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Essay

A call for compassionate opioid overdose response

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ABSTRACT

High dose and long-acting opioid overdose reversal drugs can precipitate withdrawal in people who are opioid dependent. Products recently brought to market for community use in the United States (US) have drawn international concern because of their increased risk of withdrawal. At the March 18–19, 2024, *Compassionate Overdose Response Summit & Naloxone Dosing Meeting*, a panel of harm reduction experts issued the following call to action: 1) people who use drugs should be directly 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 longer-acting opioid antagonists; 3) take-home naloxone kits should include at least two doses of an intramuscular (IM) product containing 0.4 mg or an intranasal (IN) product containing ≤4 mg; 4) At this time, high dose and long-acting opioid antagonists have no use in acute opioid overdose response; and, 5) overdose response educational materials, instructions on overdose response, and training should emphasize the restoration of breathing, avoiding withdrawal, and compassionate post-overdose support and care. High dose and long-acting opioid overdose reversal drugs were approved without testing for withdrawal and are often aggressively marketed despite decades of evidence from naloxone distribution programs worldwide that the ideal dose of naloxone is one that restores breathing without inducing withdrawal. Government agencies should direct resources to harm reduction programs to make standard dose take-home naloxone products widely available among people who use drugs. Lay bystanders, people who use drugs, their families, and professional first responders can learn and apply a compassionate approach to opioid overdose response.

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Call to action

We call for an opioid overdose response standard of care that centers the voices of people who use drugs. Pharmaceutical companies are developing and aggressively marketing high dose (>0.4 mg for intramuscular (IM) injection and >4 mg intranasal (IN) spray) and long-acting opioid antagonists (such as nalmefene) in the United States (US). As synthetic opioids become more prevalent worldwide, we anticipate these opioid antagonists will also be marketed in other countries. Use of these products will increase the risk, duration, and complications of precipitated withdrawal. A compassionate overdose response restores breathing and avoids withdrawal. To this end:

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 0.4 mg or an IN product containing ≤4 mg.
4. At this time, high dose and long-acting opioid antagonists have no use in acute opioid overdose response.
5. Overdose response educational materials, instructions on overdose response, and training should emphasize the restoration of breathing, avoiding withdrawal, and compassionate post-overdose support and care.

This call to action is directed to lay responders and the public health programs that support them with take-home naloxone. The principles also apply to emergency medical services (EMS), emergency department staff, and other uniformed responders.

A major factor in the surge of opioid overdose deaths is that people are using alone with no bystander available to respond to an overdose. People use alone because of stigma, fear of law enforcement, and mistreatment in healthcare systems (Bennett et al., 2022; Fernando et al., 2022; McLean, 2016). To substantially reduce the number of overdose deaths, government agencies must sanction, fund, and facilitate strategies that increase the proportion of overdose events that are witnessed (either in person or virtually). Interventions that reduce stigma, threats of law enforcement, and improve treatment in medical settings can increase the proportion of witnessed overdoses and the possibility for effective overdose response to save lives (Zang et al., 2024).

Compassionate Overdose Response Summit and Naloxone Dosing Meeting

This call to action was developed and vetted by a panel of harm reduction experts at the *Compassionate Overdose Response Summit & Naloxone Dosing Meeting* on March 18–19, 2024, in Pittsburgh, Pennsylvania. The panel applied affinity clustering, a technique for generating, categorizing, and choosing among ideas from a group of people, to develop consensus for the definition of compassionate overdose response, standard response steps, and the recommendations in this paper. While this call to action emerged from a US-based meeting, the issue of high dose and long-acting overdose reversal products being marketed without medical evidence of need is an international concern.

Organizers held three planning calls to define the goals of the meeting and solicit input on the structure, audience, and invite list. The criteria for invitation to the Naloxone Dosing Meeting included experts with:

- Living and lived experience of opioid overdose and willingness to speak about it
- Experience reversing multiple overdoses
- Research conducted on overdose reversal, naloxone, and its impact
- Willingness to work collaboratively with experts in the room, especially those with living and lived experience, and contribute to the creation of written products

Panelists were identified through recommendations from recognized experts, including people who have firsthand experience using naloxone and/or have published on the topic. Of the 37 panelists, 27% had lived or living experience, 27% were medical providers working in emergency medical services, toxicology, or emergency departments, 24% represented a harm reduction organization, including safe consumption spaces and overdose prevention sites, 19% worked in research, and 3% in policy. Researchers specialize in pharmacy, law, and drug policy. The panel included one representative from the United Kingdom and two from Norway.

The conclusions of the March 18, 2024 Naloxone Dosing Meeting were shared through a hybrid, live-streamed event called the *Compassionate Overdose Response Summit* on March 19, 2024, which was free and open to the public. Panelists presented data, stories, and reports of national and international concern. In addition to the in-person panelists, more than 400 people from government agencies, harm reduction programs, and national associations provided feedback and comments using Zoom platform features. The outcomes of the event were summarized in a report published alongside the event's recording on the host's website (Health Management Associates, 2024)

Background

Overdose, naloxone access, and distribution

Overdose is a global crisis that causes over 600,000 deaths annually, more than 100,000 of which occur in the United States (Ahmad et al., 2024; World Health Organization, 2023). Opioids contribute to nearly 80% of these deaths. A high dose of opioids affects the part of the brain that controls the rate of breathing and reduces the number of breaths. Reduced breathing leads to less oxygen in the blood (hypoxia). Very high opioid doses can completely stop breathing which can cause death because the brain and body do not receive enough oxygen.

When widely available at the community level, the opioid reversal drug naloxone can significantly reduce overdose mortality and morbidity (Bird et al., 2015; Håkansson et al., 2024; Irvine et al., 2022). Naloxone is a non-addictive, highly competitive antagonist of mu-opioid receptors that can rapidly reverse opioid-induced respiratory depression when administered intranasally, intravenously, or intramuscularly. The 0.4 mg vial of IM naloxone is included in the World Health Organization's (WHO) Essential Medicines List. Naloxone was developed in the 1960′s to reverse opioid overdoses and has been widely used in medical settings since the 1980′s. It was first made available for community use in 1996 (Campbell, 2019). Harm reduction programs around the world have expanded community distribution of naloxone to people at high risk of overdose (Burton et al., 2021; WHO, 2017).

An increasing variety of overdose rescue products for community use are available globally. In Europe, naloxone products range from 0.4 – 1 mg IM and up to 2 mg IN spray. While a 4 mg IN spray was developed and launched in the US in 2015, lower dose naloxone formulations are generally available in other countries. The French National Commission on Narcotics and Psychotropic Substances started piloting a 0.9 mg IN spray in 2015. In 2017, the European Commission authorized the first IN naloxone spray for European Union-wide marketing, a 2 mg product, and a 1.4 mg nasal spray was approved in 12 European countries (Skulberg et al., 2019; Strang et al., 2019). A European randomized controlled study in opioid overdose patients determined the clinical efficacy of an approved nasal naloxone spray (Skulberg et al., 2022).

Policies to increase access to naloxone vary globally. In 2011, Scotland established the first national distribution program, followed by

Australia in 2012 (Dwyer et al., 2018; McAuley et al., 2016). Italy, in the 1990′s, was the first county to remove prescription requirements for naloxone. Canada removed naloxone's prescription requirement in 2016. In the US, the Food and Drug Administration (FDA) approved the first over-the-counter (OTC) naloxone in March 2023 and has approved two formulations of IN products for OTC marketing at the time of writing: 3 mg (RiVive™), 4 mg (Narcan™), and at least two 4 mg generic products (Davis & Carr, 2020; Evoy et al., 2021). Naloxone access laws were implemented across all 50 US states as the overdose crisis intensified (Lambdin et al., 2018). These laws generally allow almost anyone to carry and use naloxone, including family members, service providers, law enforcement, and the public.

Community take-home naloxone distribution to people likely to witness an opioid overdose is a critical, rational response to surging overdose deaths. This approach is promoted by the World Health Organization and the US Department of Health and Human Services. The WHO's Expert Committee on Drug Dependence issued guidelines in 2014 stating 1) people who use drugs should have access to naloxone; 2) people who use drugs can select the route of administration based on the formulation available, their skills, the setting and the local context; and, 3) responders (i.e., people who use drugs) should focus on airway management, supporting breathing, and giving naloxone (World Health Organization, 2014). The AHA 2021 Scientific Statement on Opioid-Associated Out-of-Hospital Cardiac Arrest recommends "the lowest effective dose of naloxone that restores adequate respirations and protective airway reflexes should be used" (Dezfulian et al., 2021).

Harm reduction programs, particularly syringe services programs (SSPs), are highly effective at reaching people at risk of overdose (Frost et al., 2022; Lambdin et al., 2020; Wheeler et al., 2015). Evidence-based best practices for implementing overdose education and naloxone distribution in SSPs can increase the reach and impact of overdose prevention (Clark et al., 2014; Lambdin et al., 2018, 2020, 2024; Patel et al., 2023; Wegner et al., 2021; Wenger et al., 2022). These include, at every encounter, offering naloxone proactively at no cost to people who use drugs at risk of overdose and reducing barriers to access such as simplifying training requirements and limiting the collection of non-essential data. Policies should also promote and facilitate naloxone possession during opioid use events as research shows that even among those equipped with and trained to administer naloxone, opioid use continues to occur in unprotected contexts, without naloxone or someone to administer it present (Bennett et al., 2022; Zang et al., 2024).

Opioid withdrawal

Opioid withdrawal is a potentially life-threatening condition that occurs when someone who is dependent on opioids is deprived of them or receives an opioid antagonist (e.g. naloxone, naltrexone, or nalmefene) or a partial agonist (e.g. buprenorphine). Opioid antagonists compete with opioids to occupy the mu-opioid receptors. Withdrawal symptoms include nausea, vomiting, agitation, pain, and aspiration (Schiller et al., 2023). A person who is opioid dependent experiencing withdrawal will often attempt to consume more opioids to relieve those symptoms (Bennett et al., 2022; Neale & Strang, 2015).

Administering too much naloxone in an opioid overdose reversal can precipitate withdrawal (Neale & Strang, 2015). High doses of naloxone used to reverse an opioid overdose are associated with more frequent, severe, and prolonged withdrawal symptoms when evaluated in emergency departments and community or street-level overdose response settings (Moustaqim-Barrette et al., 2021; Payne et al., 2024; Purssell et al., 2021). A study comparing 4 mg and 8 mg initial IN doses administered by New York State troopers in 2023 found people who received the higher dose were 2.5 times more likely to experience withdrawal symptoms, with no difference in survival (Payne et al., 2024). A study from two urban hospitals in Canada compared opioid withdrawal symptoms retrospectively among emergency department patients who received high and low dose regimens of naloxone. Four times as many patients who received high doses of naloxone had withdrawal symptoms compared to those who received the standard low dose (Purssell et al., 2021).

The administration of multiple or high doses of naloxone by uniformed first responders (i.e. EMS personnel or law enforcement) and medical professionals can be perceived as punitive by people who use drugs (Neale & Strang, 2015). Fear of punitive treatment from unformed first responders and medical professionals can deter people from calling EMS or seeking help in overdose emergencies (Latimore & Bergstein, 2017; Latkin et al., 2019). People who received high doses of naloxone report they may subsequently choose to avoid using opioids around other people for fear of punitive response, making the potentially dangerous decision to use alone (Health Management Associates, 2024). Withdrawal can undermine the therapeutic alliance between overdose survivors and responders, leading to worse patient outcomes (Dezfulian et al., 2021; Stolbach et al., 2023).

Seeking opioids and other substances to alleviate withdrawal must be considered in the context of the social, cultural, economic, legal, policy and political environments in which they occur (McLean, 2016; Rhodes, 2009). Studies show attempts to mitigate withdrawal symptoms can lead to potentially dangerous drug use practices like sharing needles, ignoring fentanyl test strip results, and speeding up the injection process (Bluthenthal et al., 2020; Frank et al., 2023; Wagner et al., 2010). A qualitative study of people who use drugs in New York City found withdrawal was ubiquitous and "heightened" and "stronger" after the widespread availability of fentanyl (Frank et al., 2023).

People who use drugs and harm reduction programs are concerned by the recent approval and intensive marketing of high dose and long-acting opioid antagonists to treat opioid overdose in the US because of the severe consequences of withdrawal.

High dose opioid overdose reversal products are not needed and cause harm

In 2021, due to the widespread availability of high-potency synthetic opioids like fentanyl, the US FDA approved two high-dose naloxone products, an 8 mg IN spray (Kloxxado) and a 5 mg IM injectable (Zimhi). The only studies reported in the FDA package inserts for both products are pharmacokinetic studies in healthy volunteers, which demonstrated substantially higher naloxone plasma levels than standard doses of naloxone (0.4 mg IM vs. 8 mg IN and 2 mg IM vs. 5 mg IM, respectively). In April 2024, based on a pharmacokinetic study of 30 healthy adult subjects, the FDA approved a 10 mg IN naloxone, Rezenopy. None of these approval trials was conducted among opioid overdose patients at risk for naloxone-precipitated withdrawal. In 2023, the FDA approved a 2.7 mg IN formulation of nalmefene (Opvee), a more potent and longer acting opioid antagonist than naloxone. The approval of nalmefene was also based on pharmacokinetic studies performed in healthy volunteers that showed higher plasma levels than standard naloxone doses and one pharmacodynamic study among opioid-experienced, but "non-dependent" participants which showed successful reversal of respiratory depression induced by laboratory administered remifentanil.

Studies in two states in the US have found that there is no association between the introduction of fentanyl into the drug supply and naloxone dosing required to reverse opioid overdoses. This conclusion emerged from data collected over four years at a SSP in Pittsburgh, PA, that distributed primarily 0.4 mg IM naloxone to people who use drugs (Bell et al., 2019; Bell & Dasgupta, 2024). Although the proportion of opioid overdose deaths attributed to fentanyl grew from 3.5% in 2013 to 68.7% in 2016, the average number of doses of naloxone administered by SSP participants to reverse overdoses did not change significantly, 1.62 doses in 2013 and 1.52 doses in 2016. An additional study of the naloxone doses used in opioid reversals reported to this Pittsburgh SSP, from August 2005 to January 2023, found that from 2010 to 2023, the average dose per reversal was below two administered doses (Bell & Dasgupta, 2024). In Kentucky, Rock et al. evaluated emergency services

personnel-administered intranasal-equivalent naloxone doses and observed a clinically insignificant increase from 4.5 mg to 4.7 mg over four years to reverse overdoses during which fentanyl became ubiquitous in the drug supply (Rock et al., 2024). In both studies, the rate of successful overdose reversal was 99%.

Administration of additional doses of naloxone or increasing the dose or half-life of a single product do not reverse an opioid overdose more quickly (Hill et al., 2022; Klebacher et al., 2017). In a 2018 literature review of naloxone dosing, administration, and timing, Lynn and Galankin conclude, "the interactions between the opioid agonist and the mu-opioid receptor may be the greatest determinant of the speed of recovery from the respiratory effects of many opioids, which may not markedly accelerate with increasing doses of naloxone, but rather respond to a minimum effective dose" (Rzasa Lynn & Galinkin, 2018).

Around the world, there is no evidence of the need or benefit of higher dose products, particularly from people to whom they would be administered (Saari et al., 2024). People who used opioids, in one qualitative study, preferred lower dose IN products (Neale et al., 2022). In 2024, the Michigan Drug User Health Alliance surveyed 108 people who use drugs about their reversal product preferences. Respondents overwhelmingly preferred standard-dose products to high dose or long-acting products (Michigan Drug User Health Alliance, 2024). Medical personnel also prefer to titrate naloxone dose based on the medical presentation of their patient (Tylleskar et al., 2020).

Context of approval of high dose and long-acting opioid overdose reversal products

For over a decade, fentanyl has dominated the unregulated drug supply, causing dramatic increases in overdose deaths and intense public and political concerns in North America. Within the context of US drug criminalization, fear of fentanyl, and a lack of FDA guidance on naloxone dosing, stronger naloxone products were seen as a logical response to synthetic opioids. Federal and state agencies and public health programs have been distracted from implementing evidence-based overdose response guidelines by the development and marketing of new stronger and longer-acting opioid overdose reversal products.

Fentanyl panic has proliferated, particularly on social media platforms, leading to the swift spread of misinformation about how to respond to a fentanyl overdose (Beletsky et al., 2020). A pervasive myth is that people can overdose from passive exposure to fentanyl, by touching it, coming in contact with the bodily fluids of someone who has used it, or unintentionally breathing it in. The Drug Enforcement Administration (DEA) and the Centers for Disease Control and Prevention overstated the risks of an overdose when fentanyl is touched or inhaled (Drug Enforcement Administration, 2017). Though the DEA retracted this statement, many video reports show law enforcement and other professional first responders appearing to have adverse reactions after touching fentanyl or other opioids. Examination of these and purported law enforcement "overdoses" after exposure to fentanyl did not find evidence of fentanyl in follow-up toxicology screens and lab-based confirmatory tests (del Pozo et al., 2022; Moss et al., 2017).

Reports of opioid reversals requiring multiple doses of naloxone have been misused and sensationalized by media sources (Beletsky et al., 2020; Sutter et al., 2017; Zuckerman et al., 2014). Though people may administer more doses of naloxone for overdoses that involve fentanyl than for those that do not, this does not mean those additional doses were medically necessary (Rzasa Lynn & Galinkin, 2018). Excessive administration from delivering multiple doses of naloxone without waiting the recommended three minutes to see if breathing is restored is correlated to the responder's perception of urgency and feelings of panic (Parkin et al., 2021). Closer examination of published case reports and articles calling for stronger doses of naloxone reveal that they are either "perspective" or "debate" articles, not research, and in some cases are sponsored by for-profit pharmaceutical corporations (Bardsley, 2019; Klebacher et al., 2017; Moss & Carlo, 2019). Modeling studies are not real-world evidence. The perception that more naloxone doses are needed to reverse synthetic opioid overdoses is not supported by research studies.

To increase access to naloxone, the US FDA encouraged OTC applications for naloxone products from industry and extended the expiration dates of some commonly used products. In addition, the FDA exempted naloxone distribution from supply chain monitoring requirements (FDA, 2022). That exemption allowed Remedy Alliance for the People to provide low-cost and free naloxone to harm reduction programs (Remedy Alliance, 2024). However, in 2016, the FDA Anesthetic and Analgesic Drug Products Advisory Committee concluded the basis for determining a standard dose was unclear, and the risk of withdrawal was acceptable compared to underdosing naloxone (Jacobs & Seifried, 2016). During this meeting, a small majority of the Committee recommended the FDA increase the minimum standard naloxone dose of products intended for community use. These conclusions spurred pharmaceutical companies to develop higher dose naloxone products. In doing so, the US diverged from other countries with similar illicit fentanyl markets (Moe et al., 2020).

Standard opioid overdose response

There is ample evidence for a standard opioid overdose response that includes naloxone dosing to restore breathing while avoiding withdrawal (Bell et al., 2019; Payne et al., 2024; Rock et al., 2024). That standard dose is 0.4 mg IM and $\leq$4 mg IN spray.

The Fig. 1 is a decision flow chart for community-based opioid overdose response by lay bystanders. A call-out box lists context considerations, such as the setting in which the overdose takes place, the drugs involved, and resources available. The first step in the Fig. 1 is to establish that the person is unresponsive. An unresponsive person will not react to attempts to wake them, such as gentle shaking or shouting their name. If they can open their eyes and speak, the responder should stay with them, reassessing symptoms every two minutes if suspected, based on the context, that an overdose may occur.

Blue, paler, or ashen lips and/or fingertips are a sign that the person is not breathing sufficiently. If this is observed, as shown in the Fig. 1, give the standard dose of naloxone (0.4 mg IM injection, $<$4 mg IN spray) and call EMS, if possible.

If the person's skin tone looks healthy, is not blue, ashen or pale, then assess breathing. If the person is breathing and is in a heavy nod or sleeping, continue to monitor them every two minutes if suspected, based on context, that an overdose may occur.

If the person is not breathing, or breathing less than one breath every five seconds, give rescue breaths. Tilt the head back to open the airway. Using one's mouth or a device that creates a seal over the mouth, give one breath every five seconds, watching the person's chest rise and fall. Responders can maintain oxygenation during an opioid overdose by providing supplemental oxygen or by rescue breathing when naloxone is not available. If they do not begin breathing on their own, and naloxone is available, give one standard dose. As shown in the Fig. 1, wait three minutes between doses of naloxone and continue to support breathing. If for any reason, rescue breathing cannot be implemented, tilting the head back can be helpful to keep the airway open.

As the person wakes up, the responder should stay with the person as long as possible. Place the person on their side to avoid asphyxiation and create a calm environment by clearing the space of people, reducing noise, and speaking in a gentle tone as the person wakes up (Neale et al., 2020). Law enforcement should not be present, if possible.

Pre-acute overdose

If a person is unresponsive, they may be in a deep nod or sleeping, which is called a "pre-acute" overdose (Health Management Associates, 2024). An observer should monitor symptoms, observe and count breaths to determine intervention. Oximeters can assist people who use

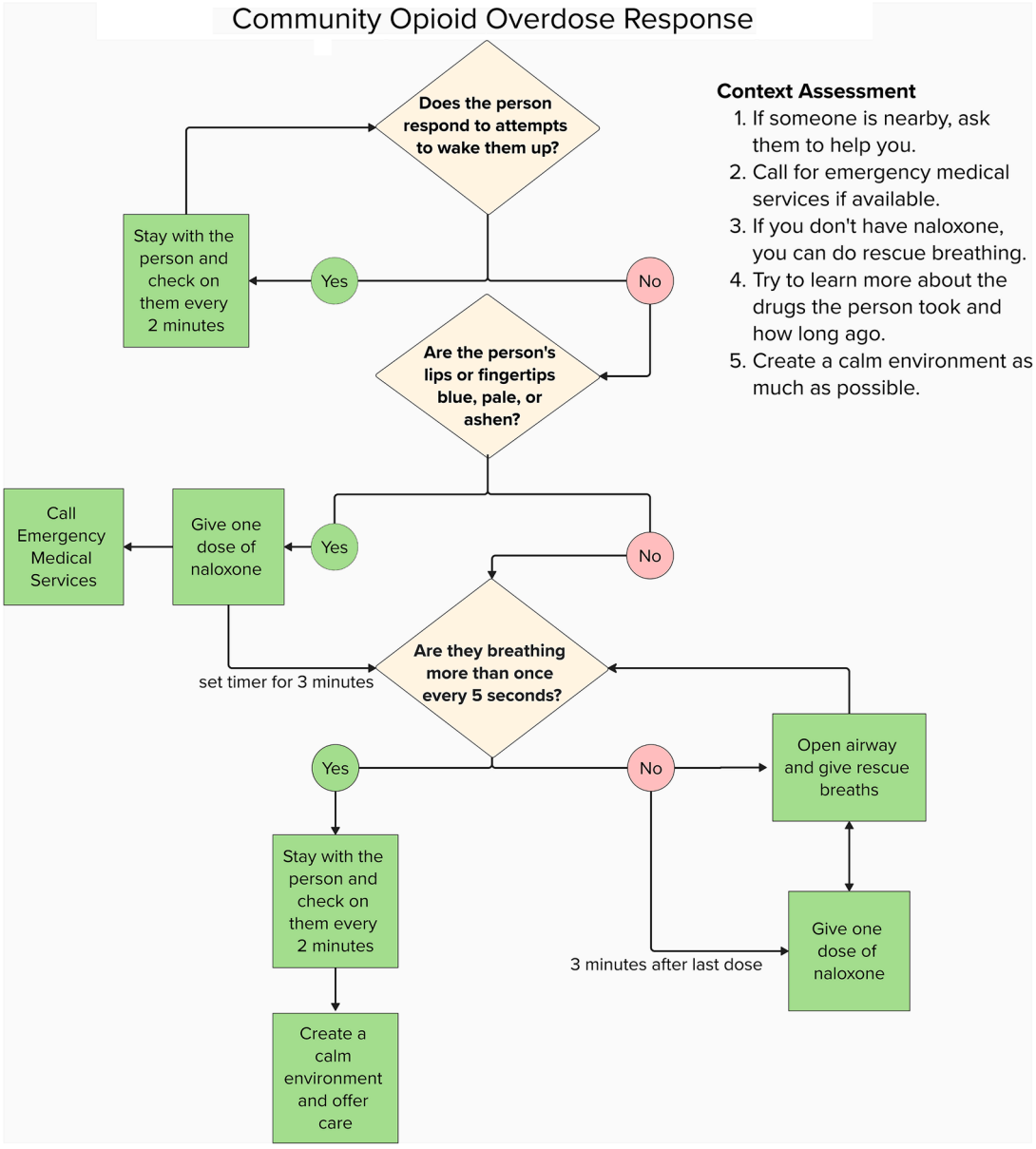

Fig. 1. Community opioid overdose response flowchart.

drugs and harm reduction program staff by monitoring oxygen levels (Mamdani et al., 2022). Well-resourced settings, like safe consumption spaces or overdose prevention sites, can monitor a person's oxygen level and, if needed, administer oxygen. Tanks and other devices used to give supplemental oxygen by harm reduction programs improve participant and staff experience of overdose response and reduce need for naloxone (Harocopos et al., 2022; McAteer et al., 2024; Suen et al., 2023). Naloxone may not be necessary when effective rescue breathing or supplemental oxygen prevent hypoxia.

Among people who use drugs, prevention begins with knowing the drug supply by testing drugs, using a small amount to gauge potency, and knowing one's tolerance level. When using, it's safer to have an observer who can monitor and, if needed, provide support. This could be a friend, or mobile and phone-based technologies like motion detection devices, peer-run hotlines, and apps that direct overdose response teams (Park et al., 2023).

Context considerations

A compassionate opioid overdose response must consider context. Responders differ in training, the resources available to them, and their abilities. General discomfort as well as fear of contracting disease may deter people from performing mouth to mouth rescue breaths. Devices that create a seal over the mouth may mitigate these concerns. Delivering effective rescue breathing generally requires training which needs to be balanced against feasibility (Jones et al., 2022; Paal et al., 2008). That training should be prioritized for those people most likely to witness and respond to opioid overdose (Dezfulian et al., 2021).

Context also includes the overdose patient's characteristics and the setting in which the overdose takes place. Individual characteristics include their physiology, pre-existing conditions, and the drugs consumed. Comorbidities such as chronic obstructive pulmonary disease and other health issues may impact the person's ability to breath.

The majority of overdoses occur from opioids used in combination with other drugs. Central nervous system depressants, including benzodiazepines and alcohol, increase risk of opioid overdose and

complicate effective response (Tori et al., 2020). Recently, overdoses involving xylazine, a veterinary tranquilizer, have sharply increased in North America(Ahmad et al., 2024; Zhu, 2023; Friedman et al., 2022; Zagorski et al., 2023). When other non-opioid respiratory depressing substances such as xylazine are present, breath support and oxygen monitoring are essential (Perrone et al., 2024).

Setting is the location in which the overdose occurs, whether it is private or public, and the availability of an observer or emergency medical services to respond. Overdose response will be influenced by the length of time an observer can stay with the person experiencing an overdose and the training they received prior to the event (Bennett et al., 2022). They may also consider the legal environment in which the overdose takes place when deciding when to call EMS, particularly if law enforcement will be sent to the scene (Latimore & Bergstein, 2017). Law enforcement may enforce drug laws or seek information about dealer networks from the person post-overdose. A person may fear law enforcement involvement because they have outstanding warrants or be in violation of parole or probation.

Post overdose care

A compassionate response includes post-overdose care. Most people wake up confused from an overdose and do not remember the event. People who have experienced an overdose may require emotional support and help getting oriented. Instead of aggressive conversations about behavior change or referrals to treatment this is a time to provide support and address the person's immediate physical and emotional needs. Communicate in a gentle tone when they wake up, informing them of what just happened (Neale et al., 2020).

Lay responders who provide care for people experiencing an acute overdose also require support and care after such an event (Marks & Wagner, 2022). While responding to overdoses and saving lives can be empowering, many responders experience stress, grief, and trauma – particularly those who respond to many overdoses or who provide acute overdose care for partners and loved ones (Kolla et al., 2024; Wagner et al., 2014).

Discussion

An opioid overdose response guided by compassion for the person experiencing an overdose, prioritizes restoring breathing without precipitating withdrawal. Withdrawal is a life-threatening concern among people who use drugs and should be taken seriously by first responders, medical providers, regulatory agencies, pharmaceutical manufacturers and lay responders.

Government agencies can increase access to standard formulations of naloxone among people who use drugs in their jurisdictions by using overdose prevention resources to purchase and provide them at no cost to harm reduction programs. Public awareness messaging should encourage rescue breathing techniques, the use of standard doses of naloxone, avoiding withdrawal, and promoting a calm, compassionate environment when the person wakes up.

Conclusions

This call to action endorses opioid overdose responses that continue to be effective in the synthetic opioid-era. High dose and long-acting reversal products are not needed, and cause harm by precipitating opioid withdrawal. People are not dying because of a lack of stronger naloxone. In fact, the overdose crisis in the US continues because existing, highly effective products are not readily available to people most likely to witness overdose, people who use drugs and their immediate friends and family. We call for compassion to be centered in opioid overdose responses that avoid withdrawal and improve the wellbeing of everyone involved.

People who use drugs have implemented overdose prevention, treatment, and post-event care for decades, developing a standard approach that is evidence-based, effective, and compassionate. Their voices should be central to the development, design, and distribution of all overdose reversal products. In partnership with people who use drugs, regulatory agencies can require clinical efficacy trials for overdose reversal products.

The marketing of high dose and long-acting opioid overdose reversal agents in the US has global implications. It is very likely that fentanyl, its analogues, and other synthetic opioids will be introduced into the illicit drug supplies of many countries (Griffiths et al., 2024). Those countries will look to how the US responded to wide-spread use of fentanyl.

The US should change its approach to the opioid overdose crisis by adopting a compassionate response to opioid overdoses that uses standard doses of naloxone, does not precipitate withdrawal, is guided by people who use drugs, and does not use high dose or long-acting opioid reversal products.

Ethics approval

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CRediT authorship contribution statement

Erin Russell: Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Data curation, Conceptualization. **Mary Hawk:** Writing – review & editing. **Joanne Neale:** Writing – review & editing. **Alex S. Bennett:** Writing – review & editing. **Corey Davis:** Writing – review & editing. **Lucas G. Hill:** Writing – review & editing. **Rachel Winograd:** Writing – review & editing. **Lauren Kestner:** Writing – review & editing. **Amy Lieberman:** Writing – review & editing. **Alice Bell:** Writing – review & editing. **Tim Santamour:** Writing – review & editing. **Stephen Murray:** Writing – review & editing. **Kristin E. Schneider:** Writing – review & editing. **Alexander Y. Walley:** Writing – review & editing. **T. Stephen Jones:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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