MedStar Health

Prevention of Fatalities from Opioid Overdose: Prescribing Naloxone in the Outpatient Setting

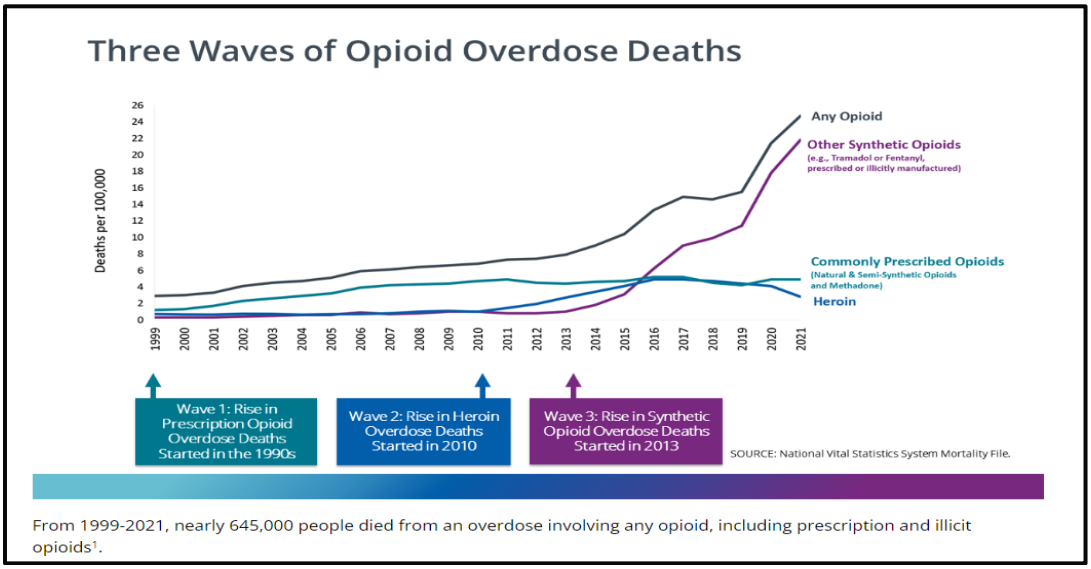
Clinical Practice Guideline

"These guidelines are provided to assist physicians and other clinicians in making decisions regarding the care of their patients. They are not a substitute for individual judgment brought to each clinical situation by the patient's primary care provider-in collaboration with the patient. As with all clinical reference resources, they reflect the best understanding of the science of medicine at the time of publication but should be used with the clear understanding that continued research may result in new knowledge and recommendations."

Background:

The United States continues to experience a crisis of preventable overdose death and disability. Over 107,000 people died of a drug overdose in 2021, the highest number on record.[1] Over 75% of the nearly 107,000 drug overdose deaths in 2021 involved an opioid.[2] Around 91% of opioid related deaths were found to be accidental.[1, 2,3.]

The CDC categorizes the rise in opioid related deaths as a multi-layer problem that occurred in three waves: first, an increase in prescription opioids, second an increase in heroin use, and finally an increase in synthetic (non-methadone) opioid use (particularly illicitly manufactured fentanyl). Nearly 88% of opioid-involved overdose deaths involved synthetic opioids. The market for illicitly manufactured fentanyl continues to change, and it can be found in combination with heroin, methamphetamine, counterfeit pills, and cocaine.[1]



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District of Columbia has close to 430 opioid related deaths per year – contributing to the second highest opioid mortality rate in the country with 63.6 deaths per 100,000 persons compared to the national average of 32.4 per 100,000 population. In 2021, Maryland ranked 11th in the nation with the highest number of drug-related overdose deaths. Maryland experienced 42.8 deaths per 100,000 people with the total number being 2,737 deaths.[1,2,3,8.]

Risk factors associated with overdose include [4, 7]:

- 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.
- Use of other respiratory depressants, sedatives/alcohol concurrently.
- Recent abstinence increases the risk of overdose from relapse by lowering the patient's tolerance to opioids as after release from incarceration, during/after hospitalization or following a medically supervised abstinence-based treatment of OUD.
- Use of non-prescribed opioids when injected due to variations in purity and potency of heroin. Injection of heroin or fentanyl is approximately 2-8 times likely to result in overdose, respectively.
- Higher prescribed doses of opioids.
- Discontinuation of long-term opioid therapy.
- Existing chronic pulmonary diseases or sleep apnea.
- Genetic predisposition to respiratory depressive effects of opioids.
- Social determinants of health possibly due to unstable life situations and interruption in opioid tolerance.

Clinical Presentation of overdose [4,7]:

It is important to educate patients to recognize the signs of opioid overdose:

- small, constricted pin-point pupils
- slow shallow/no breathing, choking/gurgling breath sounds.
- Drowsy/Nonresponsive
- cold/clammy skin
- bluish/purple discoloration lips & nails.

Overdose prevention:

Involves education and provision of take-home naloxone to patients at risk of an overdose and their care givers. The US surgeon general recommends broad access to Naloxone.[5] **This guideline focuses specifically on the use of prescription naloxone to treat opioid overdose.**

Naloxone a pure opioid antagonist, displaces opioids from the receptors to which they attach, quickly and effectively reversing opioid overdose before it can become fatal. Nearly every person who died of a witnessed opioid overdose could have been saved if those present had naloxone with them. Per CDC only 1 naloxone prescription is dispensed for every 70 high-dose opioid prescriptions.[4] As a healthcare professional, we play a critical role in raising awareness about naloxone and promoting its use by engaging in conversations to educate and counsel patients and families about its benefits; offering naloxone when prescribing opioids, especially to patients at increased risk for overdose; providing education on overdose prevention.

Co-prescribing naloxone to individuals at elevated risk of having or witnessing an opioid overdose has been endorsed by the American Medical Association (AMA)[25] and recommended by the Centers for

Disease Control and Prevention (CDC). Maryland regulations (COMAR 10.13.03) support the co-prescribing of naloxone for patients at elevated risk of experiencing or witnessing an overdose[26].

Who Should Receive Naloxone [4, 7]:

When prescribing opioids, to note that everyone is at risk for opioid overdose. Naloxone prescribing is strongly encouraged in situations and conditions that may make an opioid overdose more likely. The following factors increase risk of opioid overdose:

- Any nonprescribed opioid use especially in those:
  - Patients at risk of returning to a high dose for which they have lost tolerance (e.g., patients undergoing tapering or recently released from prison).
  - who are receiving or discontinuing treatment for opioid use disorder.
- Substance use disorder:
  - Use of cocaine/methamphetamine or other illicit street drugs due to frequent presence of fentanyl in these drugs or counterfeit pills.
  - Opioid Use disorder
- Prescription opioids and any of the following:
  - Patients taking 50 mg MME daily or higher.
  - A history of overdose from opioids
  - Any history of substance use disorder.
  - Concurrent alcohol, benzodiazepines, or other sedating drugs
  - Patients with sleep disordered breathing, COPD, liver disease, mental health disorders.
- Naloxone should also be prescribed if voluntary request/risk of witnessing an opioid overdose.

Naloxone Overview[9, 27]:

- Opioid antagonist that competes for the opioid receptor with strongest affinity for the mu receptor.
- Has been used in emergency settings for many decades.
- Often used by EMT's and other emergency non-physician personnel.
- FDA approved formulations include IV and IM injections (including an auto-injector) and an intranasal formulation.
- Safe for pregnant women & children
- Only reverses overdose from all opioids, heroin, fentanyl, and prescription opioid medications. Cannot reverse overdose from benzodiazepines, cocaine/ ecstasy, methamphetamines, however in situations of overdose patients should be advised to administer naloxone just in case, since drugs are increasingly mixed with opioids like fentanyl without a person knowing it. It will not hurt someone if overdosing on drugs other than opioids. Once overdose has progressed to cardiac arrest, naloxone is insufficient to reverse the event, regardless of dose or formulation. If no response to naloxone, an alternative explanation should be considered.
- Works quickly, acts in 2-3 minutes and lasts on average 30-90 minutes.
- Note that repeated administration is often necessary since the half-life of naloxone is much shorter than that of most opioids. Consequently, EMS should be called immediately when naloxone is given. Patient should not be left alone till EMS arrives and often need monitoring for several hours till breathing returns to normal.
- To remind patients, it is a safe medicine, easy to use, will not harm someone if have not taken opioids. Most states have Good Samaritan laws to protect those who are overdosing and anyone assisting them from arrest/charges or combination of these.[6]
- No potential for misuse/addiction.
- Adverse effects are rare:

- Patients who experience an allergic reaction from naloxone, such as hives or swelling in the face, lips, or throat, should seek medical help immediately.
- Most common are acute opiate withdrawal (unpleasant but almost never fatal)

- Most serious include:
  - Seizures, occurring in 0.6% and causing death in 0.2% of cases.
  - Pulmonary edema, occurring in 1.5% and causing death in 0.2% of cases.
  - Pneumonia, occurring in 0.3% and causing death in 0.3% of cases.
  - Cardiovascular arrest, occurring in 1.7% and causing death in 0.9% of cases. Note: Consensus is that the above fatal events may be due to the overdose rather than the naloxone.

❖ Naloxone markedly decreases fatalities from opioid overdose.

Naloxone Formulations
(Adapted from the Medical Letter [28, 29,30, 31], and UpToDate Sept 2023)

Route	Dose	Formulation	Cost/each
IV/IM/SC	0.4-2mg Can be repeated every 2-3 minutes. 1mg per nostril if converted to intranasal administration using a mucosal atomization device	Generic solution in 1 mL or 10 mL vials	1mL: $24 10mL: $150
IM/SC	5-10mg (one prefilled syringe) Can be repeated every 2-3 minutes	Zimhi® and generic prefilled syringes (Zimhi-Instructions for Use)	Zimhi®: $75 Generic: $40
Intranasal*	4-8mg in one nostril Can be repeated every 2-3 minutes in alternating nostrils	Kloxxado®, Narcan®, or generic	Kloxxado®: $75 Narcan®: $72 Generic: $27

*Nasal spray has slower onset than IM or IV formulations
For more detailed information about formulations, visit PrescribetoPrevent[12]
Please note, the prescription may be written for the patient (and likely administered by a 3rd party) Or it may be prescribed directly to a significant other who will administer it to the patient.

How to prescribe

Intramuscular:
Rx = Naloxone injection 0.4mg/1ml vial and 3cc, 23g, 1-inch syringes
Unit: 1 ml vial
Disp.: two vials
Refill = PRN
Sig: For suspected opioid overdose, inject 1ml IM in deltoid or thigh, may repeat after 3 minutes if no or minimal response.

Intranasal:
Rx = Naloxone 1mg/ml needless syringe and intranasal mucosal atomizer device
Unit: 2 ml vial
Disp.: two vials
Refill = PRN
Sig: For suspected opioid overdose, spray 1ml in each nostril, may repeat after 3 minutes if no or minimal response.

Intranasal:
Rx= Narcan nasal spray
Unit: 4 or 8 mg
Disp.: one carton (2 devices)
Refill= PRN
Sig: For suspected opioid overdose, spray the contents of one device in either nostril, may repeat after 3 minutes if no or minimal response

Nalmefene
Nalmefene is another opioid antagonist approved as an injection or an intranasal spray for emergency treatment of known or suspected opioid overdose. 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.

Formulations:

Route	Dose	Formulation	Cost/each
Intranasal	2.7mg in one nostril Can repeat every 2-5 minutes in alternating nostrils	Opvee® (brand only)	$59
IV (Primary Route) Can also be given IM or SC if venous access cannot be established	If non-opioid dependent: Initial dose: 0.5mg /70kg Second dose: 1mg/70kg may be given in 2-5 minutes if needed. If opioid dependent: Challenge dose: 0.1/70kg If no evidence of withdrawal in 2 minutes, proceed with initial dose. Initial dose: 0.5mg/70kg Second dose1mg/70kg may be given in 2-5 minutes if needed.	Generic only 2mL vial	$36

* In both cases, if a total dose of 1.5mg/70kg has been administered without clinical response, additional Nalmefene injection is unlikely to have an effect. Patients should not be given more Nalmefene injection than is required to restore the respiratory rate to normal, thus minimizing the likelihood of cardiovascular stress and precipitated withdrawal syndrome. (See Nalmefene dosing and administration)

Side effects, which largely consist of opioid withdrawal signs and symptoms, include nausea, vomiting, hypertension, and tachycardia.

Prescribing
Naloxone standing orders[33] allow pharmacists to dispense naloxone to any person without a prescription and irrespective of training on use.
Maryland Standing Order:

Patients may obtain naloxone from a pharmacy by presenting a prescription written by their health care provider. In the absence of such a prescription, individuals in Maryland can obtain naloxone from a pharmacy through the statewide standing order allowing all Maryland-licensed pharmacists to dispense naloxone, including the necessary supplies for administration, to anyone who may be at risk for opioid overdose or in a position to assist someone believed to be experiencing opioid overdose. A person-specific paper or electronic prescription is not required for a pharmacist to dispense naloxone under the standing order. For more information visit: Maryland Naloxone Standing Order

- Naloxone is not free at a pharmacy, but it is covered by many insurance plans (copays vary) and Maryland Medicaid.

- Overdose Response Programs provide naloxone for free. Residents in certain Maryland counties may be eligible to receive free naloxone delivered to their home. Please view Maryland ORP map Reach out to ask if they offer mail delivery naloxone.

Naloxone in DC
Naloxone is available in every ward in the District at no cost and no ID or prescription at multiple locations.

- The map shows where to get naloxone.
- Patients can text LiveLongDC to 888-811 and an outreach worker will deliver it within two business days to addresses in DC.
- Patients can also order naloxone to be mailed directly to their home here. Naloxone is shipped within 5-7 business days using discrete packing.
  For more information visit: Naloxone-in DC

Regulatory Update:
On March 29th, 2023, the FDA announced that it was approving Narcan, 4mg naloxone hydrocholoride nasal spray to be distributed for OTC nonprescription use. Moving naloxone to OTC distribution is a crucial step in making full use of its lifesaving capacity and likely increase awareness of its role in overdose prevention and uptake. It will need to be affordable to be accessible.[11.]
Other Maryland Regulatory Updates are available here.

Legal & Liability considerations
Naloxone is FDA-approved for treatment of opioid overdose; prescribers need not worry about legal risks.[8] Studies have not shown an increase in abuse or in overdose with naloxone prescriptions.[8,9.]
Most state laws and regulations now permit physicians to prescribe naloxone to a third party, such as a potential overdose witnesses.[8] More information on state policies is available from the Prescription Drug Abuse Policy System's Naloxone Overdose Prevention Laws web page: https://pdaps.org/

Screening patients for opioid use disorder:
SBIRT (Screening, Brief Intervention, and Referral to Treatment) is an evidence-based, comprehensive, and integrated public health approach to the delivery of early intervention and treatment services to patients who have risky alcohol or drug use.
https://health.maryland.gov/bha/Pages/SBIRT.aspx

Billing & Coding:
SBIRT can be used to bill time for counseling a patient. Complete the screening/brief intervention, counsel patient on how to recognize overdose and how to administer naloxone, refer to drug treatment program if

appropriate. The codes for Screening, Brief Intervention, and Referral to Treatment (SBIRT) can be used to bill time for counseling a patient about how to recognize overdose and how to administer naloxone. Billing codes: https://www.samhsa.gov/sbirt/coding-reimbursementCMS-SBIRT Services

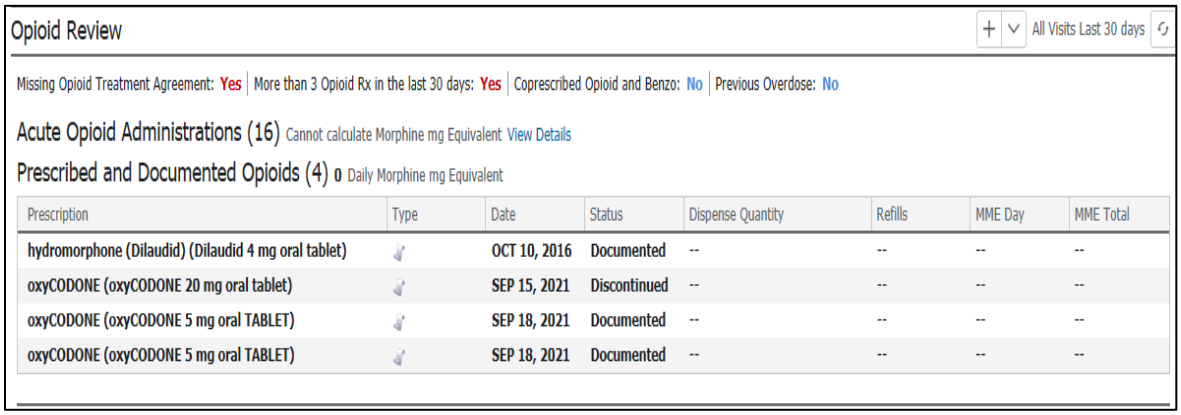
For counseling and instruction on the safe use of opioids, including the use of naloxone outside the context of SBIRT services, providers should document the time spent in medication education and use the E&M (Evaluation and Management) code that accurately captures the time and complexity. For example, for new patients deemed appropriate for opioid pharmacotherapy and when a substantial and an appropriate amount of additional time is used to provide a separate service such as behavioral counseling (e.g., opioid overdose risk assessment, naloxone administration training), consider using modifier– 25 in addition to the E&M code.

Resources

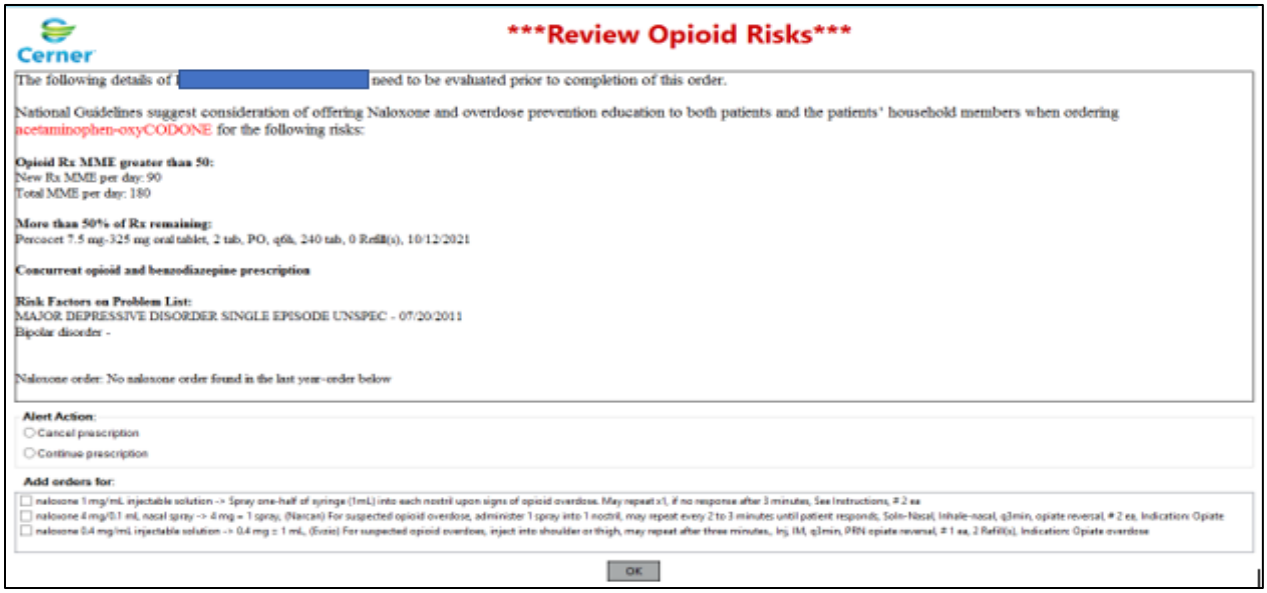
- Learn how to use naloxone.
- Talking with patients about the role Naloxone can have in saving lives:
  - CDC-Talking About Naloxone with Patients Prescribed Opioids
  - CDC-Naloxone Fact Sheets
  - CDC-Naloxone Training
  - CDC MME Conversion Factors Table: The 2022 Opioid Clinical Practice Guideline provides an MME conversion factors table for opioids which account for over 99% of opioid pain medications dispensed from 2018-2021 by retail pharmacies in the U.S. As such, this table is CDC's sole resource related to MME conversion factors.
- Before it's **too late:**
  - Naloxone988 Crisis Hotline
  - Substance Use Treatment Locator-Find Treatment (Search)
  - Good Samaritan Law
- Maryland Get Connected Get Help: MD 211
- Learning about harm reduction:
  - The National Harm Reduction Coalition has a great resource center.
  - The Maryland Harm Reduction Training Institute (MaHRTI) website includes live and on-demand courses.
- Materials to assist healthcare providers in prescribing, dispensing, or educating about naloxone are available at the PrescribeToPrevent website.
- Substance Abuse and Mental Health Services Administration in the United States provides lay educational material on the preventive intervention. SAMHSA toolkit

Resources MedStar:

- Peer Recovery Coach Support: Enter orders: *Consult Peer Recovery Coach in MedConnect*
- Social Needs Tool: In dark blue MENU bar OR
- Non MedConnect users can go to Find Help Tool
- MedConnect Opioid Review: Point of care decision support within MedConnect opioid review component available in the primary care provider view provides information for (see image below):
  - Controlled substance agreement available
  - more than 3 opioids have been prescribed in the past 30 days.
  - If concurrent prescriptions for opioids and benzodiazepines
  - Documentation of a prior overdose.



- MedConnect Prompt for Naloxone Prescribing:
  When prescriptions are entered or renewed for patients at risk for overdose, prescribers receive a prompt suggesting that a prescription for naloxone be provided as well (see image below). These risks include:
  - Prescribing an extended-release opioid when the patient is opioid naïve.
  - Daily MME > 50
  - 3 or more narcotic analgesic prescriptions in the past 30 days
  - More than 50% of prescribed narcotic remaining (looking at the last 120 days)
  - Concurrent opioid and benzodiazepine prescriptions
  - Active Problems documented: Alcoholism, Misuses drugs, Opioid abuse, Breathing-related sleep disorder, Depressive disorder, Disorder of liver, Illicit drug use, Mental disorder, Mood disorder, Overdose of drug groups primarily affecting the central nervous system, Renal impairment, Severe depression, Sleep apnea.
  - History of the following diagnoses: Poisoning by opioids/ heroin/ benzodiazepines/ synthetic narcotics/unspecified narcotics
  - 2 or more ED visits with narcotic administration in the past 30 days



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