Q&A from the Opioid Abatement Academy session titled "Virginia's NEW naloxone distribution plan and statewide contract for naloxone purchase" held on August 29, 2024.

Administrative Note from the OAA: Due to technical difficulties during the live webinar, one of the panelists, Dr. Alexis Page, was not able to connect. Dr. Page had been prepared to answer clinical questions, but since she was not able to join the webinar the host encouraged attendees to type their questions into the "Q&A" feature so that written responses could be provided later.

This document provides the questions that were submitted by webinar attendees and subsequent answers provided by Dr. Page and VDH pharmacy staff.

1. **Can you speak about injectable vs. intranasal naloxone - How do differences in dosage impact the people receiving the naloxone? Is one more effective?**

   Dosages of medications administered through different routes (intranasal vs. intramuscular) cannot be compared 1:1 as the medication is metabolized differently based on the route of administration. For example, doses of intramuscular (IM) naloxone can range from 0.4mg to 2mg while doses for intranasal (IN) naloxone can range from 3mg to 8mg. IM naloxone is absorbed quickly and has a longer duration of action due to the depot of drug in the muscle. IN naloxone is absorbed slightly slower and is metabolized more quickly than IM naloxone. Studies suggest that the slower onset of action for IN naloxone is offset by the extended length of time it takes to administer an IM dose. In other words, IM naloxone works more quickly in the body, but IN naloxone is quicker to administer since it is faster to administer a nasal spray then to prepare and administer an injection.

2. **Can you speak about how nalmefene works differently in the body compared to naloxone? Thank you!**

   Nalmefene and naloxone both work the same way in the body. Both medications act as a competitive opioid receptor antagonist, displacing opioids bound to opioid receptors in the brain. Nalmefene binds tighter to the opioid receptor than naloxone, extended its duration of action.

3. **Please explain again why a prescription naloxone cannot go in a first aid kit.**

   Prescription naloxone may be stored in a first aid kit, as long as it is being stored in compliance with manufacturer storage conditions. If acquired from VDH, storage conditions must be compliance with terms and conditions of VDH

agreement. Controlled substance registrants (partners with CSR) need to adhere to 18VAC110-20-710 for the storage and security of controlled substances, such as prescription opioid reversal agents as well as VDH agreement terms.

4. **To be included in vending machines and first aid kits, why does the product need to be OTC? Why can't it be any product that is covered by the State Standing Order?**

   If utilizing the Statewide Standing Order to provide **prescription medication** to individuals, medications must be dispensed in compliance with the Virginia Board of Pharmacy Naloxone Protocol. Vending machine programs may not be able to comply with the requirements of the Board of Pharmacy Protocol, which requires the following:

   - The dispenser shall affix a label to the naloxone container that bears the name and strength of the dispensed naloxone, directions as indicated on the standing order, name of prescriber, date of dispensing, and name and address or telephone of dispensing entity. The name of the recipient does not have to appear on the label. Optional items that may be dispensed that do not require labeling include rescue breathing masks and latex-free gloves.
   - The dispenser shall maintain a record of dispensing indicating the name of the recipient, the name, strength, and quantity of naloxone dispensed, date of dispensing, and name or initials of dispenser. Such record shall be maintained for two years from the date of dispensing.
   - If the dispenser is dispensing an injectable naloxone formulation with a hypodermic needle or syringe, the dispenser shall comply with the requirements of Board of Pharmacy Regulation 18VAC110-20- 735, in lieu of the requirements listed above in section (i) and (ii).
   - The naloxone, hypodermic needles, and syringes shall be stored and transported under appropriate storage conditions in accordance with the manufacturer's directions to protect from adulteration and unlawful use.

   OTC medication does not been to be dispensed in compliance with this protocol as the protocol pertains only to prescription opioid reversal agents. Please reach out to pharmbd@dhp.virginia.gov if you have additional questions about the protocol.

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5. **Chemically, what is the difference between narcan/naloxone compared to nalmefene? And why the change in product for the same purpose?**

   Naloxone and nalmefene are structurally very similar but nalmefene has a slightly different carbon chain, which changes the affinity of the chemical to its receptor. It's a common practice in the pharmaceutical industry to take one chemical structure (e.g., naloxone) and modify it to create a new chemical with potentially different chemical properties. In this instance, nalmefene is structurally similar to naloxone, but has differing chemical properties that provides different clinical effects, such as more rapid onset of action and time to peak.

6. **Which products does VDH currently offer through its free naloxone distribution program? Are there any plans to expand the options that are offered?**

   Currently, VDH provides OTC generic 4 mg nasal naloxone to eligible partners. Select partners, i.e. authorized comprehensive harm reduction sites, are also eligible to receive intramuscular naloxone (injectable naloxone).

   In the state budget, VDH has received funding for naloxone, with $1 million allocated to purchase 8 mg naloxone. VDH will make 8 mg naloxone available to some partner this fiscal year.

7. **Should we be asking what the product dating is before receiving vs. just assuming Narcan has a longer shelf live over others? I am assuming others will have longer shelf very soon and at a lower price.**

   Yes! Always ask about the dating for a particular order of products before placing an order. This is because the shelf life dates from the date of manufacture; the vendor can provide you with the most accurate dating for the product you will actually receive. Many products are also receiving approvals for later expiration dates from the FDA; the vendor will provide the current expiration date.

8. **I work with a Non Profit coalition partnering with local CSB, VDH, Free Clinic, DSS, Homeless services/ transportation and Community College. I provide REVIVE training to staff/community members and students. How do I best provide Naloxone to participants?**

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Please contact the program at opioidreversal@vdh.virginia.gov.

9. **Do the prescription versions not have the instructions on the box?**

   OTC medications have more detailed instructions on the packaging. Prescription products often do not include instructions for use, as it is expected they will be dispensed by an authorized dispenser, affixing appropriate labeling with instructions. OTC medications are required by the FDA to contain many items on the packaging, including indicated use, warnings, and when not to use. Prescription opioid reversal agents may include instructions for use on the box but not all do. It is the responsibility of the dispenser to ensure that recipients understand how to use prescription opioid reversal agents.

10. **Are you aware of jurisdictions (local governments) that have narcan in county first aid or naloxboxes as part of their employee safety efforts (over the counter medication - and in places like government offices, libraries, community centers, etc.). We are working on an effort, that would include a brief employee training, and would like to learn from other jurisdictions that may have this as a part of their employee training, policy, and site first aid/safety station.**

    We are not aware of any such jurisdictions. Please keep us informed of your efforts; we would be happy to share sample products with other jurisdictions!

11. **Can you elaborate on why 8mg naloxone was included in the state budget?**

    This was a decision made by legislators; we cannot speak to why this decision was made.

12. **The OTC products you are sending to outside organizations should we dispose of them based on the expiration date**

    Please return any expired product that you received from VDH to VDH.

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13. **There was a JAMA study that found that administering 8mg upfront reduced the period the individual spends in a hypoxic state and reduced the risk of cardiac arrest. Can you speak to that study?**

    Administrative Note from the OAA: There was a discussion on the webinar in response to this question. During this discussion OAA host Tony McDowell typed the following in the Q&A for attendees:

    > *"OAA has access to several published research papers demonstrating that 8mg is not more effective than 4mg."*

    After the webinar, Mr. John Paul Fiore (government alliances director for Hikma Community Health) subsequently requested those papers and Mr. McDowell responded with the following:

    - https://pubmed.ncbi.nlm.nih.gov/38127361/
    - https://journals.sagepub.com/doi/10.1080/08897077.2018.1449053
    - https://www.harmreductiontherapeutics.org/wp-content/uploads/2024/08/High-Dose-Naloxone-Statement.pdf
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8454200/#:~:text=The%20development%20and%20marketing%20of,can%20impact%20thousands%20of%20individuals.
    - https://www.health.ny.gov/diseases/aids/general/opioid_overdose_prevention/docs/naloxone_data_brief.pdf
    - https://scholars.uky.edu/en/publications/examination-of-naloxone-dosing-patterns-for-opioid-overdose-by-em
    - https://doi.org/10.1080/15563650.2023.2283391

    Mr. Fiore forwarded an analysis of these papers, completed by Hikma, and Mr. McDowell offered to provide that analysis as part of these notes. The analysis is provided below verbatim.

Amount of naloxone used to reverse opioid overdoses outside of medical practice in a city with increasing illicitly manufactured fentanyl in illicit drug supply (Bell et al., 2019)

- Study actually supports making higher doses of naloxone available given the result that in 43% of overdoses events, multiple doses of naloxone were administered.

Statement Regarding High Dose Naloxone and Long Acting Nalmefene Opioid Overdose Reversal Formulations (New Mexico Letter) (Bhatt et al., 2022)

- Letter does not differentiate between naloxone with nalmefene. Nalmefene (Opvee) is a separate medication, with a significantly longer half-life (e.g., 11.4 hours) compared to any formulation of naloxone, including Kloxxado (half-life: 1.76 – 2.69 hours). This difference is essential to note.
- Any dose of naloxone carries the warning of precipitated withdrawal, including the 0.4 mg dose. Neither the letter nor the research referenced therein offers evidence that the use of Kloxxado results in more or worse withdrawal symptoms.

Increasingly powerful opioid antagonists are not necessary (Hill et al., 2021)

- Not a research study, but rather a brief review of previously published articles. Ironically, it downplays or overlooks data in the cited studies that could support making higher doses of naloxone more widely available (Carpenter et al., 2020; Geiger et al., 2020; Purssell et al., 2021), and omits recent data describing the non-fatal outcomes of those who survive an opioid overdose but experience hypoxia (lack of oxygen to the brain caused by the overdose), as reported in the Department of Health and Human Services report (2019).

Examination of naloxone dosing patterns for opioid overdose by emergency medical services in Kentucky during increased fentanyl use from 2018 to 2021 (Rock et al., 2024)

- Although the Kentucky EMS data did not show a dramatic increase in naloxone doses from 2018-2021, it is important to note that this data was collected during a time when fentanyl was the primary driver of opioid overdoses. In contrast, a national EMS study from 2015 (pre-fentanyl) to 2020 (fentanyl) did show an increase in multiple doses of naloxone, indicating more naloxone is required to reverse overdoses now than before fentanyl became prevalent.

American College of Medical Toxicology and the American Academy of Clinical Toxicology position statement: nalmefene should not replace naloxone as the primary opioid antidote at this time (Stolbach et al., 2023)

- Document pertains to nalmefene, not naloxone. Since Kloxxado is a naloxone product and does not contain nalmefene, this document is not relevant to the current discussion.

Intranasal Naloxone for Opioid Overdose (Taylor et al., 2024)

- Does not present any studies or data contraindicating the use of the 8 mg naloxone HCl medication, Kloxxado. The only comment pertains to its lack of over-the-counter availability, which is not a safety concern but rather due to the fact that the 8 mg formulation was never submitted to the FDA for over-the-counter approval, unlike the 4 mg option.
- One cited study (Dietze et al., 2019) found that 0.8 mg of naloxone HCl administered via intramuscular injection was more effective than intranasal administration. This is expected, as

medications delivered via injection are metabolized differently and may require lower doses compared to intranasal administrations

Naloxone NY Data Brief (2023)

- This is the data brief that the CDC MMWR paper is based on. See email chain below for concerns that Dr. Crèvecoeur-MacPhail shared with VDH staff.

Thank you for the informative webinar yesterday. I wanted to reach out to provide additional research on the use of naloxone. I am also available to address any questions you or your team may have regarding the 8 mg naloxone HCl nasal spray, Kloxxado®. Thank you for your time and consideration and I apologize, in advance, for the long email.

Research Summary

Support for Higher Dose Naloxone Formulations

- Dahan et al., 2024; Strauss et al., 2024; Moss et al., 2020: These studies discuss the naloxone doses required to effectively reverse an overdose, thereby preventing death (defined as cardiac arrest in the study) and hypoxic brain injury.
- Abdelal et al., 2022; Avetian et al., 2018: Data on community reversals indicate multiple doses of 4mg intranasal naloxone are used to reverse the overdose.
- Marks et al., 2023; Strickland et al., 2022: Research shows a preference for the 8mg intranasal naloxone among bystanders and opioid users compared to the 4mg formulation.

Thus, there is growing evidence and user preference supporting the availability of higher-dose naloxone formulations like the 8mg.

Dangers of Hypoxia in Opioid Overdoses

- Winstanley et al., 2022; Zibbell et al., 2019: These reviews highlight the significant risks of hypoxia associated with opioid overdoses, including brain and organ damage.
- Strauss et al., 2024: Administering 8mg naloxone upfront (defined in the study as 2x 4mg) versus administering one dose of 4mg, then waiting before administering the second dose of 4mg could reduce the time a patient spends in a hypoxic state, which is crucial, especially with fast-acting opioids like fentanyl.

The risk of hypoxia is something we do not discuss enough when it comes to opioid overdoses. Rapid administration of a higher dose of naloxone medication can be critical in minimizing hypoxia-related injuries during an opioid overdose.

4th Wave of the Opioid Overdose Crisis

- Friedman and Shover, 2023; Ciccarone, 2022: Studies indicate an alarming increase in overdoses involving both fentanyl and stimulants, disproportionately affecting African American, Hispanic, and Native American communities. These communities might not know that the stimulants they use contain fentanyl. Therefore, they are not aware that they should have naloxone with them. In addition, due to the lack of tolerance, these communities might be at greater risk for a fatal overdose.
- Jenkins, 2021: Highlights the heightened risks for rural populations due to limited access to treatment.

The opioid crisis now affects diverse populations and users of non-opioid substances, further underscoring the need for effective overdose reversal options.

Additionally, for opioid-naïve individuals, higher doses of naloxone may be necessary to reverse an overdose effectively, without risk of precipitated withdrawal.

Concerns regarding the interpretation of the CDC MMWR paper comparing naloxone formulations

While the MMWR paper is frequently cited, there are several limitations that raise concerns about its conclusions, particularly regarding the interpretation that 8 mg intranasal naloxone medication, Kloxxado®, causes more withdrawal symptoms compared to 4 mg and offers no additional benefits. Key limitations include:

Insufficient Controls

- The study did not account for the opioid use history of individuals whose overdoses were reversed, such as whether they were frequent, occasional users, or non-users accidentally exposed to opioids.
    - This is critical because withdrawal symptoms occur only in those who are dependent on opioids. With a growing number of overdoses involving stimulant users unintentionally exposed to opioids, this lack of control challenges the claim that 8mg naloxone universally causes more withdrawal symptoms.

Vague Definition of Withdrawal Symptoms

- The paper provides limited detail on the specific symptoms used to define withdrawal, apart from vomiting, which showed no significant difference between the 4mg and 8mg doses.
    - Symptoms like vomiting, nausea, dizziness, headaches, and pain which are attributed to withdrawal, can also result from opioid toxicity or hypoxia, especially in non-dependent individuals. Without detailed background

information on the overdose victims, distinguishing these symptoms is difficult, further complicating the study's claims.

Lack of Specificity in Dose Administration

- The study did not clearly specify the exact number of naloxone doses administered, providing only means and confidence intervals. Since police often administer two doses, the comparison between the 4 mg and 8 mg doses is not directly equivalent. This omission is significant because many individuals likely received at least 8 mg of naloxone, either through a single 8 mg dose or multiple 4 mg doses.
    - To credibly claim that 8 mg causes more withdrawal symptoms or offers no additional benefit, the study would need to directly compare a single 8 mg dose to one or two 4 mg doses. The current data does not support such a conclusion.

In summary, these limitations cast doubt on the paper's conclusions regarding the comparative effectiveness and safety of 8 mg versus 4 mg naloxone. Further research with more rigorous controls and detailed dosing information is necessary to draw definitive conclusions.

Please find additional detailed information in the attachments. And although, the 8 mg naloxone nasal spray, Kloxxado®, might not be appropriate for all communities, it can be an invaluable tool for addressing opioid overdoses. I am available to meet with you or your team to answer any further questions or to discuss the research in more depth.

Thank you again for your time and have a great Labor Day weekend.

Desirée

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