U.S. Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 74 / No. 15
May 1, 2025

Overdoses Involving Medetomidine Mixed with Opioids — Chicago, Illinois, May 2024

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Abstract

Medetomidine, a nonopioid sedative not approved for use in humans, has periodically been detected in illegally manufactured opioids across North America since 2022. On May 11, 2024, the Chicago Department of Public Health (CDPH) and the Illinois Department of Public Health were alerted by hospitals and the Illinois Poison Center to an increase in emergency medical services responses for suspected opioid-involved overdoses with atypical symptoms, mostly clustered on Chicago's West Side. CDPH and CDC investigated and identified 12 confirmed, 26 probable, and 140 suspected overdoses involving medetomidine mixed with opioids among patients treated at three hospitals in Chicago's West Side during May 11–17, 2024. Medetomidine had not been previously identified in Chicago's illegal drug supply. Fentanyl was identified in all drug samples and blood specimens containing medetomidine. Most patients were male, non-Hispanic Black or African American, and aged 45–64 years; most patients with confirmed cases experienced bradycardia and had no or only a partial response to naloxone. This cluster is the largest reported for confirmed medetomidine-involved overdoses. Multisector surveillance, including by health care providers, toxicology laboratories, and public health personnel, was essential for quickly identifying and responding to new adulterants in the illegal drug supply. Because all specimens and samples in this investigation that contained medetomidine also contained natural or synthetic opioids, administering naloxone for all suspected opioid-involved overdoses remains crucial.

[*] These authors contributed equally to this report.

Introduction

On May 11, 2024, the Chicago Department of Public Health (CDPH) and the Illinois Department of Public Health (IDPH) were alerted by the Overdose Detection Mapping Application Program[†] that 50 emergency medical services (EMS) responses for suspected opioid-involved overdoses occurred that day, a number more than two standard deviations above the 2023 daily average (27.4) in Chicago. Events were mostly clustered on Chicago's West Side. Area hospitals and the Illinois Poison Center (IPC) also notified CDPH of several patients observed with bradycardia and suspected opioid-involved overdose symptoms not fully reversed by naloxone during the weekend of May 11.

[†] The program, developed by the Office of National Drug Control Policy, links first responders and records management systems to a mapping tool to track overdoses and stimulate real-time response and strategic analysis across jurisdictions. ODMAP

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Methods

Initial toxicologic tests from samples of bagged powders in the possession of five patients in the emergency department (ED) detected medetomidine mixed with fentanyl, in varying concentrations and ratios. Medetomidine, a central nervous system depressant not approved for use in humans and potentially more potent than xylazine (*1*), had recently appeared as an adulterant in the national illegal drug supply (*2*); this medetomidine detection represented the first detection in Chicago.

On May 17, CDPH requested CDC assistance to investigate the suspected opioid-involved overdose cluster. The investigation used four data sources for analysis: 1) blood specimen and drug sample results sent by hospitals on the advice of IPC to the Drug Enforcement Administration's Toxicology Testing Program's (DEA TOX) contract laboratory at University of California, San Francisco, and the Center for Forensic Science Research and Education with the assistance of the Chicago Recovery Alliance, 2) mortality data from the Cook County medical examiner's office, 3) EMS records from the Chicago Fire Department, and 4) medical records from three EDs on Chicago's West Side that received the most patients from suspected opioid-involved overdose EMS responses during May 11–17, 2024.

Using these data sources, a case identification algorithm was developed defining patients as having a confirmed, probable, or suspected overdose involving medetomidine mixed with opioids. A confirmed case was defined as a case in a patient treated for suspected opioid-involved overdose[§] whose blood specimen tested positive for medetomidine. A probable case was defined as a case in a patient who 1) possessed a drug sample containing medetomidine or 2) experienced bradycardia (heart rate less than 60 beats per minute) with symptoms not fully reversed by naloxone (defined as persistent altered mental status after naloxone administration) during the EMS response or upon ED arrival. Suspected cases were all other suspected opioid-involved overdoses among patients who were admitted to one of the three hospital EDs, even without clinical or testing evidence for medetomidine, because the patients were admitted during a time of medetomidine infiltration of the drug supply. A patient was considered to not have a case of overdose involving medetomidine mixed with opioids if their blood specimen tested negative for medetomidine.

Demographic characteristics, clinical signs and symptoms, and clinical course were abstracted from medical charts for confirmed and probable cases. Partial chart abstractions[¶] were completed for suspected cases. Descriptive data were managed and analyzed using SAS software (version 9.4; SAS Institute). This activity was

[§] *International Classification of Diseases, Tenth Revision* codes and chief complaints for suspected opioid-involved overdoses were identified on the basis of the CDC definition for ED visits. CDC All Opioid Overdose v4 Parsed

[¶] Partial chart abstractions included demographic information, naloxone doses received, response to naloxone, patient symptoms and vital signs, and hospital admission and disposition. Full chart abstractions included the partial chart data as well as substance use history, underlying health conditions and medications, overdose event details, hospital treatments, complications, and linkage to care. Not all data obtained are included in this report.

The *MMWR* series of publications is published by the Office of Science, U.S. Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30329-4027.

Suggested citation: [Author names; first three, then et al., if more than six.] [Report title]. MMWR Morb Mortal Wkly Rep 2025;74:[inclusive page numbers].

reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.**

Results

Among 181 patients treated for suspected opioid-involved overdose at the three EDs during May 11–17, CDPH identified 12 confirmed, 26 probable, and 140 suspected cases; three patients were determined to not have experienced a medetomidine-involved overdose (Figure 1) (Figure 2).

Confirmed and probable cases were identified using results from 15 blood specimens from unique patients and 10 drug samples from unique patients sent for testing; three patients had both blood specimens and drug samples sent for testing (Figure 1). Among the 15 blood specimens, 12 tested positive for medetomidine in combination with the following substances: diphenhydramine (12 patients), fentanyl (12), quinine (11), benzoylecgonine (10),†† morphine (six),§§ xylazine (six),¶¶ and bromazolam (six).*** Among the 10 drug samples, five tested positive for medetomidine and fentanyl,††† and among these five, medetomidine was also present in corresponding blood specimens for three. Thus, drug sample testing identified two additional probable cases; the remaining 24 probable cases were identified using clinical data.

The 38 confirmed and probable cases were among mostly male persons (84%), non-Hispanic Black or African American persons (87%), and persons aged 45–64 years (63%) (Table). Among all 38 confirmed and probable cases, 18 (47%) patients reported heroin as the intended drug of use at the time of overdose. Snorting was the most common route of administration, reported by eight (21%) patients. However, the drugs that patients intended to use and route of administration were unknown for most patients. The most common clinical signs and symptoms were hypertension (36; 95%), bradycardia (33; 87%), altered mental status (32; 84%), pinpoint pupils (32; 84%), and hypoxemia with blood oxygen saturation <90% (18; 47%). Five persons required treatment with atropine, a first-line medication for the treatment of bradycardia. Elevated systolic blood pressure ≥180 mm Hg was observed in 16 (42%) patients. Among 12 confirmed cases, 11 (92%) patients experienced partial or no improvement of symptoms after naloxone administration. One patient had full reversal of symptoms; this patient also had the lowest serum concentration of medetomidine among those with blood specimen results. Blood medetomidine concentrations ranged from 0.7 ng/mL to 63.7 ng/mL.

Among the 38 patients with confirmed and probable cases, 16 were admitted to the hospital, nine required admission to an intensive care unit, 16 received respiratory support, and five required intubation. One death in a patient with a suspected opioid overdose was classified as a suspected medetomidine-affected overdose case; however, in the absence of toxicologic confirmation, the death was not definitively linked to medetomidine.

Public Health Response

On May 14, CDPH released a health alert§§§ describing the increase in EMS responses for suspected opioid-involved overdoses during the weekend of May 11. After medetomidine was detected in multiple drug samples, CDPH released a second health alert¶¶¶ on May 20. Medical and public health personnel were advised to inform IPC of suspected opioid-involved overdoses that appeared atypical, report overdose clusters at a single facility to CDPH, and pursue toxicology testing through programs such as DEA TOX,**** which tests biologic specimens from patients who experience drug overdoses for new psychoactive substances. On May 21, IDPH expanded the health alert statewide.

CDPH collaborated with partners to promote community-based point-of-care drug checking†††† and monthly reporting in areas with the highest number of EMS transports for suspected opioid-involved overdoses. CDPH also advised EDs that treat the highest numbers of suspected opioid-involved overdoses on recommended protocols and practices for predischarge administration of medications for opioid use disorder and linking patients to care.

Discussion

Although medetomidine has periodically been detected in multiple states and in Canada since 2022, this report is the first to characterize demographic and clinical characteristics of a cluster of overdoses involving medetomidine mixed with opioids (*2*–*4*). Efficient collaboration across sectors, including health care, toxicology laboratories, and public health, was essential in identifying and swiftly responding to the emergence of medetomidine in Chicago's illegal drug supply.

** 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

†† Benzoylecgonine is a cocaine metabolite.

§§ Morphine is an opioid agonist and also a metabolite of heroin and codeine.

¶¶ Xylazine is a nonscheduled, nonopioid sedative not approved for human use and has been increasingly detected in illegal opioids.

*** Bromazolam is a benzodiazepine.

††† Three of the five drug samples had a similar composition of medetomidine in the highest concentration, followed by diphenhydramine, heroin, and trace amounts of fentanyl. Xylazine was detected in two of the five samples, having higher concentrations of xylazine than medetomidine. One of the five contained trace amounts of nitazenes (metonitazene and *N*-pyrrolidinometonitazene), synthetic opioids more potent than fentanyl.

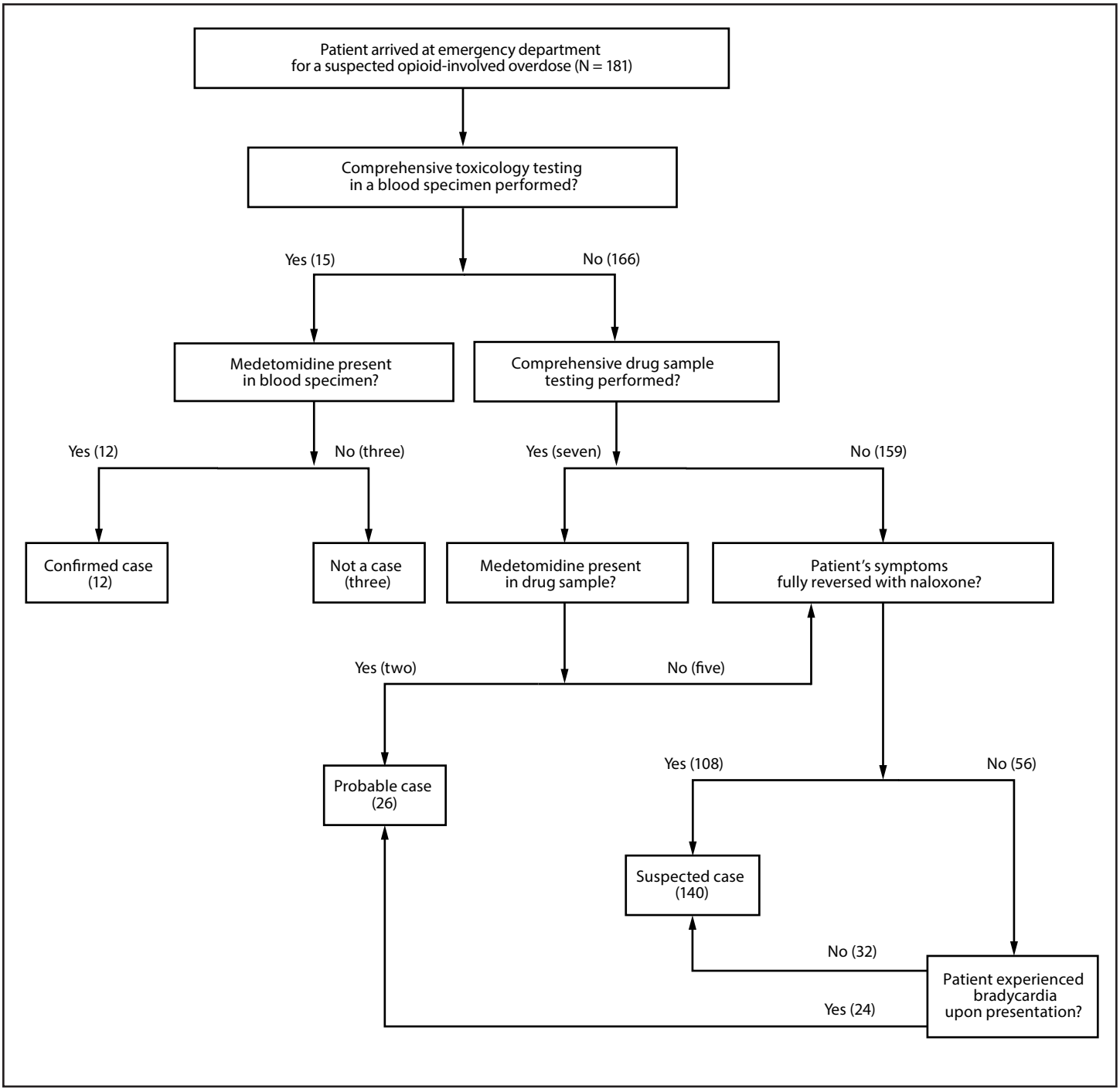
§§§ Increase in Opioid Overdoses May 14, 2024

¶¶¶ Medetomidine in Chicago's Drug Supply May 20, 2024

**** DEA TOX Toxicology Testing Program

†††† Drug Checking Programs in the United States and Internationally: Environmental Scan Summary

FIGURE 1. Case identification algorithm used for patients admitted to three emergency departments for overdoses involving medetomidine mixed with opioids — Chicago, Illinois, May 11–17, 2024[*,†,§,¶,**,††]



* Three patients for whom comprehensive toxicology testing of blood specimens was performed also had drug sample testing; medetomidine was present in the blood specimens and drug samples from all three patients.

† For the patient blood specimens in which medetomidine was detected, diphenhydramine (12 patients), fentanyl (12), quinine (11), benzoylecgonine (a cocaine metabolite) (10), bromazolam (a benzodiazepine) (six), morphine (six), and xylazine (six) were also detected.

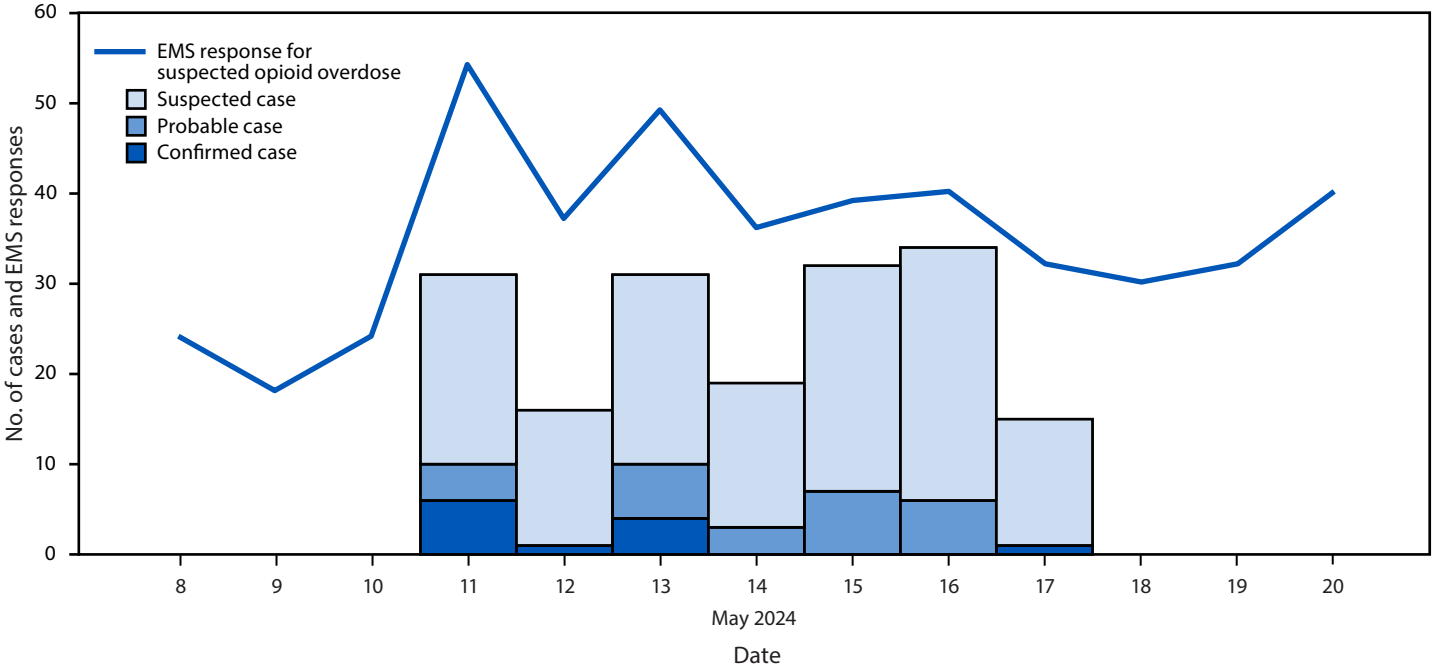
§ For the patients for whom medetomidine was present in drug samples, the drug samples were bagged powders that were in the patients' possession at the initial health care contact.

¶ A patient was classified as not having symptoms fully reversed with naloxone if the patient experienced persistent altered mental status after naloxone administration.

** Suspected cases were defined as other suspected opioid-involved overdoses in patients who were admitted to the emergency departments of the three hospitals even without clinical or testing evidence for medetomidine because the patients were admitted during a time of medetomidine infiltration of the drug supply.

†† Bradycardia was defined as heart rate less than 60 beats per minute.

FIGURE 2. Overdose cases involving medetomidine mixed with opioids and emergency medical services responses* for suspected opioid-involved overdose cases per day† — Chicago, Illinois, May 8–20, 2024§



Abbreviation: EMS = emergency medical services.

* EMS responses data are from the Chicago Fire Department. Numbers might differ from near real-time EMS response data from the Office of National Drug Control Policy's Overdose Detection Mapping Application Program, which links first responders and records management systems to a mapping tool to track overdoses. The finalized Chicago Fire Department data indicated that there were 54 opioid-related EMS responses on May 11, 2024.

† Twelve confirmed, 26 probable, and 140 suspected medetomidine-involved overdose cases were identified.

§ During May 11–17, total EMS responses for suspected opioid-involved overdoses included confirmed, probable, and suspected cases of medetomidine-involved overdose. Suspected cases were defined as suspected opioid-involved overdoses in patients who were admitted to the emergency departments of the three hospitals even without clinical or testing evidence for medetomidine because the patients were admitted during a time of medetomidine infiltration of the drug supply.

Comprehensive toxicology testing initiated by hospitals, their reports to IPC, and timely coordination and testing of drug samples and blood specimens identified medetomidine as the contributing factor of the overdose cluster.

Since 2023, CDC has supported toxicologic testing of illegal drug paraphernalia or samples in 18 local jurisdictions (including Chicago) (*5*). Additional analyses of data collected can provide states and local jurisdictions with critical information to lessen the public health risks caused by changes in the illegal drug market, including introduction of new drugs or adulterants like medetomidine, that can increase the risk for overdose or other negative outcomes.

The emergence of medetomidine in the illegal drug supply can complicate responses to suspected opioid-involved overdoses and necessitates educating persons who use drugs, clinicians, and public health personnel about the adverse effects of medetomidine. Bradycardia, a side effect typically more intense with medetomidine than with opioids, was observed frequently in this investigation and might help to clinically distinguish overdoses involving medetomidine mixed with opioids from those involving only opioids. Hypertensive urgency was also observed. Cardiovascular and respiratory support are crucial to the management of medetomidine toxicity (*6*). Although peripheral vasoconstriction caused by medetomidine has been described in animals, whether medetomidine exacerbates skin and soft tissue damage that is associated with xylazine in humans remains unclear (*7*).

Clinicians who observe an atypical toxidrome associated with a suspected opioid-involved overdose should administer naloxone and provide supportive care and should have a low threshold for contacting their local health department, especially regarding clusters of overdoses with atypical, similar toxidromes. Poison centers can provide clinical guidance on patient care and assist with coordination of toxicology testing.

All blood specimens and drug samples in this investigation that contained medetomidine also contained natural or synthetic opioids, the effects of which are reversible with naloxone. Despite the emergence of new adulterants, administering naloxone for all suspected opioid-involved overdoses remains important, including for those overdoses involving medetomidine mixed with opioids. The effects of medetomidine cannot be reversed with naloxone. In addition, the antidote for medetomidine

TABLE. Demographic and clinical characteristics of patients with confirmed, probable, and suspected cases of overdose involving medetomidine mixed with opioids — Chicago, Illinois, May 11–17, 2024

Characteristic	No. (%)			
	Confirmed (n = 12)	Probable (n = 26)	Suspected* (n = 140)	Total (N = 178)
Median age, yrs (range)	59.8 (38.2–69.6)	59.1 (32.5–86.5)	54.9 (22.1–78.7)	**55.8 (22.1–86.5)**
Age group, yrs				
<34	0	1 (3.8)	19 (13.6)	**20 (11.2)**
35–44	2 (16.7)	2 (7.7)	20 (14.3)	**24 (13.5)**
45–64	7 (58.3)	17 (65.4)	80 (57.1)	**104 (58.4)**
≥65	3 (25.0)	6 (23.1)	21 (15.0)	**30 (16.9)**
Sex				
Female	2 (16.7)	4 (15.4)	29 (20.7)	**35 (19.7)**
Male	10 (83.3)	22 (84.6)	111 (79.3)	**143 (80.3)**
Race and ethnicity†				
Black or African American	10 (83.3)	23 (88.5)	97 (69.3)	**130 (73.0)**
White	2 (16.7)	0	15 (10.7)	**17 (9.6)**
Hispanic or Latino	0	1 (3.8)	8 (5.7)	**9 (5.1)**
Other	0	1 (3.8)	11 (7.9)	**12 (6.7)**
Unknown	0	1 (3.8)	9 (6.4)	**10 (5.6)**
History of substance use				
Yes	10 (83.3)	16 (61.5)	—	**26 (68.4)**
No	0	2 (7.7)	—	**2 (5.3)**
Unknown	2 (16.7)	8 (30.8)	—	**10 (26.3)**
Reported drug used immediately before overdose event§				
Heroin	5 (41.7)	13 (50.0)	—	**18 (47.4)**
Other opiate	1 (8.3)	2 (7.7)	—	**3 (7.9)**
Unknown	6 (50.0)	11 (42.3)	—	**17 (44.7)**
Route of drug used before overdose event				
Snorting	4 (33.3)	4 (15.4)	—	**8 (21.1)**
Unknown	8 (66.7)	22 (84.6)	—	**30 (78.9)**
Response to naloxone¶				
Full reversal of symptoms	1 (8.3)	0	108 (77.1)	**109 (61.2)**
Partial improvement of symptoms**	7 (58.3)	19 (73.1)	19 (13.6)	**45 (25.3)**
No improvement of symptoms	4 (33.3)	6 (23.1)	5 (3.6)	**15 (8.4)**
Naloxone given but response not documented	0	0	1 (0.7)	**1 (0.6)**
Naloxone not given	0	1 (3.8)	6 (4.3)	**7 (3.9)**
Sign or symptom§,††,§§				
Hypertension	12 (100)	24 (92.3)	100 (71.4)	**136 (76.4)**
Bradycardia	9 (75.0)	24 (92.3)	23 (16.4)	**56 (31.5)**
Pinpoint pupils	10 (83.3)	22 (84.6)	86 (61.4)	**118 (66.3)**
Altered mental status	12 (100)	20 (76.9)	82 (58.6)	**114 (64.0)**
Hypoxemia	7 (58.3)	11 (42.3)	27 (19.3)	**45 (25.3)**
Systolic blood pressure ≥180 mm Hg	8 (66.7)	8 (30.8)	35 (25.0)	**51 (28.7)**
Bradypnea	2 (16.7)	6 (23.1)	20 (14.3)	**28 (15.7)**
Downward gaze	3 (25.0)	0	0	**3 (1.7)**
Twitching	1 (8.3)	0	1 (0.7)	**2 (1.1)**
Apnea	0	5 (19.2)	4 (2.9)	**9 (5.1)**
Hypotension	0	3 (11.5)	3 (2.1)	**6 (3.4)**
Dilated pupils	0	0	1 (0.7)	**1 (0.6)**
Hypothermia	0	0	1 (0.7)	**1 (0.6)**
Admitted to hospital				
Yes	8 (66.7)	8 (30.8)	26 (18.6)	**42 (23.6)**
Yes, to intensive care unit¶¶	5 (62.5)	4 (50.0)	9 (34.6)	**18 (42.9)**
Length of inpatient stay, median days (range)	3.5 (0.4–5.8)	2.0 (0.5–2.7)	1.2 (0.1–5.0)	**1.9 (0.1–5.8)**
No	4 (33.3)	18 (69.2)	113 (80.7)	**135 (75.8)**
Received medications for opioid use disorder				
Yes	9 (75.0)	6 (23.1)	—	**17 (44.7)**
No	3 (25.0)	20 (76.9)	—	**24 (63.2)**
Received atropine				
Yes	3 (25.0)	2 (7.7)	—	**5 (13.2)**

See table footnotes on the next page.

TABLE. (*Continued*) Demographic and clinical characteristics of patients with confirmed, probable, and suspected cases of overdose involving medetomidine mixed with opioids — Chicago, Illinois, May 11–17, 2024

Characteristic	No. (%)			
	Confirmed (n = 12)	Probable (n = 26)	Suspected* (n = 140)	Total (N = 178)
No	9 (75.0)	24 (92.3)	—	**33 (86.8)**
Received respiratory support				
Yes§	7 (58.3)	9 (34.6)	—	**16 (42.1)**
Supplemental oxygen***	6 (85.7)	6 (66.7)	—	**12 (75)**
Continuous positive airway pressure***	0	1 (11.1)	—	**1 (6.25)**
Intubation***	3 (42.9)	2 (22.2)	—	**5 (31.3)**
No	5 (41.7)	17 (65.4)	—	**22 (57.9)**
Disposition after discharge				
Home	8 (66.7)	25 (96.2)	120 (85.7)	**153 (86.0)**
Left against medical advice	3 (25.0)	0	18 (12.9)	**21 (11.8)**
Referral to other health care facility	1 (8.3)	1 (3.8)	0	**2 (1.1)**
Deceased	0	0	1 (0.7)	**1 (0.6)**
Unknown	0	0	1 (0.7)	**1 (0.6)**
Linkage to care and harm reduction resources§				
Provided patient naloxone	5 (41.7)	12 (46.2)	—	**17 (44.7)**
Provided patient informational resources	1 (8.3)	2 (7.7)	—	**3 (7.9)**
Referral to behavioral health treatment for substance use disorder	8 (66.7)	11 (42.3)	—	**19 (50.0)**
Prescribed medications for opioid use disorder	3 (25.0)	1 (3.8)	—	**4 (10.5)**
Referral to treatment for other comorbidities	0	1 (3.8)	—	**1 (2.6)**
None	0	3 (11.5)	—	**3 (7.9)**
Unknown	0	1 (3.8)	—	**1 (2.6)**

* Time and resource constraints resulted in the completion of only partial chart abstractions for suspected cases, and data were not collected for all variables; data not collected are indicated with a dash.
† Persons of Hispanic or Latino (Hispanic) origin might be of any race but are categorized as Hispanic; all racial groups are non-Hispanic.
§ Not mutually exclusive.
¶ Differences in response to naloxone are partially attributable to case definitions of probable and suspected cases.
** Partial response to naloxone is defined as a patient having some remaining opioid-involved overdose symptoms (i.e., prolonged altered mental status) after naloxone administration.
†† Ordered by descending frequency of symptoms among confirmed and probable cases combined; if frequency was equal among confirmed and probable cases, confirmed ranked above probable.
§§ Signs and symptoms were based on emergency medical services or vital signs data collected on arrival at the hospital or if noted in the medical record. Criteria were 1) systolic blood pressure ≥140 mm Hg for hypertension; 2) heart rate less than 60 beats per minute or demonstration on electrocardiogram for bradycardia (differences in bradycardia are partially attributable to the case definitions of probable and suspected cases); 3) respiratory rate less than 12 breaths per minute for bradypnea; 4) systolic blood pressure ≥180 mm Hg for hypertensive urgency; 5) oxygen saturation level <90% for hypoxemia; and 6) systolic blood pressure <90 mm Hg for hypotension.
¶¶ Among patients who were hospitalized.
*** Among patients who received respiratory support.

and dexmedetomidine, atipamezole, is not approved for use in humans (*8*). Clinicians should continue to provide medications for opioid use disorder, linkage to care, and harm reduction services for persons experiencing opioid use disorder (*9*).

Limitations

The findings in this report are subject to at least four limitations. First, suspected cases might have been overestimated because no clear toxidrome for medetomidine-involved overdoses exists, a result of minimal published data on its effects in humans. For the purposes of the investigation, sensitivity was prioritized over specificity for suspected cases during this period so as to not miss any potential cases in patients with increased risk for medetomidine exposure. Second, most patients had no toxicology testing, which might have contributed to an underestimation of confirmed cases. Because medetomidine is an emerging adulterant, it is not part of standard urine drug screening. Testing for medetomidine requires sending specimens and samples to a specialized toxicology laboratory, increasing the barrier for identifying cases. Third, time and resource constraints limited the investigation to three hospitals; local hospitals not included in the study might have received patients with overdoses involving medetomidine. Therefore, these findings might not be generalizable. Finally, the investigation was conducted during May 11–17, 2024, and additional cases might have occurred outside of this time frame. No additional clusters attributable to medetomidine have since been identified in Chicago; however, additional

Summary

What is already known about this topic?

Medetomidine, a nonopioid sedative not approved for use in humans, has been detected in illegally manufactured opioids across North America since 2022.

What is added by this report?

Twelve confirmed and 26 probable cases of medetomidine-involved overdose occurred in Chicago, Illinois, during May 11–17, 2024, mostly among non-Hispanic Black or African American men aged 45–64 years. Bradycardia and lack of response to naloxone were defining clinical features. Fentanyl was present in all blood specimens and drug samples that tested positive for medetomidine.

What are the implications for public health practice?

Multisector surveillance is needed to quickly identify and respond to new adulterants introduced into the illegal drug supply. Clinicians who observe atypical toxidromes associated with suspected opioid-involved overdoses should contact their local health department and continue to provide naloxone and linkage to evidence-based treatment.

drug samples obtained since that time have tested positive for medetomidine.[§§§§]

Implications for Public Health Practice

This cluster of confirmed medetomidine-involved overdoses is the largest yet reported, and the landscape of adulterants in the illegal drug supply is ever-changing and expanding. The recent addition of xylazine has led to a concerning trend in deaths potentially resulting from adulteration in the fentanyl supply (*10*), and the emergence of medetomidine further complicates the opioid overdose crisis. Clinicians and persons who use illegal drugs should be aware that medetomidine can be present in the drug supply. Although medetomidine effects cannot be reversed with naloxone, if a person might be overdosing, the use of naloxone or any other opioid overdose reversal medication is recommended. In addition, connecting persons at risk for overdose to evidence-based treatment, services, and support can save lives.

[§§§§] Overdose Cluster Associated with Nitazenes and the Novel Adulterant BTMPS November 8, 2024

Acknowledgments

Joshua DeBord, Center for Forensic Science Research and Education; Sean Johnston, David Peress, Chicago Recovery Alliance; Graham Briggs, Sarah Patrick, Illinois Department of Public Health; Lauren Haindfield, Margot Harle, Jaime Moreno, Adriana Rodriguez, Crystal Valdez, Mount Sinai Medical Center; Adil Baig, Dagoberto Camacho, Griselda Haro, Daisy Rodriguez, Yasmin Santos, Humboldt Park Health; Clarissa O'Conor, Tiffany Tahata, West Suburban Medical Center.

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All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

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Notes from the Field

Suspected Medetomidine Withdrawal Syndrome Among Fentanyl-Exposed Patients — Philadelphia, Pennsylvania, September 2024–January 2025

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Medetomidine, a synthetic alpha-2 adrenoreceptor agonist, is a new drug adulterant that was detected in 72% of illegal opioid samples tested in Philadelphia, Pennsylvania, during the last 4 months of 2024. During the same period, detection of xylazine (previously the most common adulterant) decreased from 98% to 31% of samples (*1*), and health care providers at hospitals in Philadelphia noticed an increasing number of hospitalized patients with a severe drug withdrawal syndrome distinct from fentanyl and xylazine withdrawal, characterized by profound autonomic dysfunction, such as severe hypertension and tachycardia. This report aims to increase awareness of the presence of medetomidine in the illegal opioid supply, characterize the emerging medetomidine withdrawal syndrome, and describe measures to provide effective patient care for this life-threatening syndrome.

Investigation and Outcomes

During fall 2024, in response to emerging awareness of a newly recognized medetomidine withdrawal syndrome, addiction medicine and medical toxicology faculty members at three Philadelphia health systems (health systems A, B, and C) began maintaining a list of patients identified with the syndrome, including those they had helped care for or provided consultation for, as well as patients referred by other health care providers. The faculty members reviewed electronic health records of patients who were admitted to the three health systems during September 1, 2024–January 31, 2025, and whose withdrawal syndrome was characterized by severe signs and symptoms that were not resolved by established treatment protocols for fentanyl and xylazine withdrawal. Overall, 165 patients were identified who demonstrated one or more signs or symptoms such as agitation, anxiety, severe hypertension, tachycardia, tremor without clonus or hyperreflexivity, and vomiting, resistant to increasing doses of opioids (e.g., fentanyl, hydromorphone, methadone, or oxycodone), sedatives (e.g., diazepam, droperidol, haloperidol, lorazepam, midazolam, phenobarbital, or propofol), and adjunctive opioid and xylazine withdrawal medications (clonidine, ketamine, olanzapine, ondansetron, or tizanidine) (*2*). Median age was 38 years (IQR = 33–43 years). This evaluation was reviewed and approved by the institutional review boards of health systems A, B, and C.

Among the 165 patients, 150 (91%) required intensive care unit (ICU) care, including 39 (24%) who received endotracheal intubation (Table). A total of 137 (83%) patients were treated with and responded to dexmedetomidine* infusion, a drug eventually recognized as potentially effective; medetomidine is an enantiomer† of dexmedetomidine, and prolonged dexmedetomidine exposure can induce a withdrawal syndrome manageable with controlled weaning from the drug. Traditional dosages of dexmedetomidine (0.2–1.5 μg/kg/hr) (*3*) were used and titrated to control symptoms or sedate patients with intubation. In a majority of patients requiring dexmedetomidine, the drug was titrated to a maximum dosage of 1.5 μg/kg/hr. Duration of infusion varied, depending on the patient. Use of oral alpha-2 agonists, such as clonidine, was limited because of vomiting. Patients were also treated with antihypertensive medications titrated to blood pressure levels ≤180/120 mm Hg. Complications secondary to severe hypertension or tachycardia included altered mental status with computed tomography (CT)- or magnetic resonance imaging (MRI)-documented posterior reversible encephalopathy syndrome§ in three patients, and non-ST elevation myocardial infarction (NSTEMI) secondary to demand ischemia (insufficient blood supply to meet the heart's oxygen demand) with positive high-sensitivity troponin, indicating potential damage to the heart muscle in a substantial number of patients¶. Findings of severe withdrawal syndromes typically associated with other sedatives (alcohol, barbiturate, or benzodiazepine), such as seizures or hallucinations, were infrequent. Routine testing of specimens from all 165 patients by hospital laboratories confirmed universal fentanyl exposure. Testing for medetomidine or its metabolites using liquid phase chromatography with mass spectrometry was available at health system A; all 55 patients treated at health system A received a positive test result for 3-hydroxy medetomidine.

* Dexmedetomidine is an alpha-2 agonist medication that is used for sedation in an ICU and operating room.

† Enantiomer molecules are mirror images of each other and are not superimposable (e.g., right and left hands).

§ Posterior reversible encephalopathy syndrome is a neurologic disorder characterized by brain swelling that can arise when blood pressure is severely increased. The syndrome is diagnosed by cross-sectional brain imaging such as CT or MRI scan.

¶ Only health system C collected these data, although the patient population at health systems A and B were similar to that of health system C. NSTEMI was defined as a positive high-sensitivity troponin. Of health system C's 62 patients, 39 patients had an NSTEMI, and 13 had a normal or negative high-sensitivity troponin test result. Ten patients were not tested for high-sensitivity troponin.

TABLE. Characteristics of patients hospitalized with combined opioid and suspected medetomidine withdrawal syndrome — three health systems, Philadelphia, Pennsylvania, September 2024–January 2025

Characteristic	No. (%)			
	Health system A (n = 55)	Health system B (n = 48)	Health system C (n = 62)	Total (N = 165)
Age, yrs, median (IQR)	37 (33–45)	38 (35–41)	38 (32–45)	**38 (33–43)**
Sex				
Female	12 (22)	20 (42)	17 (27)	**49 (30)**
Male	43 (78)	28 (58)	45 (73)	**116 (70)**
Race and ethnicity*				
Black or African American, non-Hispanic	6 (11)	6 (13)	15 (24)	**27 (16)**
White, non-Hispanic	44 (80)	34 (71)	25 (40)	**103 (62)**
Hispanic or Latino	5 (9)	0 (—)	18 (29)	**23 (14)**
Other	0 (—)	8 (17)	4 (7)	**12 (7)**
Clinical findings and hospital course				
Maximum heart rate (beats per minute), median (IQR)	144 (125–155)	136 (118–156)	148 (140–157)	**145 (132–156)**
Maximum systolic blood pressure (mm Hg), median (IQR)	191 (172–211)	196 (171–224)	200 (185–215)	**195 (175–215)**
Maximum diastolic blood pressure (mm Hg), median (IQR)	111 (103–123)	127 (109–137)	131 (119–143)	**122 (109–136)**
Treated with dexmedetomidine	51 (93)	35 (73)	51 (82)	**137 (83)**
Intubation/Mechanical ventilation	12 (22)	11 (23)	16 (26)	**39 (24)**
Admitted to intensive care unit	49 (89)	44 (92)	57 (92)	**150 (91)**
Disposition				
Home	15 (27)	28 (58)	32 (52)	**75 (45)**
Patient-directed discharge	14 (26)	13 (27)	25 (40)	**52 (32)**
Residential drug treatment	14 (26)	7 (15)	0 (—)	**21 (13)**
Law enforcement custody	12 (22)	0 (—)	5 (8)	**17 (10)**

* Persons of Hispanic or Latino (Hispanic) origin might be of any race but are categorized as Hispanic; all racial groups are non-Hispanic.

Preliminary Conclusions and Actions

The syndrome described in this report is similar to that described among ICU patients with days-long exposure to dexmedetomidine, an enantiomer of medetomidine, who experience an autonomic withdrawal syndrome with vomiting and agitation when dexmedetomidine is discontinued (*4*,*5*). In the patients described in this report, these signs and symptoms were not resolved by increasing doses of medications previously effective in managing fentanyl and xylazine withdrawal; however, they were responsive to dexmedetomidine, as described in the management of dexmedetomidine withdrawal (*4*,*5*). Health care providers and public health agencies need to be aware of this life-threatening withdrawal syndrome because it can require substantial escalations in care compared with the typical opioid and xylazine withdrawal syndromes. Public health agencies should consider testing for medetomidine in their regional drug supplies.

Summary

What is already known about this topic?

Medetomidine, a nonopioid sedative not approved for use in humans, replaced xylazine as the most common drug adulterant in the Philadelphia, Pennsylvania, illegal opioid supply during the last 4 months of 2024.

What is added by this report?

During September 2024–January 2025, 165 patients at three Philadelphia health systems were hospitalized for fentanyl withdrawal complicated by profound autonomic dysfunction, including severe hypertension and tachycardia. This syndrome was resistant to medications that had previously been effective in managing fentanyl and xylazine withdrawal but was responsive to dexmedetomidine.

What are the implications for public health practice?

Health care providers and public health agencies should be aware of shifts in the drug supply over time that might change patient signs and symptoms. The findings in this report indicate that medetomidine withdrawal syndrome is life-threatening and can require a substantial escalation in care compared with the typical opioid and xylazine withdrawal syndromes. Public health agencies should consider testing for medetomidine in their regional drug supplies.

Acknowledgments

Bridget Durkin, Department of Medicine, Perelman School of Medicine, University of Pennsylvania; Rebecca Jaffe, Department of Medicine, Thomas Jefferson University; Jennifer Kahoud, Megan Reed, TaReva Warrick-Stone, Department of Emergency Medicine, Thomas Jefferson University; Keira Chism, Christopher Martin, Department of Psychiatry & Human Behavior, Thomas Jefferson University; Alberto Martinez Mencia, Douglas Stickle, Department of Pathology, Anatomy & Cell Biology, Thomas Jefferson University; Susannah Berry, Aidan Rogers, Department of Social Work, Thomas Jefferson University Hospital; Maria Foy, Department of Pharmacy, Jefferson Abington Hospital; Maeve Montesi, Jefferson Addiction Multidisciplinary Service, Thomas Jefferson University Hospital;

Wayne Satz, Department of Emergency Medicine, Temple University Hospital; Alex Krotulski, Sara Walton, Center for Forensic Science Research and Education; Shelby Kehoe, Daniel Teixeira da Silva, Division of Substance Use Prevention and Harm Reduction, Department of Public Health, City of Philadelphia.

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Notes from the Field

Severe Medetomidine Withdrawal Syndrome in Patients Using Illegally Manufactured Opioids — Pittsburgh, Pennsylvania, October 2024–March 2025

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Various adulterants within the illegally manufactured opioid supply have emerged in the United States during the last several years (*1*–*3*). Medetomidine, an alpha-2 adrenoreceptor agonist that is not approved for human use in the United States, became increasingly detected in the drug supply in 2024. Medetomidine is a racemic mixture of levomedetomidine and dexmedetomidine, an intravenous sedative used in the critical care setting. A clinical syndrome of autonomic hyperactivity (i.e., hypertension, tachycardia, and agitation) has been observed after abrupt discontinuation of dexmedetomidine (*4*).

Investigation and Outcomes

During October 2024–March 2025, the University of Pittsburgh medical toxicology service evaluated 23 patients at two Pittsburgh, Pennsylvania hospitals who experienced severe autonomic hyperactivity after abrupt cessation of illegally manufactured opioid use. Among the 23 patients, 20 (87%) underwent comprehensive urine drug screening (liquid chromatography-quadrupole time of flight-mass spectrometry testing) during their hospitalization. Medetomidine parent compound was detected in two patients; the test was technically unable to detect medetomidine metabolites. As concern grew about an emerging outbreak of a novel withdrawal syndrome, retrospective analysis of this comprehensive drug screening data was performed for 10 patients after they had been discharged; medetomidine metabolites were detected in all 10 samples* (*5*). These 10 patients with detectable medetomidine metabolites, which included the two with detectable parent medetomidine, were included in the current analysis. A retrospective analysis using a University of Pittsburgh institutional review board–approved single-center toxicology registry was performed.† This approval allows collection and publication of deidentified registry data.

Of the 10 patients, two arrived at an emergency department (ED) with nausea, vomiting, tremulousness, and autonomic hyperactivity; the other eight experienced similar symptoms several hours after arrival at an ED. All required hospitalization. Nine patients who were admitted to an intensive care unit (ICU) received dexmedetomidine to treat autonomic hyperactivity, and the tenth patient was treated with oral and transdermal clonidine and guanfacine in addition to phenobarbital with sufficient relief to avoid ICU admission (Table). The rationale for using dexmedetomidine included minimal response to other agents including opioids and sedatives, knowledge that medetomidine was an emerging adulterant in the illegal drug supply, and suspicion that medetomidine's withdrawal state would be effectively treated with dexmedetomidine given the agents' shared pharmacologic properties. Four patients received treatment for concomitant withdrawal syndromes (e.g., from alcohol or benzodiazepine). None had alternative causes identified to better explain their symptoms. The following two cases are representative of the entire 23-patient cohort and are part of the 10 patients with confirmed medetomidine exposure:

Patient A was a man aged 39 years with opioid use disorder treated with daily methadone. He was seen in an ED for nausea and vomiting, and he had bradycardia (heart rate = 54 beats per minute [bpm]) in triage. Over the next 5 hours, he developed tremulousness, agitation, and severe autonomic hyperactivity: tachycardia (103–170 bpm) and diaphoresis. Treatment with methadone, clonidine, tizanidine, benzodiazepines, and phenobarbital did not result in substantial improvement. Tachycardia improved within 3 hours after dexmedetomidine initiation and admission to an ICU. He was discharged on hospital day 5. Results of enzyme immunoassay urine drug screening collected in an ED after treatment initiation were positive for fentanyl, barbiturates, and benzodiazepines. Comprehensive urine drug screening, collected in the ED with results available on day 3, demonstrated fentanyl and fentanyl analogs, methadone, and medetomidine.

Patient B was a man aged 36 years with opioid use disorder who sought treatment in an ED for opioid withdrawal. During 3 hours in the ED, he developed progressive tachycardia up to 163 bpm, hypertension up to 156/134 mmHg, agitation, encephalopathy, severe metabolic acidosis (venous blood pH <6.8), hypokalemia (2.5 mmol/L [reference value = 3.4-5 mmol/L]), and prolongation of the corrected QT interval (QTc = 526 ms). He underwent rapid sequence endotracheal intubation using rocuronium and etomidate, which was complicated by cardiac arrest requiring

* Mass spectrometry datasets were accessible for retrospective analysis for medetomidine metabolites.

† All chart review was done by two authors who are emergency physicians and medical toxicology fellows using a standardized data abstraction form in REDCap. Source information included toxicology and intensive care unit clinical notes, vital signs, laboratory data, and medication administration records.

TABLE. Clinical characteristics of 10 patients who used illegally manufactured opioids and were treated for medetomidine withdrawal — Pittsburgh, Pennsylvania, October 2024–March 2025

Characteristic	No. (%)
Mean age (range)	**34.2 (22–54)**
Male sex	**6 (60)**
Race and ethnicity	
Black or African American, Hispanic or Latino	1 (10)
Black or African American, non-Hispanic	1 (10)
White, non-Hispanic	8 (80)
Rapid clinical deterioration during ED stay*	**8 (80)**
Concomitant GABAergic withdrawal requiring treatment	**4 (40)**
ICU admission	**9 (90)**
Total hospital length of stay, hrs (median)†	**93.3**
Intubation/Mechanical ventilation	**1 (10)**
Vital signs	
Peak temperature (°C), median (range)	37.6 (36.9–38.6)
Peak heart rate (beats per minute), median (range)	165 (133–178)
Peak systolic blood pressure (mm Hg), median (range)	200 (146–236)
Peak diastolic blood pressure (mm Hg), median (range)	114 (91–140)
Alpha-2 agonist therapy	
Dexmedetomidine infusion	9 (90)
Clonidine (cumulative dose),§ mg, median	0.7
Tizanidine (cumulative dose),§ mg, median	8
Guanfacine (cumulative dose),§ mg, median	3
Cumulative benzodiazepine dose,§,¶ mg, median	**10**
Cumulative phenobarbital dose,§ mg, median	**520**
Clinical outcome	
Cardiac arrest or ventricular dysrhythmia	1 (10)
Metabolic acidosis	7 (70)
Acute kidney injury	3 (30)
Rhabdomyolysis	1 (10)
Myocardial injury	3 (30)
Compounds detected in urine**	
Fentanyl parent, metabolite, or analog	10 (100)
Xylazine	6 (60)
Cocaine parent or metabolite	4 (40)
Lorazepam, temazepam, or diazepam metabolite	6 (60)
Medetomidine parent††	2 (20)
Medetomidine metabolite††	10 (100)

Abbreviations: ED = emergency department; ICU = intensive care unit.
* Patient's condition in an ED initially assessed as mild, but quickly deteriorated requiring rapidly escalating interventions and an ICU.
† Total hospital length of stay = time (in hours) from initial ED presentation to discharge.
§ Cumulative dose is the sum of doses within the first 48 hours of hospital stay beginning from arrival at an ED.
¶ Reported in lorazepam equivalents: 1 mg lorazepam = approximately 2 mg midazolam = approximately 5 mg diazepam.
** Urine drug testing conducted using liquid chromatography quadrupole time of flight mass spectrometry.
†† One patient had received pharmaceutical dexmedetomidine before collection of urine drug sample.

defibrillation, cardiopulmonary resuscitation, and epinephrine. He was admitted to an ICU and received multiple sedating infusions, including dexmedetomidine, ketamine, propofol, midazolam, and fentanyl. He was extubated several days later without apparent neurologic deficits. Comprehensive urine drug screening, collected in the ED and available on hospital day 3, detected fentanyl and fentanyl analogs, cocaine, ketamine, and sulfamethoxazole-trimethoprim but no parent medetomidine was detected. He was discharged home on hospital day 8. Post-discharge analysis of his urine drug specimen detected medetomidine metabolites.

Preliminary Conclusions and Actions

The 10 patients who used illegally manufactured opioids with confirmed medetomidine exposure based on retrospective identification of medetomidine metabolites exhibited a withdrawal syndrome characterized by severe autonomic hyperactivity with rapid symptom onset often requiring dexmedetomidine and ICU admission. The emergence of this syndrome temporally correlated with an increased medetomidine prevalence in the regional illegally manufacture opioid supply. On December 18, 2024, the Pennsylvania Department of Health issued a health advisory describing severe withdrawal observed in patients who use drugs in the Philadelphia area associated with medetomidine exposure.§ Although only two patients had detectable parent medetomidine on comprehensive urine drug screening, all 10 patients had samples with detectable medetomidine metabolites identified retrospectively. Although a rapid clinical test for medetomidine is not available, providers should maintain awareness of this emerging medetomidine withdrawal syndrome when treating persons who use illegally manufactured opioids.

§ Hospitals and Behavioral Health Providers are Reporting Severe and Worsening Presentations of Withdrawal among People who Use Drugs (PWUD) in Philadelphia

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Summary

What is already known about this topic?

Medetomidine is an increasingly common adulterant of illegally manufactured opioids.

What is added by this report?

During October 2024–March 2025, a total of 23 adult patients who used illegally manufactured opioids sought treatment within a health care system in Pittsburgh, Pennsylvania. All exhibited severe autonomic hyperactivity, and most required dexmedetomidine infusion and intensive care unit–level management. Medetomidine metabolites were detected in all 10 patients for whom retrospective analysis was performed, despite only two having detectable parent compound (medetomidine) on comprehensive urine drug screening.

What are the implications for public health practice?

Health care providers in regions where medetomidine has been detected in the drug supply should be prepared to manage a severe withdrawal syndrome among patients who use illegally manufactured opioids, even if drug testing for medetomidine is negative.

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Simon J. Ostrowski reports receipt of grants or contracts from the Society of Academic Emergency Medicine/Medical Toxicology Foundation, and travel support from the American College of Medical Toxicology's ANTIDOTE program to attend the 2024 American College of Medical Toxicology annual conference. Kenichi Tamama reports receipt of an honorarium from the University of Massachusetts for an invited continuing medical education lecture. Michael J. Lynch reports institutional support from the Pennsylvania Department of Health, the Pennsylvania Department of Health ODSMP, and the Allegheny County Opioid Settlement Agreement and Vital Strategies; receipt of honoraria from Tower Health, Reading, Pennsylvania and from Baylor University Medical Center for grand rounds lectures; and receipt of payment from Summers, McDonnell, Hudock, Guthrie & Rach, P.C. for expert opinion report. No other potential conflicts of interest were disclosed.

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ISSN: 0149-2195 (Print)