Harm Reduction Coalition comments on naloxone dosing in community settings

Submitted for the October 5th, 2016 joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

September 21, 2016

Harm Reduction Coalition is a national advocacy and capacity-building organization addressing the intersection of substance use and health. Harm Reduction Coalition has extensive experience with naloxone in community settings, and has worked for years to expand access to naloxone to reverse the opioid overdose epidemic. Harm Reduction Coalition’s longstanding Drug Overdose Prevention and Education (DOPE) Project in California and SKOOP Project in New York have trained and equipped with naloxone thousands of laypersons, particularly people who use drugs. These programs have also provided technical assistance to community-based programs across the country, provided training to law enforcement, worked with pharmacies to establish standing orders for naloxone, developed training programs in jails and prisons to provide naloxone to incarcerated persons upon release, and supported policies, legislation and funding at the state and federal levels to expand access to naloxone. Harm Reduction Coalition also coordinates a national survey on community-based naloxone programs, with results published in CDC’s MMWR.

The following comments draw upon Harm Reduction Coalition’s broad experience with community naloxone programs.

The expansion of access to naloxone to laypersons for use outside of hospital settings has become a core strategy at both the federal and state levels in responding to the prescription opioid and heroin overdose epidemic. This strategy emerged twenty years ago in the harm reduction community, pioneered by syringe exchange programs working with people who inject drugs. A number of early feasibility studies and pilot projects established the viability of layperson administration of naloxone to reverse opioid overdoses, and subsequent research has validated this approach on broader scales and in diverse settings. As of June 2014, surveyed community-based programs had trained and equipped over 150,000 laypersons – primarily people who use drugs – with naloxone since 1996, and received reports of over 26,000 successful opioid overdose reversals. In recent years, the overwhelming majority of states have enacted legislation to facilitate broader access to naloxone, a growing number of pharmacies have made naloxone available through standing orders, prescribing and co-prescribing of naloxone to patients at increased risk of opioid overdose has been recommended by CDC and professional societies and implemented by the Veterans Administration, and federal and state funding to support broader access to naloxone has increased in parallel with the growth of community-based naloxone programs.

overdose education and naloxone distribution programs alongside measures to train and equip law enforcement and other first responders.

These efforts have collectively contributed to saving countless lives. However, surveillance data indicates that opioid overdose mortality continues to increase, driven in recent years by an increase in heroin overdose deaths and most recently by deaths involving illicitly manufactured fentanyl. Anecdotal reports suggest that a proportion of overdose reversals involve administration of multiple doses of naloxone, and some have suggested that illicitly manufactured fentanyl and fentanyl analogues in particular may require greater amounts of naloxone than have typically been the case with heroin and prescription opioid overdoses. These disturbing trends pose a number of dilemmas for overdose education and naloxone distribution programs and policymakers, particularly in geographic regions experiencing an increase in fentanyl-involved overdoses.

Unfortunately the data to support dosing recommendations remains limited. Available pharmacokinetic data can provide insight into several traditional parameters of potential interest, including $t_{\text{max}}$, $C_{\text{max}}$, AUC and $t_{1/2}$. However the questions posed by overdoses involving illicitly manufactured fentanyl, or otherwise requiring multiple doses of naloxone, are fundamentally pharmacodynamic in nature. There is a severe paucity of PD data to guide dosing recommendations, and as the illicit opioid and heroin market evolves, it is unclear which possible PK/PD models would be most predictive and relevant to optimize dosing. For ethical as well as practical reasons, it would not be possible to assess pharmacodynamics in a typical controlled clinical trial. Therefore the best available data comes from field experience with naloxone administration in community settings.

Four naloxone products have generated a substantial amount of field experience outside of hospital settings, with differing concentrations and modes of administration: generic intramuscular (0.4 mg/mL), generic (2 mg/2 mL) administered intranasally off-label, branded auto-injector (0.4 mg/0.4 mL), and branded intranasal (4 mg/0.1 mL). Community-based overdose education and naloxone distribution programs providing the generic products generally include two doses per overdose reversal kit, and both branded products come packaged in two-dose kits. The branded products received FDA marketing approval in mid-2014 and late 2015, respectively; therefore, to date the majority of field experience in community settings derives from the generic products. National survey data from 2013, prior to approval of the branded products, indicates that roughly half of responding community-based overdose education and naloxone distribution programs reported distributing only generic injectable naloxone, over a third only provided generic off-label intranasal naloxone, and the remainder provided both.\(^2\) Selection of naloxone product for community distribution generally prioritizes affordability and availability (e.g. through product donation), with other parameters playing a secondary role. Over the past two years, community-based programs have accumulated some field experience with the newer branded products.

Community-based programs have an array of methods to collect data on field experience; however, protocols for systematic data collection are not standard across programs, and some programs are limited in data collection capacity and infrastructure. The primary means of collecting field experience data comes from self-reports by laypersons of overdose reversal attempts; secondary means include informal on-going interactions with program participants who have received overdose reversal training. Some efforts to collect prospective data on naloxone use by laypersons have been initiated in recent years and can further supplement and contextualize qualitative accounts from community-based
programs. Field experience data have inherent gaps and limitations, as well as limits in the ability to infer comparisons between products on clinical parameters (i.e. relative safety and efficacy in community settings). However the value of field experience data should not be underestimated, and reflects our best understanding of the collective and cumulative wisdom and experience of laypeople – and particularly people who use drugs – with naloxone administration.

By community standards, currently available field experience data indicates that all four available naloxone products fall within acceptable safety and effectiveness thresholds, though field experience is still accumulating for the newest branded intranasal product. Available anecdotal data indicates that a minority of overdose reversals entail administration of multiple (> 2) doses of naloxone, and there is some perception that multiple dose administration reports may be more common in geographic areas with higher rates of overdoses involving illicitly manufactured fentanyl. However, it is important to contextualize this information:

- Reports of multiple dose administration have also come from geographic areas with little to no documentation of fentanyl-involved overdoses
- Reports of multiple dose administration are not limited to specific products or concentrations, nor is comparative data available to indicate whether one product/concentration may be more or less likely to require multiple doses to achieve effect
- The number of doses administered is subject to variability in layperson practice; in particular, some laypersons may not wait for an interval to monitor whether the subject responds to the initial dose(s) due to concern or panic, and thus administer more doses than necessary to achieve a response
- To the extent that certain areas with higher rates of fentanyl-involved overdose may overlap with increased reports of multiple dose administration, it is difficult to rule out the possibility that users are primed to adopt a more aggressive dosing strategy – that is, that the perception of danger from fentanyl overdose biases laypersons towards administering more doses more rapidly

Harm Reduction Coalition’s DOPE Project assessed layperson naloxone utilization during a fentanyl overdose outbreak in San Francisco, CA in 2015. The DOPE Project began receiving reports from drug users via syringe exchange programs of a batch of white powder heroin-like drug that was circulating through a specific downtown San Francisco neighborhood in late June and early July of 2015 that were causing multiple, rapid overdoses. Users referred to the drug as "china white", believing it to be a powder form of heroin. Anecdotal descriptions of their experience with the drug indicated that it could possibly be fentanyl (short acting, powerfully strong, causing rapid respiratory depression). DOPE Project staff obtained a sample for laboratory testing, and results confirmed it as fentanyl. Between June and October 2015, this batch of fentanyl caused several hundred non-fatal overdoses in one downtown neighborhood, resulting in over 300 overdose reversals with naloxone that were reported to the DOPE Project by drug users who were trained and equipped with naloxone. In 76 of these reversal reports, off-label intranasal naloxone was used, with an average of 1.42 doses administered. In 136 of the reversals, generic injectable naloxone was used with 1.58 average doses administered. In another 136 cases, naloxone auto-injectors were used with an average of 1.7 doses (multiple forms of naloxone were used in some reversals). 15% of the reversals responded to naloxone administration in under one minute, 29% took 1-3 minutes, 23% took 3-5 minutes, and 23% took more than 5 minutes. There was one confirmed fentanyl related death in this period of time.
For additional perspective, the CDC conducted an EpiAid investigation in Ohio to evaluate risk factors for fentanyl-involved overdose deaths. As part of the investigation, CDC reviewed EMS data on naloxone administration, including administration of multiple doses (defined as two or more) from January 2014 through March 2015, a period of significant increase in fentanyl-involved overdose fatalities. CDC found that:

Ohio EMS reported that 2,669 EMS patients were administered naloxone two or more times in 2014, referred to as multiple naloxone administrations. The rate of multiple naloxone administrations in 2015 appears slightly higher than in 2014 with 1,571 EMS patients receiving multiple naloxone administrations by mid-year. From another perspective, the percent of patients receiving naloxone who received multiple naloxone administrations increased from 21% in 2014 to 25% in the first half of 2015.

The number of patients receiving multiple naloxone administrations steadily increased through 2014 with a 28% increase from the first quarter of 2014 to the final quarter. The rate of increase slowed in 2015 with multiple naloxone administrations increasing only 5% from the last quarter of 2014 to the second quarter of 2015 (See Figure 5). This indicator did not parallel the tripling in fentanyl-related deaths from June 2014 to April 2015 or the pattern in fatal overall opioid-related deaths.3

The CDC analysis of Ohio EMS data during a period of dramatically increasing fentanyl-involved overdose mortality complicates the emerging perception of a fentanyl overdose crisis that would invariably require administration of multiple naloxone doses. However, while suggestive, it remains unclear whether the Ohio trends will be sustained, and the degree to which they are generalizable. Ultimately these findings highlight the substantial gaps in both relevant PK/PD modeling and robust protocols for collection of field experience data to inform optimal dosing recommendations at this time. While it is apparent that some overdose reversals entail multiple dose administrations, considerable ambiguity surrounds the context and circumstances of these events, and the degree to which they reflect significant trends or impact morbidity and mortality outcomes.

The dosing dilemmas are complicated by the challenges of the naloxone market for community-based overdose education and distribution programs, which still remain the primary naloxone source for laypersons despite recent initiatives on co-prescribing and pharmacy access. Community programs have to balance a range of potential considerations in sourcing naloxone, including ease of use, training and assembly requirements, and end user acceptability. Some of these factors are distinct to particular target populations. For example, programs providing naloxone to people who use drugs frequently report the desirability of formulations that allow for titration of naloxone dose, to mitigate against the possibility of an excessive dose precipitating acute opioid withdrawal. Titration is possible with the generic injectable and intranasal products; the branded auto-injector and intranasal devices deliver a fixed dose.

Ultimately, an implicit axiom of community programs still holds true: the best naloxone device is the one you can access. In recent years, prices for the generic products have increased substantially, while the branded products have been priced at levels higher than what community-based programs were paying even a few years ago for generic naloxone. The overall pricing trends have substantially eroded the purchasing power of community programs, even with increased availability of public funding. These pricing dynamics further constrain the ability of programs to consider providing more than two doses of naloxone in response to signals of increased reversals involving multiple dose administration. Similar market dynamics are not unique to naloxone and have been observed across the branded and generic pharmaceutical sectors. However, community-based distribution of naloxone poses a distinct challenge, as price increases are not buffered or absorbed by third-party payers. At the same time, novel branded products have been priced at higher levels for a traditional health care marketplace reliant on formulary coverage by third-party payers. While available data suggests that naloxone prescribing and dispensing has been trending upwards, these channels remain relatively negligible forms of access compared to the volume of naloxone distributed by community programs.¹

While pricing consideration fall outside of FDA’s purview, they take on heightened salience in the context of discussing naloxone dosing recommendations. Any such recommendations would need to consider several stakeholders, including current and future product sponsors and manufacturers, prescribers, and patients. However, the impact of new dosing recommendations would be felt most immediately by the array of programs and purchasers which acquire naloxone directly for distribution to laypersons and first responders. This segment of the naloxone market is most sensitive to price, and has the least flexibility in response to any recommendations which would either narrow the range of available products deemed to meet dosing criteria, or providing additional doses beyond the current two-dose standard. None of these stakeholders would support providing suboptimal doses or devices if better alternatives were available; however, a recommendation to provide, for example, four doses instead of two as standard would invariably result in trade-offs between the number of people who can be equipped with naloxone and the number of doses they have available. There is no reason to believe that providing fewer laypeople with more naloxone doses will reduce opioid overdose mortality, and much reason to fear the opposite outcome. Similarly, any recommendation to encourage use of certain products or concentrations while discouraging or omitting others would result in similar access trade-offs. In addition, any such dosing recommendations could prematurely delegitimize certain products despite ample field experience. These scenarios represent the very tangible stakes of this discussion, and the considerable risks of setting policy in an environment where the hypothetical risk of suboptimal dosing is overshadowed by the material reality of suboptimal access.

Harm Reduction Coalition offers the following conclusions and recommendations:

- Federal and state governments must commit to mobilizing additional resources to scale up and support adequate and sustainable supplies of naloxone for community distribution.
- FDA, CDC, and NIDA should collaborate to build capacity and provide resources for more thorough and real-time field experience data collection on naloxone administration patterns across community programs.

Decisions on modifying dosing and formulation should be guided by the best available local epidemiologic and field experience data. There is a role for federal public health officials in consulting with community programs and other stakeholders in identifying and evaluating potential criteria and triggers for modifying naloxone strategies at the local level.

In its regulatory capacity, FDA should continue to support a robust ecosystem of diverse naloxone products and continue to encourage new entrants to the naloxone market, for both generic and novel products. FDA should particularly prioritize facilitating the development and approval of low-cost naloxone products, including injectables, and exercise discretion in applying latitude to evaluating the PK profiles of new products by incorporating relevant field experience.

The Advisory Committees and FDA should exercise caution and restraint in advancing new dosing recommendations or labelling language that undermines confidence in products with long histories of successful field experience.

Harm Reduction Coalition highly commends FDA’s efforts to facilitate manufacturers in pursuing approval for an over-the-counter naloxone product. Harm Reduction Coalition encourages FDA to expand these efforts to include developing a model Drug Facts Label (DFL) for generic intramuscular naloxone. Harm Reduction Coalition also notes that availability of an OTC product will complement and supplement, but not supplant, the need for continued and increased support for community-based overdose education and naloxone distribution programs.

In summary, Harm Reduction Coalition appreciates the opportunity to share our community’s insights and experiences with the Advisory Committees, and remains committed to partnering with FDA and other federal agencies to end the opioid overdose epidemic.

Yours respectfully,

Daniel Raymond, Policy Director on behalf of Harm Reduction Coalition

Contact:

22 W. 27th Street, 5th Floor
New York, NY 10001
Direct: (212) 377-9121
raymond@harmreduction.org
www.harmreduction.org