The Truth About Naloxone Dosing

- Numerous studies have shown that new substances in the drug supply do not require stronger or longer-acting versions of naloxone or other opioid antagonists to reverse overdoses.
- Severe withdrawal from high doses of naloxone can be dangerous. Not only can it lead to serious side effects, but it can also lead to riskier use – such as immediately redosing with opioids or using alone in the future. This increases risk of subsequent overdose.
- New nalmefene products (Opvee and Zurnai) have never been tested in the current North Carolina drug supply or on people using street fentanyl. Their real-world effectiveness remains unknown.
- There is no urgency to switch to pharmaceuticals that are untested. Overdose rates in North Carolina are dropping with continued distribution of standard forms of naloxone.

The Issue

As the overdose crisis continues to take a devastating toll, pharmaceutical companies have seen an opportunity to find a market niche. They've used justified concern about fentanyl and other strong opioids to lead people to believe that these opioids require stronger or longer-acting opioid antidotes. While this may seem intuitive, research and real-world experience do not support these claims. Standard formulations of naloxone – meaning doses of 0.4 mg intramuscularly or 4 mg or lower intranasally – work very well to block the brain's opioid receptors, reversing overdose.

This is a case where "an abundance of caution" may not be better.

Stronger and longer-acting overdose reversal agents come with risks: severe withdrawal, including vomiting, diarrhea, extreme sensitivity to pain, and life-threatening lung complications.

These consequences may lead people to using opioids again right away and to being more apt to use alone in the future to avoid a similar experience. Using alone is known to increase overdose risk. 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.

Naloxone distribution as we know it today, where the medication is distributed to laypeople to use in case of an emergency, was started in the US by Dan Bigg and colleagues at the Chicago Recovery Alliance nearly 30 years ago, when he began giving people use who drugs injectable naloxone to prevent fatal overdose. The evidence for community naloxone comes from this injectable product.

Only the injectable form of naloxone is listed on the World Health Organization "Essential Medicines List."

High-dose naloxone is a US anomaly: In Australia and Europe, where synthetic opioids more potent than fentanyl are also found, the approved nasal dose is just 1.4mg or 1.8mg.

The Evidence

Numerous studies have now been done looking at the need for stronger naloxone products. Studies with law enforcement responders in New York, a harm reduction program in Pennsylvania, and EMS in Kentucky, Missouri and Georgia have all found that 1-2 standard doses of naloxone are sufficient to reverse an overdose, even in the era of fentanyl. Most studies that purport to show that stronger naloxone is needed are done by people employed by companies selling high-dose products, leading to conflicts of interest.

A service provider in Pittsburgh analyzed their naloxone data over 17 years. On average, only 1.6 doses of 4 mg nasal or 0.4 injectable were needed for 98% survival. Dose did not change with fentanyl.

References

Overdoses are stressful situations, and it is often hard to wait 3 minutes between naloxone doses. When people provide more than 2 doses, they may not be waiting for the initial dose to take effect. Or there may be other non-opioid drugs involved. This does not mean that more naloxone is helpful.

When it comes to nalmefene for community use, there are a lot of unanswered questions about its safety for key populations at risk of overdose. The pharmacological justifications for nalmefene (longer half-life, etc.) are based on just a couple of studies with a few dozen healthy volunteers who were not taking fentanyl. 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. 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."

A participant at the national forum on compassionate overdose response shared about his experience receiving high doses of naloxone:

"I tried to re-dose with heroin every 15 minutes to feel anything other than this horrible feeling"... "For months after that bad overdose, I was super hesitant to use around others.

I mostly wanted to use alone to avoid something like that from happening again, which put me at great risk."

The Bottom Line

Last year, national experts met to study naloxone dosing and they issued the following Call to Action:

1) People who use drugs should be involved in decisions regarding the research, development, selection, and distribution of opioid overdose reversal products.

2) Government agencies and pharmaceutical manufacturers should communicate risk and duration of withdrawal with higher dose and long-acting opioid antagonists.

3) Take-home naloxone kits should include at least two doses 0.4mg IM or 3-4mg nasal.

4) At this time, high dose and long-acting opioid antagonists have no evidence for use in acute opioid overdose response in the community.

5) Education materials and training should emphasize the restoration of breathing, avoiding withdrawal, and compassionate post-overdose support and care.

Currently, frontline harm reduction programs still lack access to adequate supplies of naloxone, often forcing them to ration the medicine. We must remain focused on distributing low-cost, proven (standard-dose) naloxone, in high volume, directly to people who use drugs. This is the intervention proven to reduce overdose rates.