Prevention of lethal opioid overdose in the community

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INTRODUCTION

Drug overdose, principally due to opioids, is rising in many developed countries; in the United States, drug overdose has been the leading cause of injury-related death since 2009, with opioid overdose alone the leading cause since 2016 [1].

Strategies proposed to reduce opioid overdose and subsequent mortality include treatment of opioid use disorder with opioid agonist therapies (and possibly other medications) [2], provision of naloxone to lay persons [3], and establishment of safe consumption sites [4]. At least two behavioral interventions have also shown promise in reducing overdose events in pilot randomized trials [5,6]. Increased caution in prescribing of opioids for pain management, while important in preventing cases of opioid use disorder, has uncertain effects on overdose mortality [7].

This topic describes prevention of lethal opioid overdose in the community. The epidemiology, pharmacology, screening, assessment, diagnosis, and treatment of opioid use disorder are discussed separately. Management of intoxication and withdrawal from opioids are also discussed separately, as is abuse of prescription drugs.

- (See "Opioid use disorder: Epidemiology, clinical features, health consequences, screening, and assessment".)
- (See "Opioid use disorder: Psychosocial management".)
- (See "Opioid use disorder: Psychosocial management".)

- (See "Opioid withdrawal: Medically supervised withdrawal during treatment for opioid use disorder".)
- (See "Acute opioid intoxication in adults", section on 'Clinical features of overdose' and "Pharmacologic management of chronic non-cancer pain in adults", section on 'Opioids'.)
- (See "Prescription drug misuse: Epidemiology, prevention, identification, and management".)

EPIDEMIOLOGY

Prevalence — Opioid overdose deaths are responsible for more than 30 percent of all drug-related deaths worldwide [8]. In the United States, the number of opioid-involved overdose deaths more than doubled, from 25,052 to 50,178 between 2013 and 2020 [9,10].

The rise in lethal opioid overdoses has been seen with prescription opioids, heroin, and synthetic opioids other than methadone:

- Mortality from overdoses involving opioid analgesics more than tripled from 1999 to 2013 [11-14], stabilized from 2010 to 2013 [11-14], and continued to slowly rise into 2017 [15], notwithstanding declines in the rate of opioid prescribing. Since then, overdose deaths involving opioid analgesic have slowly declined, and increasingly are also attributed to synthetic opioids (eg, fentanyl) [10].

- Synthetic opioids (eg, fentanyl) are responsible for most opioid overdoses (73 percent of opioid overdose deaths in 2020) [10]. This rise has been driven by illicitly manufactured fentanyl. Fentanyl is increasingly present in other street drugs, including cocaine, methamphetamine, and counterfeit pills, and is believed to be related to increased rates of overdose death involving those substances as well [15].

- The majority of overdose deaths involving opioids also involve other drugs, such as cocaine, methamphetamine, alcohol, or benzodiazepines [16].

Risk factors — Overdose can occur at any time with any opioid agonist. A prior overdose is the strongest predictor of a future overdose and of overdose death [17]. Risk factors associated with overdose include [18]:

- Co-occurring use of sedatives or alcohol, which are also respiratory depressants; epidemiologic data also suggest elevated risk with consumption of cocaine. (See 'Prevalence' above.)

As an example, in a retrospective analysis of 315,428 privately insured patients prescribed opioid medication, concurrent use of both opioid and benzodiazepine medications was associated with an increased risk of an emergency room visit or inpatient admission for opioid overdose compared with patients receiving an opioid but not a benzodiazepine (adjusted odds ratio 2.14, 95% CI 2.05-2.24) [19].

- Recent abstinence – A period of abstinence increases the risk of overdose from relapse by lowering the patient's tolerance to opioids. A dose that would have had minimal effects on the patient when physiologically dependent can cause overdose in the abstinent patient. Patients may be at risk due to abstinence after release from incarceration, during hospitalization or after discharge, or following medically supervised withdrawal or abstinence-based treatment of opioid use disorder [20].

- Use of nonprescribed opioids, particularly when injected [20]. Variations in the (often unknown) purity and potency of heroin account for approximately 15 percent of the variation in overdose fatality [21]. Compared with injection of prescribed opioid analgesics, injection of heroin or fentanyl is approximately two and eight times as likely to result in overdose, respectively [22].

- Among prescription opioid users, higher prescribed doses [23] and discontinuation of long-term opioid therapy [24] .

- Co-occurring pulmonary disease or sleep apnea [25].

- A genetic predisposition to the respiratory depressive effects of opioids [26].

Social determinants of health are often associated with increased risk of overdose, possibly mediated by unstable life situations and interruptions in opioid tolerance [27].

CLINICAL FEATURES OF OVERDOSE

Clinical features of opioid intoxication and overdose are discussed in detail separately, as is the pharmacology of opioids. Education on the clinical features of overdose is discussed below. (See "Acute opioid intoxication in adults", section on 'Pharmacology and cellular toxicology' and "Acute opioid intoxication in adults", section on 'Clinical features of overdose' and 'Overdose education' below.)

COMMUNITY-BASED INTERVENTION

Opioid overdose prevention involves education and provision of take-home naloxone to patients at risk of an overdose, their caregivers, and household members. Broad access to naloxone has been recommended by the United States surgeon general. Programs that provide sterile syringes and safe disposal equipment to high-risk populations are well positioned to educate their clients about opioid overdose and offer naloxone to reverse overdoses. As of 2019, 94 percent of syringe access programs in the United States had initiated naloxone distribution programming [28]. Participants are taught to recognize risk factors for overdose, signs and symptoms of overdose, and how to administer naloxone.

Who should receive? — Based on guidelines from the United States Centers for Disease Control and Prevention [29], the US Food and Drug Administration (FDA) [30], and other sources, we suggest that education and take-home naloxone be provided to patients with any of the following risk factors:

- Any nonprescribed drug use, including:
  - Opioid use, particularly those:
    - Receiving or discontinuing treatment for opioid use disorder, including medication or behavioral therapies
    - At risk of decreased tolerance due to recent abstinence, including release from prison or medically supervised opioid withdrawal
  - Use of cocaine, methamphetamine, or pills purchased on the street, due to frequent presence of illicitly manufactured fentanyl in these drugs or counterfeit pills
- Suspected opioid use disorder (mild, moderate, or severe) [29].
- Receiving prescribed opioids and any of the following:
  - Receiving ≥50 morphine mg equivalents daily of prescribed opioids [29]
  - Concomitant use of other sedating drugs or medications, such as benzodiazepines [29]
  - Any history of a substance use disorder [29]
  - Any history of overdose from opioids [29]
- Risk of witnessing an opioid overdose, if such witnessing and intervening is legally protected (see the Prescription Drug Abuse Policy System for legal protections in the United States).

Misuse of prescribed opioids is also described separately, as are risk factors for overdose among patients treated with opioids for chronic pain. (See "Prescription drug misuse: Epidemiology, prevention, identification, and management", section on 'Opioid analgesics' and "Use of opioids in the management of chronic non-cancer pain".)

Components

Overdose education — Many patients do not recognize opioid-induced respiratory depression requiring emergency medical care as "overdose," but instead consider this to be an adverse reaction to medications [31]. Participants in the preventive intervention receive education to help them identify people who are more likely to overdose, to recognize clinical signs of opioid overdose, and to intervene to prevent mortality:

- Risk factors for overdose:
  - Use of nonprescribed opioids
  - Injection of opioids
  - Use of other sedating substances with opioids
  - Use of opioids after periods of reduced use or abstinence from opioids
  - Certain comorbidities, such as lung disease or obstructive sleep apnea
- Recognition of overdose:
  - Nonresponsive
  - Decreased or stopped breathing or heart rate
  - Blue or purple cast to fingernails or fingertips
- Response to overdose:
  - Try to arouse patient by administering a firm sternal rub. (See "Stupor and coma in adults", section on 'Level of consciousness'.)
  - If in respiratory distress or not breathing, administer naloxone. (See 'Formulations' below.)
  - Call emergency medical services (EMS):
    - 911 in the United States
    - 112 common in European Union countries
    - 000 in Australia

- Perform rescue breathing, chest compressions, or cardiopulmonary resuscitation (CPR), depending on respondent's skills and guidance from emergency dispatch. (See "Adult basic life support (BLS) for health care providers", section on 'Ventilations'.)

- Stay with the patient for at least three hours or until help arrives.

  Emergency medical services differ in whether they routinely transport all opioid overdose survivors to a hospital emergency department following naloxone administration. Some allow paramedics to send home patients who respond fully following an uncomplicated overdose of a short-acting opioid.

  In the absence of a paramedic or treating clinician, a patient should always go to the emergency department after naloxone. Patients who overdosed on a long-acting opioid may initially respond to naloxone but relapse when the antagonist wears off. Naloxone may also precipitate withdrawal, which could lead to further opioid use and possible overdose, and thus the patient should be observed to ensure comfort and safety.

- Place person on their side to prevent aspiration after vomiting.

Participant education takes approximately 5 to 10 minutes. A toolkit (accessible here) developed by the Substance Abuse and Mental Health Services Administration in the United States provides lay educational material on the preventive intervention [32].

Materials to assist healthcare providers in prescribing, dispensing, or educating about naloxone are available at the PrescribeToPrevent website.

Limited data suggest that education on overdose recognition and response may be effective. A clinical trial of a brief education (5 to 10 minutes) in 10 persons with current or former opioid misuse found that, compared with no education, participants receiving education were more likely to recognize opioid overdose, identify scenarios where naloxone was indicated, and report higher perceived competency in recognition [33,34].

Community-based naloxone — Naloxone is an opioid antagonist that rapidly reverses the effects of opioid overdose. A 4 mg naloxone intranasal spray is available to purchase over the counter; some insurers may cover this product even when purchased over the counter [35].

While prescribing naloxone to a patient who uses opioids has been determined to be within the realm of usual practice [36], most states in the United States have also passed legislation authorizing prescribers to provide naloxone through standing orders and/or to potential overdose witnesses, and protecting those who administer naloxone from penalties for

practicing medicine without a license. See the National Conference of State Legislatures for details on Good Samaritan laws.

Formulations

- **Naloxone intranasal spray** – Naloxone intranasal spray is available in a dispenser that delivers a premeasured dose of 4 mg (Narcan) or 8 mg (Narcan or Kloxxado). The 4 mg intranasal spray is available over the counter. Our preference is to prescribe the 4 mg spray due to fewer side effects and lack of known benefit to the higher dose. The 8 mg intranasal spray was approved by the FDA as the 4 mg intranasal spray previously approved often required a second dose [37]. However, data from naloxone distribution programs suggest that bystanders will often administer any doses that they have available. It is uncertain if both doses of the 4 mg spray were used because a higher dose was needed or because the time waiting for the drug to take effect prompted a second dose.

  Naloxone is dispensed as two doses; repeat doses may be necessary if respiratory depression continues or recurs prior to EMS arrival. Individuals are advised to wait three to five minutes after first dose before administering another dose.

- **Naloxone injection** – Injectable naloxone for use in the community is available as prefilled syringes and kits:

  - A naloxone 5 mg/0.5 mL prefilled syringe (Zimhi) has been FDA-approved for intramuscular administration by nonmedical caregivers 12 years or older. However, until further studies support its efficacy and safety, we typically do not recommend using this product as the dose vastly exceeds doses for which any data are available [38].

  - Naloxone "kits" may include a prefilled syringe (2 mg/mL), syringe cartridge, or naloxone vials (0.4 mg/mL) prescribed with syringe and needle appropriate for intramuscular or subcutaneous administration. These injectable forms of naloxone were designed for use by medical personnel in the facility or field setting, however they have been used for decades by bystanders trained in naloxone distribution programs [39,40].

Administration — The standard dose of naloxone for out-of-hospital opioid overdose reversal is 0.4 mg to 2 mg. The higher dose is associated with severe withdrawal symptoms and reluctance to seek medical assistance in the event of overdose. Intranasal naloxone at 4 mg/0.1 mL produces a blood concentration similar to 2 mg injected in healthy volunteers but may

produce a lower blood concentration in real world circumstances and has generally been well tolerated.

The increase in opioid overdose mortality associated with fentanyl has led some to suggest that naloxone is not effective in reversing fentanyl overdose. However, this increase in mortality may be explained by the known higher risk of overdose from fentanyl use compared to other opioids [22]. This is likely due a shorter window to bystander response due to a much more rapid progression from use to respiratory and cardiac arrest after fentanyl use compared to other opioids [41]. Once an overdose has progressed to cardiac arrest, naloxone is insufficient to reverse the event, regardless of the dose or formulation.

Efficacy — Analyses of survey, population, and mortality data, though methodologically limited, have reported associations between distribution of naloxone and reductions in opioid overdose death in communities. These data suggest that many opioid overdoses have been reversed with lay use of injected or intranasal naloxone. Examples include:

- An analysis compared mortality rates related to opioid overdose in communities that did and did not implement overdose education and naloxone distribution programs, finding that communities implementing the program had a relative reduction in adjusted mortality rates. The results suggested a "dose-dependent" trend in which the more naloxone distributed in a given community, the greater the relative reduction in opioid overdose mortality (adjusted relative risk of 0.73 in communities with 1 to 100 naloxone enrollments per 100,000 population, and 0.57 in communities with >100 enrollments) [3].

- A meta-analysis of evaluations of naloxone studies found that lay administration of naloxone was associated with significantly increased odds of recovery compared with no lay naloxone administration (odds ratio 8.58, 95% CI 3.90-13.25) [42].

- A survey of United States programs that distribute naloxone for lay use reported that 644 sites had provided naloxone to 152,283 laypersons and received reports of 26,463 reversals from 1996 to 2014 [43].

- An observational study of naloxone prescription to patients who were prescribed long-term opioids for chronic pain found that receipt of naloxone was associated with a 47 percent decline in opioid-related emergency department visits over the ensuing year [44].

These studies were conducted prior to FDA-approval of the autoinjector or nasal spray.

Adverse effects — Naloxone has been used safely by emergency department personnel and first responders for many decades. Two types of adverse events are seen:

- Side effects of abrupt reversal of opioid effects include nausea, vomiting, tachycardia, elevated blood pressure, and tremulousness; these are typically transient in patients without underlying cardiovascular or pulmonary disease. Serious adverse effects may include seizures and cardiac arrest, which have been observed rarely. Studies of lay reversal have reported relatively low rates of adverse events. As an example, a study of 399 reversals reported vomiting in 13 percent, anger or "dope sickness" in 9 percent, and seizure-like activity in <1 percent [45].

- Reversal of overdose effects by naloxone may be temporary. The drug's half-life is brief. Antagonism may wane before opioids are fully eliminated from the person's body, leading to recurrence of respiratory depression. This may not be a problem clinically with short-acting opioids like heroin; large studies of patients reversed with naloxone by paramedics and then released without transport to the hospital have found little to no evidence of recurrence of overdose leading to fatality [46,47].

Follow-up — Because naloxone's overdose-reversing effects can wear off, those who may administer naloxone should be advised to seek medical help and stay with the overdosed person for three hours. Some patients may need repeated doses of naloxone, particularly if long-acting opioids such as methadone are involved.

Nalmefene — Nalmefene is another opioid antagonist approved as an injection or an intranasal spray for emergency treatment of known or suspected opioid overdose. We advise against nalmefene for community reversal of opioid overdose among opioid-experienced persons due to the expected need for additional medical management, as well as a potential negative impact on the willingness of bystanders to administer reversal agents in the future. While there are decades of experience with lay administration of naloxone, there is no such experience with nalmefene. Furthermore, while the half-life of naloxone is 90 minutes, the half-life of nalmefene is 11 hours, thus any withdrawal symptoms would be prolonged and require additional medical management. The potential role of nalmefene in the emergency department setting is discussed separately. (See "Acute opioid intoxication in adults", section on 'Basic measures and antidotal therapy'.)

The initial dose is given intravenously, intramuscularly, subcutaneously, or intranasally depending on the formulation. The nasal spray comes in a 2.7 mg dose. If no effect is seen, additional doses may be administered every two to five minutes until help arrives. Dosing for the injection formulation is 0.5 mg as initial dose and 1 mg may be given two to five minutes later if no response to initial dose. Side effects, which largely consist of opioid withdrawal signs and symptoms, include nausea, vomiting, hypertension, and tachycardia.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Opioid use disorder and withdrawal".)

SUMMARY AND RECOMMENDATIONS

- **Introduction** – Drug overdose, principally due to opioids, is rising in many developed countries; in the United States, for example, it has been the leading cause of injury-related death since 2009. The incidence of opioid overdose increased dramatically between 1990 and 2017. Opioid overdose is defined as opioid-induced respiratory depression such that assistance is needed to revive the person. (See 'Introduction' above.)

- **Overdose education** – The risk of overdose should be discussed with all patients who use opioids. Providers should clarify that "overdose" does not necessarily imply use of an abnormally large amount of opioids, but instead that respiratory depression from opioids that can occur for many reasons. (See 'Overdose education' above.)

- **Who should receive?** – We suggest that education and take-home naloxone be provided to patients with any of the following risk factors (**Grade 2B**) (see 'Who should receive?' above):

  - Any nonprescribed drug use, particularly:

    - Receiving or discontinuing treatment for opioid use disorder, including medication or behavioral therapies

    - At risk of decreased tolerance due to recent abstinence from opioids, including release from prison or medically supervised opioid withdrawal

    - Use of cocaine, methamphetamine, or pills purchased on the street, due to frequent presence of illicitly manufactured fentanyl in these drugs

  - Suspected opioid use disorder (mild, moderate, or severe) [29]

  - Receiving prescribed opioids and any of the following:

    - Receiving ≥50 morphine mg equivalents daily of prescribed opioids [29]

- Concomitant use of other sedating drugs or medications, such as benzodiazepines
- Any history of a substance use disorder
- Any history of overdose from opioids

- Risk of witnessing an opioid overdose, if such practice is legally protected (see the Prescription Drug Abuse Policy System for legal protections in the United States)

- **Community-based interventions** – Intervention to prevent opioid overdose is comprised of education and provision of take-home naloxone to patients at risk of an overdose, their caregivers, and household members. Participants are taught to recognize risk factors for overdose and signs and symptoms of overdose, and how to administer naloxone. (See 'Overdose education' above and 'Formulations' above.)

  - Take-home naloxone is available in easy-to-administer forms, using an intranasal spray or autoinjector to deliver fixed doses.
  - The usual adult dose of naloxone is 0.4 mg when injected intravenously, intramuscularly, or subcutaneously; or 4 mg of the 4 mg/0.1 mL concentration when administered intranasally.
  - Repeat doses may be necessary if respiratory depression continues or recurs prior to emergency medical services arrival.

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