July 29, 2024

Statement Regarding High Dose Naloxone and Long Acting Nalmefene Opioid Overdose Reversal Formulations

We, the undersigned, make the following statement regarding high-dose naloxone ("Kloxxado" 8 mg, "Zimhi" 5 mg) or long-acting nalmefene ("Opvee" 2.7 mg) formulations for the treatment of a suspected opioid overdose:

As clinicians, researchers, and advocates working to address the overdose crisis, we are broadly supportive of compassionate, person-centered innovations to prevent overdose deaths. Naloxone titrated for overdose reversal, using 4 milligram or lower dose, is extremely effective even in the case of overdoses involving prescription or illicitly manufactured fentanyl[1]. Accessing 911 emergency medical services is always recommended and subsequent doses of naloxone may be administered when needed. As long as ventilation can be supported, low doses of naloxone should be administered initially and additional doses titrated until adequate reversal of respiratory depression is achieved, in order to avoid precipitating opioid withdrawal.[2] Overdose prevention, recognition, and response training using naloxone can be accessed in Los Angeles by emailing HarmReduction@ph.lacounty.gov. These training sessions may also include instruction about how to administer a lower dose, intramuscular naloxone (.4mg), and supportive ventilation via mouth-to-mouth rescue breathing and, if available, supplemental oxygen.

At this time, we do not recommend the use of any high-dose or long-acting overdose reversal agents in California by harm reduction & recovery treatment providers, hospitals, EMS and other first responders, or bystanders with access to naloxone. Use of powerful (e.g. greater than 4 mg) and long-acting opioid antagonists will likely produce unintended consequences that are counterproductive to efforts to prevent opioid-related overdose deaths.[3] Consequences such as precipitated opioid withdrawal, a known effect of opioid antagonists for opioid-tolerant individuals, can produce symptoms such as hyperalgesia, diarrhea,

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[1] Carpenter J, Murray BP, Atti S, et al. Naloxone Dosing After Opioid Overdose in the Era of Illicitly Manufactured Fentanyl. J Med Toxicol. 2020;16:41–48.

[2] Moustaqim-Barrette A, Papamihali K, Williams S, Ferguson M, Moe J, Purssell R, Buxton JA. Adverse events related to bystander naloxone administration in cases of suspected opioid overdose in British Columbia: An observational study. PLoSOne. 2021 Oct 29;16(10):e0259126. doi: 10.1371/journal.pone.0259126. PMID: 34714854; PMCID: PMC8555799.

[3] Hill LG, Zagorski CM, Loera LJ. Increasingly powerful opioid antagonists are not necessary. *Int J Drug Policy*. 2022;99:103457.doi:10.1016/j.drugpo.2021.103457

and vomiting, particularly at higher doses.[4,5] Naloxone at lower doses has a relatively shorter half life, lasting less than 90 minutes. However higher doses of naloxone, and longer acting opioid reversal agents, may lead to more severe withdrawal symptoms and for a longer duration, causing unnecessary harm. Patients receiving nalmefene may need longer periods of observation, by several hours, to ensure individuals do not experience recurrent respiratory depression.[6] Indeed that nalmefene is long acting may result in a false sense of security that an overdose has been successfully reversed, exposing the treated individual to increased risk of recurrent overdose when nalmefene has worn off.

A recent The 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."[3] We agree with the authors' skepticism. The higher dose / higher affinity opioid overdose reversal medications are newer and more research is needed to determine their role as public health tools across communities. The available research has not supported that they work better in real-world / non-experimental settings,[7] and we would need more real-world evidence to support widespread adoption of alternative formulations. Further, there is a justifiable concern that these products, when used to reverse opioid overdose among people with physiologic opioid tolerance, may cause a more severe and prolonged precipitated withdrawal, which may lead to avoidance of care for overdose rescue and response. 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 on these medications.

There is a very real concern that first responders may selectively use higher dose / higher affinity opioid overdose reversal medications out of a belief they are needed for successful overdose reversal. 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 punishing or carceral responses to substance use.

Sincerely,

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[4] Purssell R, Godwin J, Moe J, Buxton J, Crabtree A, Kestler A, DeWitt C, Scheuermeyer F, Erdelyi S, Balshaw R, Rowe A, Cochrane CK, Ng B, Jiang A, Risi A, Ho V, Brubacher JR. Comparison of rates of opioid withdrawal symptoms and reversal of opioid toxicity in patients treated with two naloxone dosing regimens: a retrospective cohort study. Clin Toxicol (Phila).2021 Jan;59(1):38-46. doi: 10.1080/15563650.2020.1758325. Epub 2020 May 13. PMID: 32401548.

[5] Higher-Dose Naloxone Nasal Spray (Kloxxado) for Opioid Overdose. JAMA. 2021 Nov 9;326(18):1853-1854. doi:10.1001/jama.2021.15948. PMID: 34751711.

[6] ACMT & AACT Joint Position Statement on Nalmefene Should Not Replace Naloxone as the Primary Opioid Antidote at This Time. https://www.acmt.net/news/acmt-aact-joint-position-statement-on-nalmefene-should-not-replace-naloxone-as-the-primary-opioid-antidote-at-this-time/

[7] Payne ER, Stancliff S, Rowe K, Christie JA, Dailey MW. Comparison of Administration of 8-Milligram and 4-Milligram Intranasal Naloxone by Law Enforcement During Response to Suspected Opioid Overdose — New York, March 2022–August 2023. MMWR Morb Mortal Wkly Rep 2024;73:110–113. DOI: http://dx.doi.org/10.15585/mmwr.mm7305a4

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