Expert Statement Regarding High-Dose Naloxone and Long-Acting Opioid Overdose Reversal Formulations in North Carolina

We, the undersigned, are North Carolina-based experts in overdose reversal. We make the following statement regarding new high-dose naloxone (e.g., "Kloxxado" 8 mg, "Zimhi" 5 mg, "Rezenopy" 10 mg) or long-acting nalmefene (e.g., "Opvee" 2.7 mg, "Zurnai" 1.5 mg) formulations for the treatment of a suspected opioid overdose.

As clinicians, researchers, advocates, and frontline providers working to curb overdose, we are broadly supportive of compassionate, person-centered innovations to prevent overdose deaths.

At this time, and in alignment with other experts from across the US,[1,2,3,4,5] we do not recommend the use of any high-dose or long-acting overdose reversal agents in North Carolina by community groups, treatment providers, EMS and other first responders, or bystanders with access to naloxone. We also support the Call to Action emerging from the national Compassionate Overdose Response Summit.*

Key Points

Over 17 years, successful overdose reversals with naloxone have needed on average only 1.6 doses.

Severe withdrawal from high doses of naloxone leads to more immediate re-dosing of opioids and using alone. Risk of subsequent overdose increases.

Nalmefene nasal spray has never been tested in the current North Carolina drug supply or on people using opioids. Its real-world effectiveness is unknown.

There is no urgency to switch to pharmaceuticals that are untested. Overdose rates in North Carolina are stabilizing with continued distribution of standard forms of naloxone.

The marketing of high-dose naloxone is a historical and global anomaly. Naloxone titrated for overdose reversal, using a 4 milligram or lower dose intranasally or a 0.4 milligram dose intramuscularly, is extremely effective even in the case of overdoses involving fentanyl and other synthetic opioids currently in the drug supply.[6,7,8] Indeed, layperson naloxone distribution was an innovation started by people who use drugs nearly 30 years ago, and long employed by programs serving this population.[9] For decades, 0.4 milligram intramuscular naloxone has been used successfully to reverse overdoses; the evidence of effectiveness for this intervention largely comes from that product.[10] This formulation is listed on the World Health Organization's List of Essential Medications.[11] In Europe and Australia, where fentanyl and nitazines are also present in street drugs, the approved dose of intranasal naloxone is only 1.4 mg. The marketing of expensive high-dose naloxone

* We support the Call to Action emerging from the Compassionate Overdose Response Summit: "1) People who use drugs should be involved in decisions regarding the research, development, selection, and distribution of opioid overdose reversal products. 2) Regulatory agencies and pharmaceutical manufacturers should carefully consider and communicate the risk and duration of withdrawal associated with higher dose and long-acting opioid antagonists. 3) Take-home naloxone kits should include at least two doses of an IM product containing 0.4mg or an IN product containing ≤4 mg. 5) At this time, high dose and long-acting opioid antagonists have no use in acute opioid overdose response. 5) Overdose response education materials, instructions on overdose response, and training should emphasize the restoration of breathing, avoiding withdrawal, and compassionate post-overdose support and care." (See Russell E, Hawk M, Neale J, Bennett A, Davis C, Hill LG, et al. A call for compassionate opioid overdose response. *International Journal of Drug Policy.* 2024;133, 104587.https://doi.org/10.1016/j.drugpo.2024.104587.)

products in the United States is a global and historical anomaly. Decades of consistent FDA labeling for all other approved forms of naloxone contend that a single low dose of naloxone should be administered initially, with additional dose titration until adequate reversal of respiratory depression is achieved, in order to avoid precipitating opioid withdrawal.[12,13] A newly unveiled 17.6 year study of naloxone administration in a syringe service setting found that on average 1.63 (95% CI: 1.60, 1.65) naloxone doses were administered per reversal using intramuscular or 4 mg nasal formulations. Dose did not change substantially over the 17.6 years (x^2=0.28, 3 df, p=0.60), through phases of overdose, from prescription opioids, to heroin, to illicitly manufactured fentanyl, to xylazine.[14]

Severe Withdrawal Increases Risk for Repeated Overdose. Use of high-dose and long-acting opioid antagonists will likely produce unintended consequences that are counterproductive to efforts to prevent opioid overdose deaths.[15] Severe precipitated withdrawal is characterized by hyperalgesia, diarrhea, agitation, and vomiting, especially at higher doses.[16,17] Naloxone at lower doses has a relatively shorter half-life, lasting less than 90 minutes. However higher doses of naloxone and long-acting opioid reversal agents may lead to more severe withdrawal symptoms and for a longer duration, particularly for those with opioid tolerance, causing unnecessary harm.[18]

While pharmaceutical companies may argue that their product does not present as great a risk of precipitated withdrawal to opioid naïve individuals who experience an overdose, due to the stigma associated with drug use, naloxone distribution initiatives will not always know who is opioid naïve and who is dependent. Severe precipitated withdrawal should not be dismissed as an "unavoidable" adverse event expected to occur in some overdose reversals using antagonists. It could lead to short- and long-term changes in behavior that increase risk for subsequent overdose. For example, severe withdrawal can lead to immediate and repeated re-dosing with opioids. In the weeks that follow a reversal, negative withdrawal experiences may also lead to use of street drugs alone.[19] Concerns about subsequent overdoses from immediate re-dosing and using alone have been ignored by manufacturers of high-dose naloxone and nalmefene. The use of long-acting opioid reversal agents is also impractical in a community setting: patients receiving nalmefene may need longer periods of observation, by several hours, to ensure they do not experience recurrent respiratory depression.[20] It may also complicate initiation of medications for opioid use disorder, such as buprenorphine/naloxone.[21]

Nalmefene nasal spray has never been tested in the real-world. The marketing of nalmefene is predicated on hypotheticals. The pharmacological justifications for nalmefene (longer half-life, etc.) are based solely on a couple of studies with a few dozen healthy volunteers who were not taking opioids. Nalmefene has never been tested in cigarette smokers, people taking over-the-counter medications, vitamins, or those with severe seasonal allergies. People who drank alcohol were excluded from clinical trials. Nalmefene has not been tested in places like North Carolina, where the drug supply contains an admixture of fentanyl, xylazine, methamphetamine, and benzodiazepines. Because of these limitation, nalmefene nasal spray is not approved for use in young children (under 12 years). The manufacturer states "There are no available data on nalmefene use in pregnant women to evaluate for a drug-associated risk of major birth defects or miscarriage."[22]

Stick with what is proven: There is no urgency to switch to untested medications. A growing body of research, including by experts at the University of North Carolina, Chapel Hill, reveals that claims that additional, stronger, or long-acting doses of naloxone are needed are unfounded.[23,24,25,26,27,28,29] Research also shows that withdrawal is more likely with the higher-dose products, belying suggestions that adulterants in the drug supply, rather than high-dose formulations, are to blame for heightened withdrawal symptoms. A Viewpoint article from the International Journal of Drug Policy on these new overdose reversal agents concludes that the "development and marketing of more powerful opioid antagonists should be viewed with great skepticism."[30] We agree with the authors' skepticism. Current research has not supported that these formulations work better in non-experimental settings, and we would need more real-world evidence to support widespread adoption of alternative formulations. Development and adoption of additional dosing options for opioid overdose reversal medications and administration routes that help mitigate severity of precipitated withdrawal are important and should be the focus of research. Providing oxygen to people who use drugs experiencing respiratory depression is also a promising intervention that should be better studied.[31]

As a state, we must remain focused on distributing low-cost, proven naloxone products, in high volume, directly to people who use drugs. This is the only modality of opioid antagonist distribution shown to actually have an impact on overdose.[32] Sadly, frontline programs in North Carolina lack adequate access to the supply of naloxone they need.[33,34] Due to relentless marketing from pharmaceutical companies that make higher-dose formulations, there is a very real concern that decision makers may selectively purchase costlier high-dose and long-acting opioid overdose reversal medications out of a belief they are needed for successful overdose reversal, or out of "an abundance of caution" that ignores the real risks of these formulations. There is also a concern that they can be used to inflict harm through intentionally causing precipitated withdrawal. Overdose reversal medications should be deployed as public health tools to prevent death and not used as either a replacement for high-quality, compassionate overdose response or an extension of punitive responses to substance use.

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