Department of Public Health
CITY OF PHILADELPHIA

Philadelphia Department of Public Health
Division of Substance Use Prevention and Harm Reduction

PALAK RAVAL-NELSON, PHD, MPH
Health Commissioner

FRANK FRANKLIN, PHD, JD, MPH, FCPP
Deputy Health Commissioner

DANIEL TEIXEIRA DA SILVA, MD, MSHP
Medical Director, Division of Substance Use Prevention and Harm Reduction

Health Update

Responding to overdose and withdrawal involving medetomidine

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SUMMARY POINTS

- Since medetomidine was detected in the illicit fentanyl supply, the number of people presenting for withdrawal treatment to Philadelphia's emergency department has more than doubled.
- Medetomidine withdrawal syndrome is a severe consequence of substance use often requiring admission to an intensive care unit for treatment.
- Triaging patients with suspected medetomidine withdrawal requires early initiation of alpha-2-agonist and long-acting opioid treatments and frequent monitoring.
- Responding to opioid overdoses involving medetomidine should prioritize breathing over responsiveness.
- Use of low-dose naloxone is preferred for overdose reversal.
- Medetomidine is more prevalent in Philadelphia's illicit fentanyl supply than xylazine.
- Medetomidine use has not been shown to be associated with wounds.

Drug-related morbidity and mortality remain high in Philadelphia and is complicated by a dangerous and changing drug supply. Medetomidine, a veterinary alpha-2 agonist, is 100-200 times more potent than xylazine.[1] Medetomidine is also present in over 70% of Philadelphia's illicit fentanyl, which is more than xylazine's presence in 30-40% of Philadelphia's illicit fentanyl supply.[2–4]

Similar to xylazine, medetomidine is a synthetic alpha-2 agonist sedative used in veterinary medicine. In human medicine, medetomidine is most similar to dexmedetomidine (Precedex®) and clonidine. Medetomidine can produce a severe withdrawal syndrome that is characterized by tachycardia, severe hypertension, waxing and waning alertness, tremor, and intractable nausea and vomiting.[5–7] Since the introduction of medetomidine to Philadelphia's illicit fentanyl supply, the number of people presenting to the emergency department for withdrawal has more than doubled.[8] A Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR) described 165 hospitalized patients with suspected medetomidine withdrawal syndrome in Philadelphia, of which 91% were admitted to an intensive care unit and 24% were intubated.[5] A peer-reviewed publication describing the efficacy of withdrawal management in a local Philadelphia health system demonstrated a need to update withdrawal protocols to effectively treat medetomidine withdrawal syndrome.[9] In addition, overdoses involving medetomidine are associated with prolonged sedation that requires adapting overdose response protocols to prioritize breathing rather than responsiveness.[10,11] Lastly, presentations for substance-use related wounds have decreased by nearly 50% since medetomidine was introduced to Philadelphia's illicit fentanyl supply.[8] Xylazine-associated wounds remain a public health concern, but surveillance data suggests that medetomidine is not associated with wounds.

Below are recommendations for adapting overdose responses to address prolonged sedation from medetomidine, and tips for triaging patients with medetomidine withdrawal syndrome in behavioral health settings.

Tips for triaging patients with medetomidine withdrawal syndrome in behavioral health settings

(Note: This is an area that is evolving and there is no evidence-based consensus on management yet. The information here is based on hospital-based Addiction Medicine clinician experience to date.)

Medetomidine withdrawal syndrome has been described in two CDC MMWR's and characterized as having the signs and symptoms listed below.[5,6] The onset of signs and symptoms have been described as beginning abruptly with rapid progression within hours of last use. Local providers have described symptoms peaking within 18-36 hours. Presentations of medetomidine withdrawal syndrome have been associated with end-organ damage, such as non-ST elevation myocardial infarction (NSTEMI) and Posterior Resolving Encephalopathy Syndrome (PRES).[5] Many patients with medetomidine withdrawal syndrome need to be treated with medications that are only available in the hospital, such as dexmedetomidine. The guidance below is for clinicians who care for people who use drug outside of the hospital setting.

- **Signs and symptoms of medetomidine withdrawal syndrome:**
  - Tachycardia
  - Severe hypertension
  - Nausea and vomiting
  - Waxing and waning alertness
  - Anxiety
  - Diaphoresis
  - Restlessness
  - Tremor – also described as myoclonic jerks that can appear like seizure activity; however, to date, there has been no evidence that medetomidine is associated with seizures.

- **Treatment principles:**
  - Early and repeated screenings and clinical assessments – onset of medetomidine withdrawal can be rapid and variable.
  - Use parenteral medications (e.g., intramuscular injections and patches) because patients may not tolerate oral medications.
  - Early initiation of alpha-2 agonists.
    - Clonidine is preferred. Some patients may require maximum oral doses in addition to patches.
    - In some cases, patients may require alpha-2-agonists, such as tizanidine or guanfacine, in addition to clonidine.
  - Early and rapid initiation of long-acting opioids for treatment of fentanyl withdrawal.
    - Methadone is preferred.
  - More intensive patient monitoring and vital signs for the first 24 hours.
    - Ideally, every 1-2 hours for the first 24 hours with reduction as clinically indicated.
  - Obtain EKG to assess QTc.
    - Metabolic derangements from nausea and vomiting increases the risk of prolonged QTc interval.
    - Prolonged QTc should be taken into consideration when selecting medications. Many antiemetics and antipsychotic medications can prolong the QTc interval and increase the risk of arrhythmia.
  - Symptom management with adjunctive medications:
    - Anxiety and restlessness: Olanzapine is preferred. Consider hydroxyzine and benzodiazepines.
    - Nausea and vomiting: Olanzapine is preferred. Consider prochlorperazine and chlorpromazine.
    - Pain: Short acting opioids and ketamine are preferred concurrently with acetaminophen and NSAIDs. Consider gabapentin.
  - Screen for medical comorbidities that can impact effectiveness of treatment and/or require more intensive monitoring, such as:
    - Heart disease (e.g., heart failure, arrhythmia, hypertension)
    - Lung disease (e.g., COPD, asthma)
    - Liver disease (e.g., cirrhosis, chronic hepatitis C, alcohol-related liver disease)
    - Seizure disorders
    - Psychiatric disorders

  - Screen for substance use and substance use disorders other than opioid use and opioid use disorders that may contribute to withdrawal presentation.
    - Alcohol and sedatives (e.g., benzodiazepines)
    - Stimulants (e.g., methamphetamine, cocaine)
  - For severe symptoms that are not responsive to treatment, the patient may require transfer to a higher level of care (emergency department, acute care hospital, or intensive care unit) for continuous cardiac monitoring, airway protection, and intravenous infusions/medications.

- **Indications to consider transferring patients to a higher level of care:**
  - Severe hypertension (SBP ≥ 180 or DBP ≥ 120)
  - Intractable nausea and vomiting
  - Waxing and waning alertness/hypoactive delirium
  - Chest pain
  - Unable to sufficiently monitor patients
  - Persistent QTc prolongation (> 500 ms); particularly if patients continue to need medications that can cause QTc interval prolongation
  - Severe symptoms that do not improve within 4-6 hours of initiating treatment

Recommendations for adapting overdose response to medetomidine

After administering naloxone, the person experiencing an opioid overdose may still be sedated from medetomidine and may not be responsive.[11] Overdose response should focus on breathing and respiration instead of responsiveness. Historically, checking for responsiveness has been a first step to overdose response. However, due to medetomidine involvement in opioid overdoses, the first step should be to check for breathing.

- **Steps for overdose response:**
  1) Check for breathing
  2) Check for responsiveness
  3) Administer naloxone
  4) Call 911
  5) Administer rescue breathing

- **Methods to assess breathing include:**
  - Look for chest movement
  - Watch shoulders for rising and falling
  - Listen for breaths and if they sound strained or choked
  - Hold an object that collects condensation in front of the person's mouth, such as a glass (e.g., a phone screen), metal (e.g., a key) or a piece of plastic (e.g., rescue breathing mask)
  - Confirm 1 breath is taken every 5 seconds

Administer the amount of naloxone needed to restore breathing. Use preferred naloxone products to avoid precipitating withdrawal. On May 8, 2025, the Pennsylvania Department of Health updated their naloxone standing order with two tiers.[12] Lower dose naloxone products such as 4mg intranasal sprays (i.e., Narcan®, generic), 3mg intranasal spray (i.e., Revive®), 2mg LuerJet luer-lock prefilled syringe with atomization device, and 0.4mg intramuscular injection are preferred. The Philadelphia Department of Public Health has produced flyers providing information on different naloxone formulations for the general public and clinicians/pharmacists.

After breathing is restored by using naloxone, the person may still be sedated. Use the following methods to reduce the harms of prolonged sedation due to medetomidine:

- If lying, place the person in the recovery position.
- If sitting, reposition the person's head, possibly tilting it back and to the side, to avoid a blocked airway.
- Check that the person's limbs are not "pinned".

- Massage the person's limbs to improve circulation
- Move the person to a safe place
    - (e.g., away from/out of street, away from train tracks, not in the middle of the sidewalk).
- Plan for monitoring the person until they become responsive

Resources

Medetomidine public health reports and clinical webinars

- Division of Substance Use Prevention and Harm Reduction Medetomidine Webpage
- Penn Center for Addiction Medicine and Policy – Medetomidine Webpage and Webinar
- University of Pittsburgh Medical Center – Clinical Implications of Medetomidine Webinar
- Jefferson Center for Connected Care Evolving Overdose Response Webinar and Slides
- Philadelphia Department of Public Health – Health Alert and Community Alert on Medetomidine
- Philadelphia Department of Public Health – Health Alert and Community Alert on Medetomidine Withdrawal
- Philadelphia Department of Public Health CHART on Changes in Philadelphia's Drug Supply and Substance Use-Related Emergency Department Visits
- CDC Morbidity and Mortality Weekly Report – Severe Medetomidine Withdrawal, Philadelphia
- CDC Morbidity and Mortality Weekly Report – Severe Medetomidine Withdrawal, Pittsburgh
- CDC Morbidity and Mortality Weekly Report – Opioid Overdoses involving Medetomidine, Chicago

Harm Reduction Supplies and Trainings from the Philadelphia Department of Public Health

- Request medetomidine test strips
    - Fentanyl test strips and xylazine test strips are also available
    - Drug test strips instructions: fentanyl, xylazine, medetomidine
- Request naloxone
- Attend a virtual Overdose Prevention and Reversal Training
- Naloxone flyer for the general public
- Naloxone flyer for clinicians/pharmacists

Connect with Substance Use Disorder Treatment

- Behavioral Health Services Initiative (uninsured): 215-546-1200
- Community Behavioral Health (Medicaid): 888-545-2600
- CareConnect Warmline: 484-278-1679
- DBHIDS Medication Assisted Treatment: https://dbhids.org/services/addiction-services/mat/
- SAMHSA National Helpline: 800-662-HELP (4357)
- For a full list of resources, visit substanceusephilly.com/treatment

Recommend patients try not to use alone. If that is what they are doing, then provide these resources:

- The National tollfree Never Use Alone Hotline: 800-484-3731 or 877-696-1996
- The tollfree SafeSpot hotline: 800-972-0590

Get naloxone and fentanyl test strips at substanceusephilly.com/get-supplies or have them mailed to you for free and confidentially at https://nextdistro.org/philly

Learn how to use fentanyl test strips:

- https://www.cdc.gov/stopoverdose/fentanyl/fentanyl-test-strips.html
- https://www.youtube.com/watch?v=GmhE6UOZ9YY

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