Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Naloxone Update***
-January 2024-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) members were provided updates to naloxone use for opioid overdose reversal. The NPTC added naloxone to the IHS National Core Formulary for treatment of opioid overdoses on May 2014; it was reviewed again on August 2018. A recent NPTC-authored Medication Update regarding FDA's first OTC Naloxone Nasal spray was issued on March 2023. Following this update, the NPTC ultimately **made no modifications** to the IHS National Core Formulary.

Most overdose deaths from 2010-2021 were caused by more than one illicit substance involving various combinations of illicitly manufactured fentanyl with or without stimulants.[1-3] According to data from the U.S. Centers for Disease Control and Prevention (CDC) National Vital Statistics, in 2021, approximately 290 Americans died every day from a drug overdose. In 2021, reportedly 1,358 non-Hispanic American Indian/Alaska Native (AI/AN) people died by overdose, which was the highest rate of any racial or ethnic group.[4]

Discussion:

Naloxone works primarily as a short-acting mu-opioid receptor antagonist to safely and effectively reverse opioid overdoses when immediately administered by trained bystanders. Naloxone via intravenous injection was first FDA-approved in 1971.[5] Since then, there have been additional strengths and formulations developed including intramuscular (IM), subcutaneous (SC), and intranasal (IN) - see page 3. In 2014, Evzio® 0.4mg/0.4ml IM/SC autoinjector was approved, and later reformulated in 2016 to include a higher dosage (2 mg/0.4ml) autoinjector; both have since been discontinued.[5] Naloxone 5mg/0.5ml IM/SC (Zimhi®) was FDA-approved in 2021 and is the only self-contained injectable unit on the market.[6] Naloxone 0.4mg/ml remains available as an injectable option in a vial and for which syringes must be supplied.[7]

Prior to 2023, naloxone was available only via prescription. However, beginning in March 2023, two over-the-counter (OTC) IN naloxone products were approved and are currently available to the public; Narcan® 4mg/0.3ml IN and RiVive™ 3mg/0.3ml IN.[8,9] A higher strength (8mg/0.1ml) naloxone IN product (Kloxxado®) is also available via prescription.

There is lack of high-grade evidence in current literature on the most effective dose and preferred route for naloxone to counteract more potent opioids such as illicitly-manufactured fentanyl and its analogs.[10-12] Literature suggests that the IM naloxone formulation has a quicker onset than the IN route by about 2 minutes which was determined to be clinically significant.[10] However, the IN formulation is more widely used and may be more accessible (given the OTC status of both Narcan® and RiVive™). State specific laws govern naloxone access as there is no Federal Standing Order.[13] Literature suggests that the IN route may require repeat dosing due to recurrence of respiratory depression, and notably that repeated doses were not associated with increased adverse effects apart from precipitated opioid withdrawal.[10-12]

The Department of Veterans Affairs Naloxone Rescue Recommendations for Use of Naloxone provides a framework for developing a system where clinicians assess risk, discuss and offer naloxone to the patient or caregiver about opioid overdose, educate on overdose prevention, recognition, and response which includes proper storage and disposal.[7] It states all parts of this system should be documented in the patient's electronic health record. It further provides naloxone exclusion considerations such as those on hospice/palliative care as well low-risk patients with a history of opioid use disorder (OUD) who are on tramadol, as naloxone may precipitate seizures in cases of tramadol overdose. Intranasal naloxone formulations are preferred unless contraindicated due to nasal septal abnormalities, nasal trauma, epistaxis, excessive nasal mucus, and intranasal damage. Naloxone 8mg IN is recommended for the following:

- High risk patients who have gone through a period of abstinence where physical dependence and chances for precipitated withdrawal is lower:
- Overdose history that included fentanyl or required multiple 4mg IN administrations
- Diagnosis of OUD or substance use disorder (includes those receiving treatment)
- History of prescription opioid misuse or injection opioid use
- Use of illicit drugs due to high potential of adulteration with fentanyl

The American Society of Addiction Medicine (ASAM) National Practice Guidelines' 2020 Focused Update on the Treatment of OUD did not provide specific grades for their recommendations.[14] They do recommend that naloxone be administered in suspected opioid overdoses particularly in cases of overdoses involving pregnant people to save the pregnant person's life. Naloxone training should be provided to all being treated for OUD (especially those with a history of OUD leaving incarceration) as well as to their families. First responders, such as emergency medical services personnel, police officers, and firefighters should be authorized to carry and be trained on naloxone administration.

Naloxone training needs to encompass the effects of xylazine, a veterinary medication diverted and used as an illicit drug adulterant. Data from 2018-2021 on U.S. drug overdose causes showed that xylazine was found in combination with fentanyl (97.1%-99.4%), cocaine (40.2%), heroin (24.1%-29.4%) and methamphetamine (15.5%-18.8%).[16] Xylazine is classified by the Drug Enforcement Agency as a phenothiazine, but exerts its effects as an alpha-adrenergic agonist similar to clonidine.[17,18] This alpha-adrenergic agonist effect leads to extreme sedation and can contribute to respiratory depression that is not reversed by naloxone.[15,16,17,18] It is important to advise naloxone bystander rescuers that xylazine is often found in combination with fentanyl and to administer naloxone if the cause of the overdose is not known as misinformation on naloxone may be present in the community. In particular, respiratory support is advised until emergency medical personnel arrive. Further follow-up care should be advised especially among those who may experience multiple overdose reversals.

Findings:

The FDA's approval of two OTC naloxone products provides the opportunity for improved access to potentially life-saving measures. Continued naloxone training is essential to ensure bystanders are equipped with current information as more overdoses are attributed to illicitly-manufactured fentanyl and respiratory depression reversal is complicated by xylazine. The IHS Manual Part 3: Chapter 35 (updated in September 2023) broadens the first responder definition to include community representatives and volunteers serving tribal communities. The IHS Heroin Opioids and Pain Efforts (HOPE) Committee has compiled strategies to incorporate into routine care to assist sites with equipping patients and community members with naloxone under the banner of harm reduction. Incorporating AI/AN culture should be at the forefront of educational outreach to tribal communities as a means of harnessing its protective elements and encouraging active engagement with community members.[19,20]

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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Table 1 FDA-Approved Naloxone Formulations

ll products are FDAapproved forms of naloxone that the FDA states can be considered as options for community distribution. The Nasal Spray was specifically designed for layperson use, e.g., product labeling includes instructions for layperson use, and is ready-to-use with no assembly required.	Nasal Spray (3mg)	Nasal Spray (4mg)	Nasal Spray (8mg)	Injectable IM (0.4mg) generic	Injection (5mg/05ml)
					
Trade Name	**RiVive**	**Narcan**	**Kloxxado**	**Not applicable**	**Zimhi**
Availability	**OTC**	**OTC**	**RX**	**RX**	**RX**
Strength	**3mg/0.1ml**	**4mg/0.1ml**	**8mg/0.1ml**	**IM: 0.4mg/ml**	**5mg/0.5ml**
Dosing[a]	Spray 0.1ml into one nostril; repeat with second device into other nostril after 2-3 minutes if no/minimal response or until medical assistance arrives			IM: Inject 1ml (0.4mg) at 90º angle into large muscle (upper arm, thigh, outer buttock). Give another dose if no reaction or if breathing stops again	Administer the initial dose intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary,
Pharmacokinetics					
Dose/route	**3mg IN**	**4mg Inb**	**8mg IN**	**0.4mg IM**	**5mg IM/SUBQ**
$T_{1/2}$ (hr)	**1.36**	**2.08**	**1.76-2.69**	**1.24**	**1.5**
Tmax (hr)	**0.5**	**0.5**	**0.25**	**0.38**	**0.25**
Cmax (ng/ml)	**3.69**	**4.83**	**12.3-12.8**	**0.88**	**17.2**
AUC $_{0\text{-inf}}$ (ng·hr/ml)	**6.98**	**7.95**	**16.7-19**	**1.76**	**26.6**
Bioavailability (%)[c]	**42%**	**44.20%**	**41.6-47%**	**100%**	**100%**
Dosing	**Spray 0.1ml into one nostril; repeat with second device into other nostril after 2-3 minutes if no/minimal response or until medical assistance arrives**			**IM: Inject 1ml (0.4mg) at 90º angle into large muscle (upper arm, thigh, outer buttock). Give another dose if no reaction or if breathing stops again**	**Administer the initial dose intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary, and repeat after 2-3 minutes if no or minimal response until medical assistance arrives**
Administration	**1.** Place the patient on their back **2.** Hold the nasal spray with your thumb on the bottom of the plunger and your first and middle fingers on either side of the nozzle **3.** Gently insert the tip of the nozzle into one nostril until your fingers on either side of the nozzle are against the bottom of the person's nose. **4.** Press the plunger firmly to give the dose of naloxone **5.** Remove the nasal spray from the nostril after giving the dose **6.** Get emergency medical help (call 911) **7.** If required use a new nasal spray to give another dose in the other nostril **8.** If the person is breathing normally, turn the patient on their side (recovery position) after giving naloxone			**1.** Place the patient on their back **2**. Remove cap from naloxone vial and uncover the needle **3.** Insert needle through rubber plug with vial upside down **4.** Pull back on plunger and pull down to 1 ml **5.** Inject 1 ml of naloxone at a 90º angle into a large muscle (upper arm/thigh or outer buttocks) **6.** Get emergency medical help (call 911) **7.** If required, use a second dose of naloxone **8.** If the patient is breathing normally, turn the patient on their side (recovery position) after giving naloxone	**1.** Place the patient on their back **2.** Remove the needle cap **3**. Inject into outer thigh and push the plunger all the way down until it clicks and hold for 2 seconds **4.** After use, slide the safety guard over the needle. Put the used syringe into the blue case and close the case. **5.** Get emergency medical help (call 911) **6.** If required, give an additional dose using a new prefilled syringe. **7.** If the person is breathing normally, turn the patient on their side (recovery position) after giving naloxone
Disposal	Dispose of the used nasal spray in a place that is away from children			Dispose of the used syringe in a biohazard sharps container	Give used syringe, contained in the blue case, to the healthcare provider for inspection and proper disposal. **IM:** Biohazard sharps container

Table Adapted from VA Naloxone Rescue: Recommendations for Use February 2022.