkins School of Medicine Institutional Review Board acknowledged both surveys as exempt from human subject research.

2.2 Study Methods

Methods were identical across both cohorts. Respondents completed a brief demographic questionnaire to characterize the sample and were then provided with the following introductory statement: “Naloxone (Narcan) is an FDA-approved medication that can be administered to someone who is overdosing from opioids like heroin or prescription pain medications. Naloxone can reverse the effects of an overdose and can help the person to survive. If you give naloxone to someone who does not have any opioids in his or her body, then it will not produce any side effects. Naloxone is not addictive in any way.”

Respondents were then asked the following two questions regarding their naloxone preference: 1) “Which of the following methods would you be willing to use to administer naloxone to a person who you suspected may be overdosing from opioids like heroin or prescription pain medications? Please select all that apply” and the following six options

were provided: “Intravenous (IV): An injection directly into the vein; Intramuscular (IM): An injection directly into the muscle; Intranasal (IN): A spray that squirts naloxone into the nose; Sublingual (SL): A tablet that you place under someone’s tongue; Buccal: A patch that you stick to the inside of someone’s cheek; and None: I would never be willing to administer naloxone to someone I believed was overdosing”; and 2) (presented only when “None” was not selected) “Rank your preference for different formulations with #1 being the highest or most preferred and #5 being the lowest or least preferred method”. Product description was intentionally kept brief and did not discuss other potentially relevant features such as cost or availability of the naloxone products in an attempt to focus respondents’ choices on the route of administration, which was the primary attribute of interest for this study.

2.3 Data Analyses

Data are presented descriptively. Participant demographics were compared between cohorts using chi-square analyses with z-test post-hoc comparisons as appropriate, and post-hoc logistic regressions analyses were used to determine whether any demographic or drug use characteristics were associated with preference for injectable versus noninjectable formulations of naloxone.

3. Results

Demographics are shown in Table 1 and preference ratings are presented in Figure 1 for both cohort 1 (left side) and cohort 2 (right side). Cohorts are presented separately to demonstrate the similarity in results across two independent samples. Respondents in cohort 1 stated they were more willing to administer noninjectable formulations of naloxone (intranasal, sublingual, buccal) over injectable formulations and this same pattern was evident in cohort 2 (Figure 1, top panel). Only a small percentage of respondents in both cohorts stated they would not be willing to administer any naloxone product (8.9% – 9.8%). When asked to rank all possible formulations of naloxone on a 5-point scale from most to least preferred, both cohort 1 and 2 ranked the noninjectable formulations (intranasal, sublingual, and buccal) as more preferable than the injectable formulations (Figure 1, middle panel). When asked to select their most preferred route of administration, respondents in both cohorts overwhelmingly selected the intranasal product. Specifically, 44.9% of respondents in both cohorts rated the intranasal formulation as their number one preferred route for administering naloxone (Figure 1, bottom panel). None of the demographic or drug use characteristics examined were significantly associated with preference for injectable versus noninjectable formulations of naloxone.

4. Discussion

This study evaluated preference for naloxone formulations among patients who are being prescribed opioids for pain management. Results from two independent surveys showed these individuals reliably preferred noninjectable (intranasal, sublingual, buccal) formulations of naloxone more than injectable (intravenous, intramuscular) formulations for reversing opioid overdose. This was evident in their reports of willingness to administer the product, rankings of most to least preferred product, and categorization of intranasal as being the overall most preferred route of administration. The similarities in responses across

the two cohorts is remarkable, especially considering that data were collected two years apart and that considerable media attention has been paid to the opioid epidemic in the interim. The interest in an intranasal product supports the recent FDA approval of an intranasal product (Narcan™; Adapt Pharmaceuticals) (Traynor, 2016), which is a commercially available intranasal product that does not require application of an atomizer to an injection ampule to administer intranasally. While Narcan™ is the only currently FDA-approved intranasal product, a recent international patent search identified patents for new intranasal and sublingual formulations of naloxone (McDonald et al., 2017), and recently published studies have reported the pharmacokinetics of new intranasal (Gufford et al., 2017; Mundin et al., 2017; Tylleskar et al., 2017) and buccal products (Alqurshi et al., 2016), indicating substantial interest in development of noninjected naloxone formulations.

Initial preference for a product formulation type is an important consideration in the development of medications, however there are other aspects that are also highly likely to impact product uptake and ultimate public acceptance that were not evaluated here. For instance, while this survey ensured that all respondents had a basic understanding of how the naloxone product would be administered, respondents were not provided with information regarding the relative speed and effectiveness of the different products, and this information is also likely to impact preference. Further, the manner in which the product is packaged and the training necessary to use the product will also impact preference ratings and ultimate product acceptance and uptake. A further weakness of the study is that responses were based on verbal descriptions of the products; responses might differ with experience or with different descriptions.

Interestingly, a small percentage of respondents stated they would not be willing to administer naloxone in any formulation; more research on this group is warranted as it could help inform product descriptions and educational efforts to increase acceptance of naloxone in nonmedical settings. It should also be noted that these data did not specifically mention the recently FDA-approved Evzio naloxone autoinjector, and it is possible that the autoinjection nature of that product might reduce concerns regarding provision of injections.

These analyses were limited by the inability to verify the eligibility criteria of the respondents. Further, the description of each formulation that was provided to the respondents was limited in scope. This was done for strategic reasons to prevent any experimenter bias from being detected and so that decisions would be made with the belief that formulations were equally viable, thereby restricting decisions to the route by which the product was administered instead of features such as price, availability, or speed of effect. Yet, such features are important considerations for decision-making and providing additional information may have changed the results; more research on this topic is therefore warranted. The experience of using the product may also influence preference. Finally, these data only represent the opinions of persons who have experience using opioids for pain management. It will be necessary also to evaluate naloxone formulation preference for other relevant bystander groups, such as family members, first responders, and educators, who may or may not have direct experience using opioids but are in positions where they may need to learn to administer naloxone for overdose reversal.

5. Conclusion

Overall, these data indicate that patients receiving opioids for pain management report greater willingness to administer and preference for noninjectable versus injectable formulations of naloxone to reverse opioid overdose. Preference for formulation type represents one of the many factors that need to be considered in the development of additional naloxone products, and these study results support the conclusions of a recent systematic review (Strang et al., 2016) that proposed the development of noninjectable (e.g., intranasal, sublingual, buccal) naloxone products.

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Highlights

- Many different formulations of naloxone for overdose reversal are under development
- Patients using opioids for pain were surveyed on naloxone administration preference
- Noninjectable formulations (SL, IN, buccal) were preferred to injectable (IV, IM)
- Intranasal was the most preferred formulation overall
- Research examining the impact of other variables on preference is warranted

Figure 1.

Preference for naloxone formulation from two independent samples of respondents who are receiving opioids for pain management (N=673). Cohort 1 (N=501) is presented on the left and cohort 2 (N=172) is presented on the right. Cohorts are presented separately to demonstrate the similarity in outcomes. Values represent: A) Percent of respondents willing to administer different formulations of naloxone; B) Mean rank of formulations from Most (1) to Least (5) preferred, bars represent standard error of the mean (SEM); and C) Percent of respondents who endorsed a formulation as the most preferred. X-Axis represents formulation types: IV=Intravenous, IM=Intramuscular, IN=Intranasal, SL=Sublingual. Graphs B and C only present data from respondents who did not endorse “None” in Graph A.

Table 1

Participant Characteristics	Total Sample	Cohort 1	Cohort 2	
	(N=673)	(N=501)	(N=172)	p-value
Male (%)	44.4	44.7	44.0	0.93
Age in years (%)				<.001
18–25	16.1	13.0*	25.6*	
26–35	40.5	39.7	42.9	
36–45	24.2	13.7*	24.2*	
46–55	11.8	11.9	11.8	
56 or older	7.3	6.0	7.3	
Current living area (%)				0.38
Urban	38.4	39.9	33.9	
Suburban	45.6	44.3	49.4	
Rural	16.0	15.8	16.7	
Employed full or part time (%)	83.9	85.4	73.2	0.06
Have health insurance (%)	89.1	90.6	84.5	0.03
Duration of opioid prescription (%)				0.07
1 year or less	59.6	57.1	67.3	
1–4 years	28.1	29.9	22.6	
5 years or more	12.3	13.0	10.1	

P-values in right column are based on between-cohort chi-square comparisons. Astericks denote significant ($p < .05$) sub-group differences based upon z-test comparisons.