Medetomidine – An Emerging Adulterant of Concern

NPS Discovery Webinar Series – Thursday July 11, 2024

Sara E. Walton, M.S., & Alex J. Krotulski, Ph.D. – CFSRE

BACKGROUND

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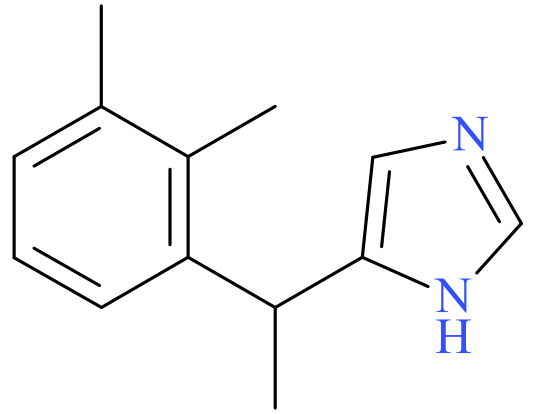
PHARMACOLOGY

- Alpha-2 adrenergic receptor agonist
  - Used for sedation, analgesia, muscle relaxation, anxiolytic
  - Similar to **xylazine**, clonidine, tizanidine
  - Exists in two enantiomeric forms →

Medetomidine



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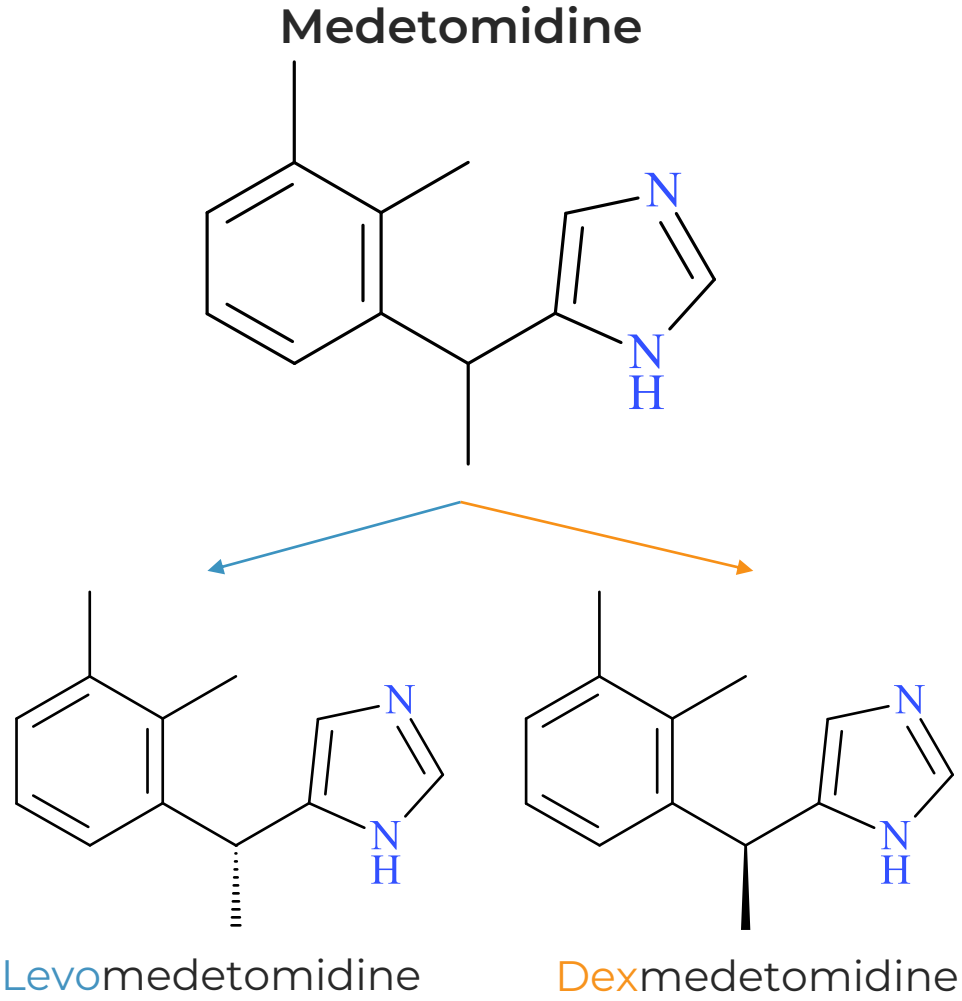
- Pharmacodynamics[1,2]
  - Dexmedetomidine
    - Active enantiomer
    - Potent alpha-2 agonist at pre- & post-synaptic sites in CNS and PNS
    - AE: hypotension, **bradycardia**, hypertension, respiratory depression
  - Levomedetomidine
    - "Inactive" enantiomer
    - Mild sedative & analgesic

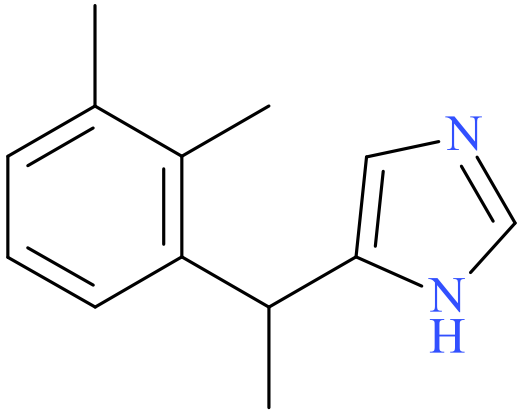


[1]Bardhi *et al.* (2021), [2]Ho *et al.* (2005)

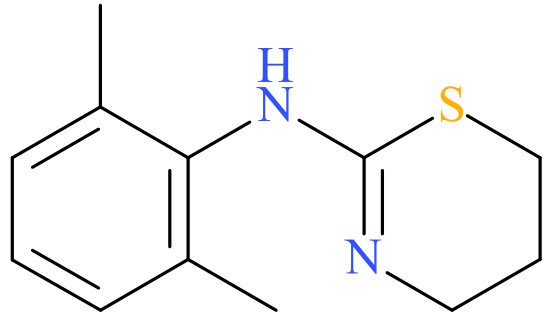
MEDETOMIDINE VS XYLAZINE

Medetomidine is approx. **200x** more potent than xylazine[1] and **10x** more selective at alpha-2 adrenoreceptor[2]

Ki (nM)[2]	α2A	α2B	α2C	α2D
Medetomidine	3.89±1.46	7.40±2.61	12.3±5.07	5.74±0.73
Xylazine	1570±240	1360±100	1200±223	1460±250



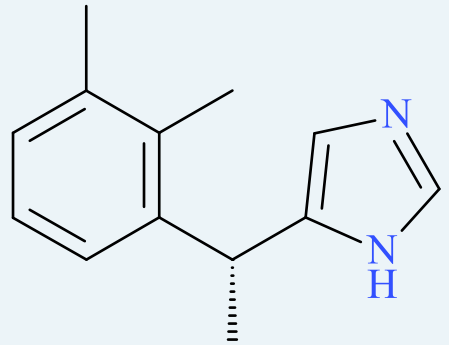
Medetomidine



Xylazine

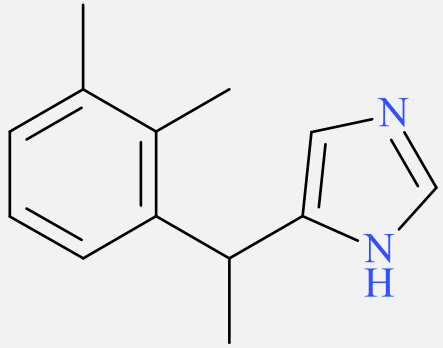
[1]Connell et al. (2022), [2]Schwartz et al. (1998)

MEDETOMIDINE USES



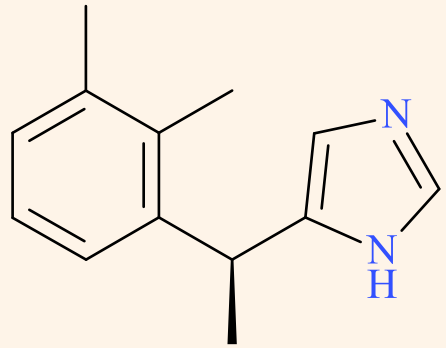
Levomedetomidine

- Not prepared or used alone
  - In veterinary or human medicine



Medetomidine

- Racemic
  - ~50% potency of dexmedetomidine
- Domitor®
  - Veterinary Medicine
  - Sedative & anesthetic



Dexmedetomidine

- Precedex™
  - Human use in USA & Canada
  - IV surgical sedative & anesthetic
  - Uncontrolled
- Dexdomitor®
  - Veterinary Medicine

MEDETOMIDINE USES

BUYING MEDETOMIDINE ONLINE

Medetomidine Hydrochloride CAS 86347-15-1

Product Code: BM-2-5-041
Eng Name: (R)-4-[1-(2,3-dimethylphenyl)ethyl]-1H imidazole hydrochloride/Medetomidine Hydrochloride
CAS No.: 86347-15-1
Molecular formula: c13h17cln2
Molecular weight: 236.74
EINECS No.: 645-306-0
Manufacturer: BLOOM TECH Wuxi Factory
Technology service: R&D Dept.-3

Dayang Chem (Hangzhou) Co., Ltd.
China
Product Name: Medetomidine hydrochloride
Price:
$Inquiry/100g
$Inquiry/1kg
$Inquiry/100kg
$Inquiry/1000kg
Purity: 98.0%
Delivery: Inquiry
Contact: Ms Wang
Email: enquiry@dycnchem.com

Top Quality Pharmaceutcial Medetomidine HCl/Hydrochloride Powder CAS 86347-15-1 Medetomidine

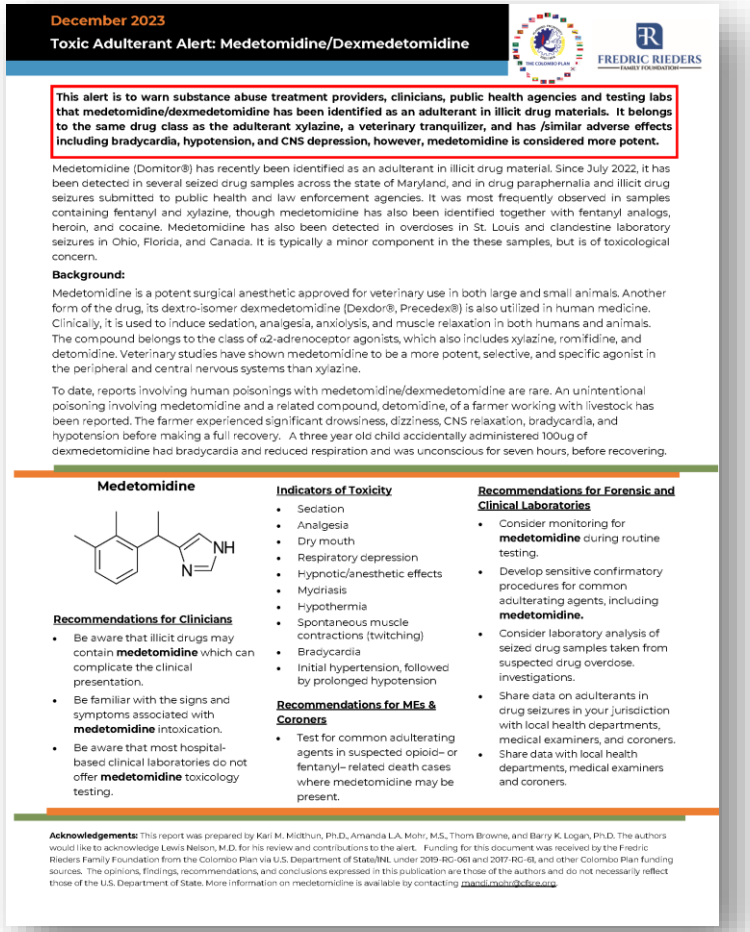
Reference FOB Price | Get Latest Price >

US $50.00-100.00 / kg | 1 kg (Min. Order)

CAS No.:	86347-15-1
Formula:	C13h17cln2
EINECS:	645-306-0

Xylazine	7361-61-7 23076-35-9	Xylazine Freebase/hydrochloride 1kg, $468/kg; 25kg, $365/kg (Powder or **Crystal**)

TOXIC ADULTERANT ALERT – DECEMBER 2023



December 2023

Toxic Adulterant Alert: Medetomidine/Dexmedetomidine

This alert is to warn substance abuse treatment providers, clinicians, public health agencies and testing labs that medetomidine/dexmedetomidine has been identified as an adulterant in illicit drug materials. It belongs to the same drug class as the adulterant xylazine, a veterinary tranquilizer, and has /similar adverse effects including bradycardia, hypotension, and CNS depression, however, medetomidine is considered more potent.

Medetomidine (Domitor®) has recently been identified as an adulterant in illicit drug material. Since July 2022, it has been detected in several seized drug samples across the state of Maryland, and in drug paraphernalia and illicit drug seizures submitted to public health and law enforcement agencies. It was most frequently observed in samples containing fentanyl and xylazine, though medetomidine has also been identified together with fentanyl analogs, heroin, and cocaine. Medetomidine has also been detected in overdoses in St. Louis and clandestine laboratory seizures in Ohio, Florida, and Canada. It is typically a minor component in the these samples, but is of toxicological concern.

Background:

Medetomidine is a potent surgical anesthetic approved for veterinary use in both large and small animals. Another form of the drug, its dextro-isomer dexmedetomidine (Dexdor®, Precedex®) is also utilized in human medicine. Clinically, it is used to induce sedation, analgesia, anxiolysis, and muscle relaxation in both humans and animals. The compound belongs to the class of α2-adrenoceptor agonists, which also includes xylazine, romifidine, and detomidine. Veterinary studies have shown medetomidine to be a more potent, selective, and specific agonist in the peripheral and central nervous systems than xylazine.

To date, reports involving human poisonings with medetomidine/dexmedetomidine are rare. An unintentional poisoning involving medetomidine and a related compound, detomidine, of a farmer working with livestock has been reported. The farmer experienced significant drowsiness, dizziness, CNS relaxation, bradycardia, and hypotension before making a full recovery. A three year old child accidentally administered 100ug of dexmedetomidine had bradycardia and reduced respiration and was unconscious for seven hours, before recovering.

Medetomidine

Recommendations for Clinicians

- Be aware that illicit drugs may contain **medetomidine** which can complicate the clinical presentation.
- Be familiar with the signs and symptoms associated with **medetomidine** intoxication.
- Be aware that most hospital-based clinical laboratories do not offer **medetomidine** toxicology testing.

Indicators of Toxicity

- Sedation
- Analgesia
- Dry mouth
- Respiratory depression
- Hypnotic/anesthetic effects
- Mydriasis
- Hypothermia
- Spontaneous muscle contractions (twitching)
- Bradycardia
- Initial hypertension, followed by prolonged hypotension

Recommendations for MEs & Coroners

- Test for common adulterating agents in suspected opioid– or fentanyl– related death cases where medetomidine may be present.

Recommendations for Forensic and Clinical Laboratories

- Consider monitoring for **medetomidine** during routine testing.
- Develop sensitive confirmatory procedures for common adulterating agents, including **medetomidine.**
- Consider laboratory analysis of seized drug samples taken from suspected drug overdose. investigations.
- Share data on adulterants in drug seizures in your jurisdiction with local health departments, medical examiners, and coroners.
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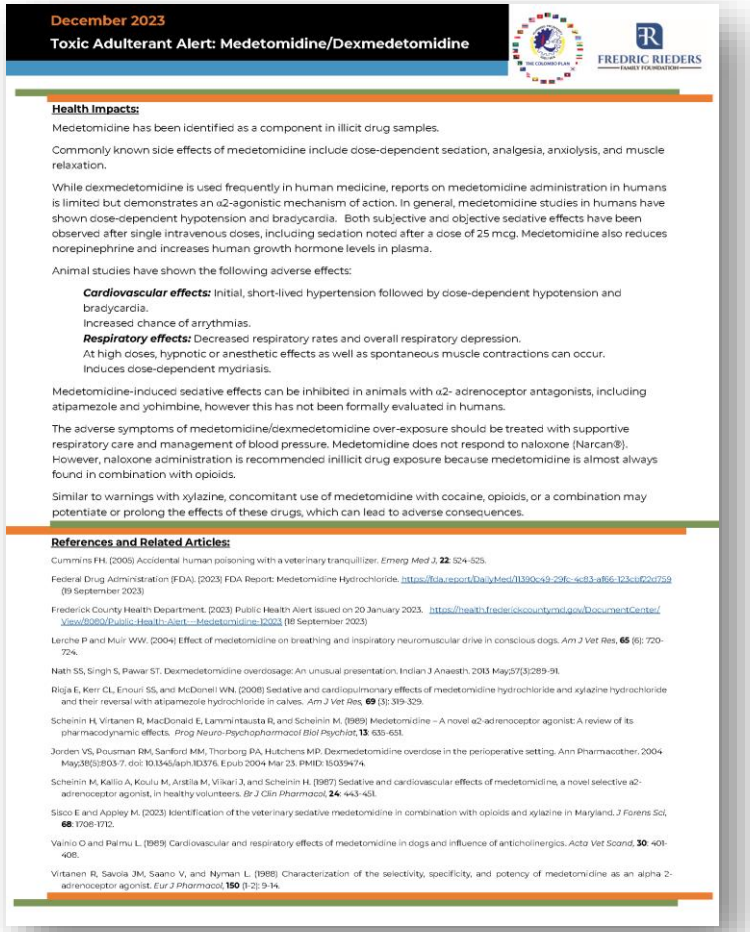
Acknowledgements: This report was prepared by Karl M. Midthun, Ph.D., Amanda L.A. Mohr, M.S., Thom Browne, and Barry K. Logan, Ph.D. The authors would like to acknowledge Lewis Nelson, M.D. for his review and contributions to the alert. Funding for this document was received by the Fredric Rieders Family Foundation from the Colombo Plan via U.S. Department of State/INL under 2019-RC-061 and 2017-RC-61, and other Colombo Plan funding sources. The opinions, findings, recommendations, and conclusions expressed in this publication are those of the authors and do not necessarily reflect those of the U.S. Department of State. More information on medetomidine is available by contacting mandi.mohr@cfsre.org.



December 2023

Toxic Adulterant Alert: Medetomidine/Dexmedetomidine

Health Impacts:

Medetomicine has been identified as a component in illicit drug samples.

Commonly known side effects of medetomidine include dose-dependent sedation, analgesia, anxiolysis, and muscle relaxation.

While dexmedetomidine is used frequently in human medicine, reports on medetomicine administration in humans is limited but demonstrates an α2-agonistic mechanism of action. In general, medetomidine studies in humans have shown dose-dependent hypotension and bradycardia. Both subjective and objective sedative effects have been observed after single intravenous doses, including sedation noted after a dose of 25 mcg. Medetomidine also reduces norepinephrine and increases human growth hormone levels in plasma.

Animal studies have shown the following adverse effects:

Cardiovascular effects: Initial, short-lived hypertension followed by dose-dependent hypotension and bradycardia.
Increased chance of arrythmias.
Respiratory effects: Decreased respiratory rates and overall respiratory depression.
At high doses, hypnotic or anesthetic effects as well as spontaneous muscle contractions can occur.
Induces dose-dependent mydriasis.

Medetomidine-induced sedative effects can be inhibited in animals with α2- adrenoceptor antagonists, including atipamezole and yohimbine, however this has not been formally evaluated in humans.

The adverse symptoms of medetomidine/dexmecletomidine over-exposure should be treated with supportive respiratory care and management of blood pressure. Medetomidine does not respond to naloxone (Narcan®). However, naloxone administration is recommended inillicit drug exposure because medetomidine is almost always found in combination with opioids.

Similar to warnings with xylazine, concomitant use of medetomidine with cocaine, opioids, or a combination may potentiate or prolong the effects of these drugs, which can lead to adverse consequences.

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PUBLIC ALERT ▸

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PUBLIC ALERT | MAY 2024

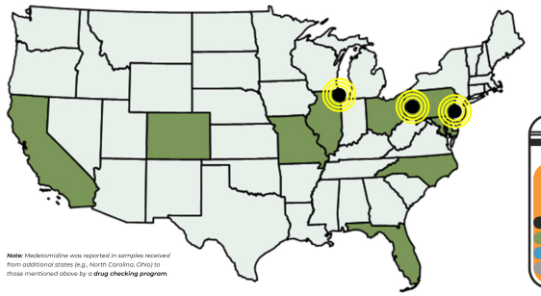
MEDETOMIDINE RAPIDLY PROLIFERATING ACROSS USA — IMPLICATED IN RECREATIONAL OPIOID DRUG SUPPLY & CAUSING OVERDOSE OUTBREAKS

PURPOSE: The objective of this announcement is to notify public health, harm reduction, first responders, clinicians, medical examiners and coroners, forensic and clinical laboratories, and all other related communities about new information surrounding the emergent adulterant **medetomidine** (also referred to as dexmedetomidine).

BACKGROUND: Medetomidine is an alpha-2 agonist, belonging to the same family of drugs as xylazine and clonidine. Medetomidine is synthetically manufactured and exists in two enantiomeric forms: **dexmedetomidine** and levomedetomidine, the former being active and potent. Dexmedetomidine is approved for use in humans and is administered in hospital, while differing forms of medetomidine are available for use in veterinary medicine. The effects of **medetomidine** can include sedation, analgesia, muscle relaxation, anxiolysis, bradycardia, hypotension, hyperglycemia, and hallucinations. Duration of action is noted to be longer for medetomidine relative to xylazine.

SUMMARY: Medetomidine is the latest CNS depressant to appear as an adulterant alongside fentanyl in the recreational drug supply. Recent mass overdose outbreaks in Philadelphia, Pittsburgh, and Chicago have all been associated with fentanyl or heroin drug products containing medetomidine, as well xylazine and/or other substances. In cases where medetomidine ingestion is suspected or confirmed, severe adverse effects have been noted, including **heightened sedation and profound bradycardia**.

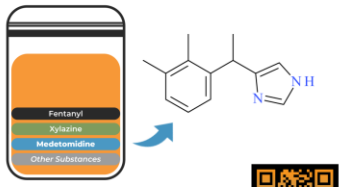
TIMEFRAME	DESCRIPTION OF MEDETOMIDINE IDENTIFICATIONS AND OVERDOSE EVENTS
Late 2022	Medetomidine begins appearing more regularly in the **Maryland** drug supply, following its first detection in July 2022. Medetomidine is commonly identified alongside fentanyl, xylazine, and other substances.
Mid-to-Late 2023	Medetomidine is sporadically identified in toxicology specimens collected from patients presenting to emergency departments after suspected opioid overdose (confirmed to not be administered). Overdose events originated from **Missouri, Colorado, Pennsylvania, California, and Maryland**. Medetomidine is commonly detected with fentanyl.
January 2024	An **alert** is issued out of **Toronto, ON**, about the emergence of medetomidine in the drug supply. This is followed by increased positivity in subsequent weeks and months, as medetomidine is found alongside fentanyl in suspected opioid products and commonly in combination with xylazine and other substances.
Early 2024	Medetomidine detections increase in drug materials and toxicology specimens originating from western Canada, including **Vancouver, BC**, commonly alongside fentanyl and other opioids.
Late April 2024	Medetomidine first appears in drug products in **Philadelphia, PA**, causing a large scale outbreak of overdoses and adverse events. Medetomidine is identified alongside fentanyl and xylazine.
Early May 2024	Medetomidine first appears in drug products in **Pittsburgh, PA**, causing a large scale outbreak of overdoses and adverse events. Medetomidine is identified alongside fentanyl and xylazine.
Early May 2024	Medetomidine first appears in drug products in **Chicago, IL**, causing a large scale outbreak of overdoses and adverse events. Medetomidine is identified alongside fentanyl and xylazine, or alongside heroin without xylazine.



Note: Medetomidine was reported in samples received from additional states (e.g., North Carolina, Ohio) to those mentioned above by a drug checking program.

◂ GEOGRAPHICAL DISTRIBUTION OF MEDETOMIDINE EMERGENCE

Medetomidine has been identified across several states in the U.S. and Canada, and is recently being observed in severe overdose outbreaks in major metropolitan areas (as marked).



ACKNOWLEDGEMENTS: This report was prepared by Alex Krotulski, Jan Shoresteil, Chris Morrell, Taylor Wood, Sara Walton, Josh DeBord, Mac Dern, Alexis Quinter, and Barry Logan at the Center for Forensic Science Research and Education (CFSRE) at the Fredric Rieders Family Foundation. The authors acknowledge scientists and staff for their involvements and contributions, as well as our many collaborators in public health agencies, clinical institutions, harm reduction organizations, and beyond for their cooperation in assessing drug outbreaks.

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ADDITIONAL INFORMATION: Contact npsdiscovery@fsu.org or visit www.npsdiscovery.org.

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"HISTORY" OF MEDETOMIDINE *(AS ADULTERANT)*

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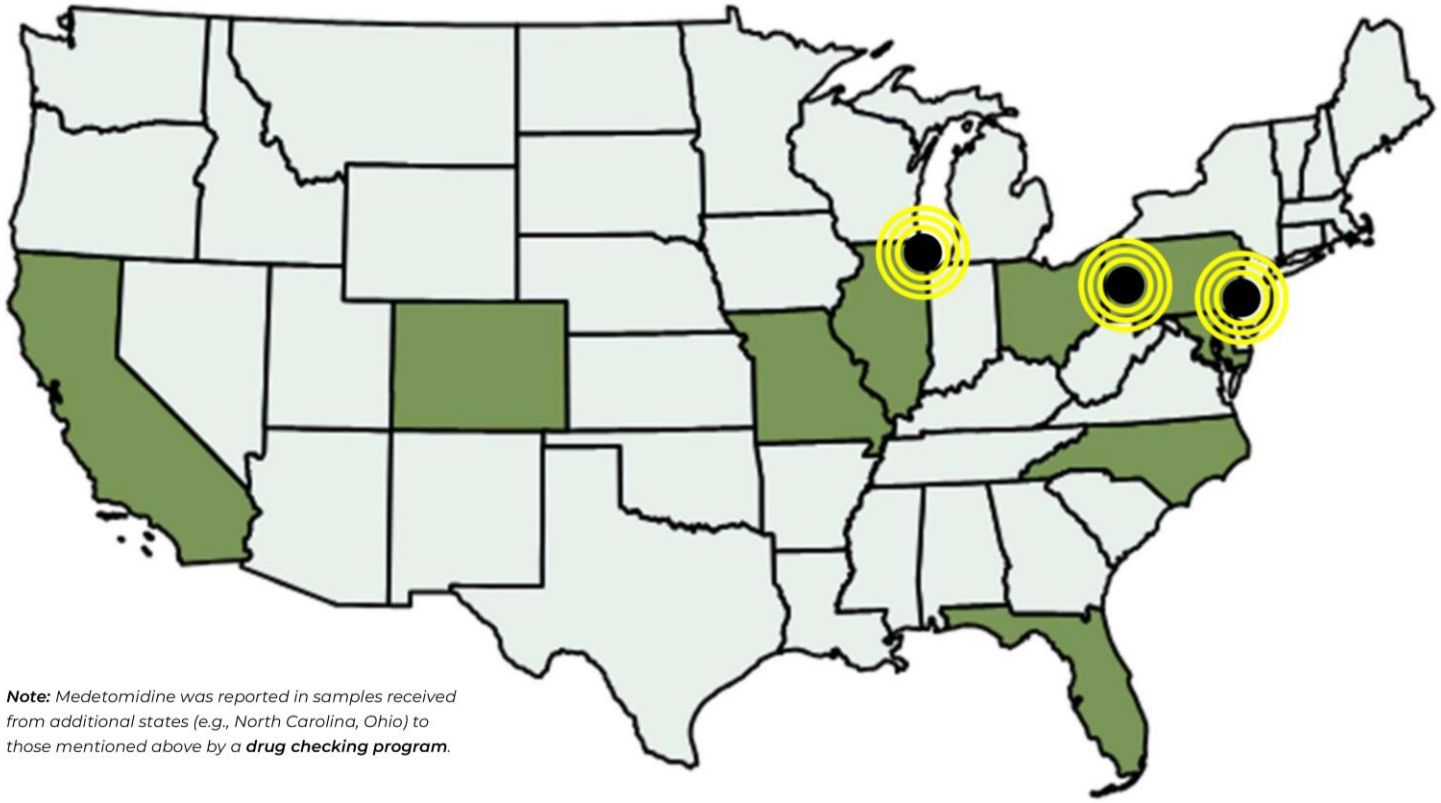
GEOGRAPHICAL DISTRIBUTION



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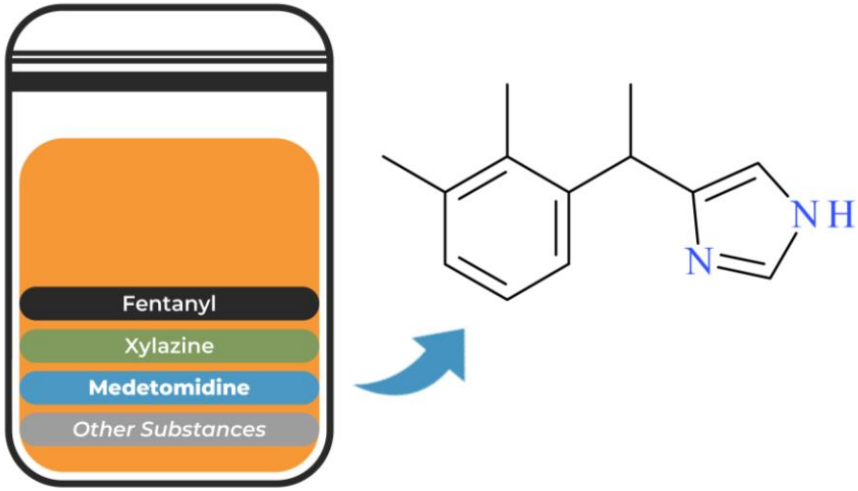
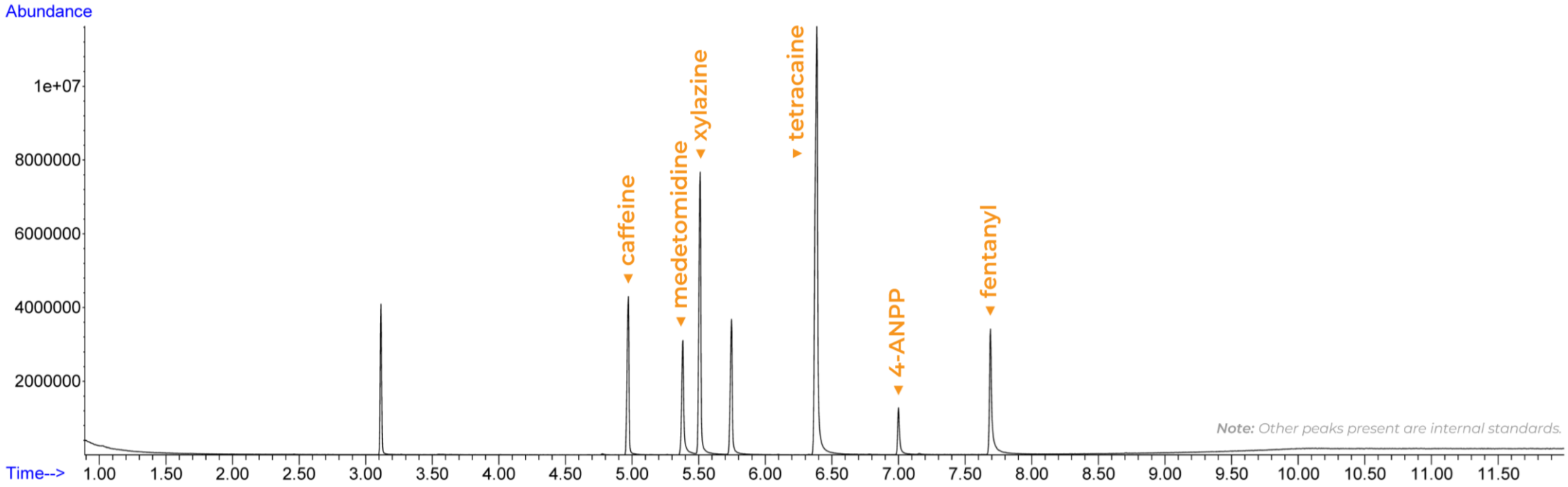


EMERGENCE OF MEDETOMIDINE AT THE CFSRE

EXAMPLE CHROMATOGRAM OF A DRUG MATERIAL CONTAINING MEDETOMIDINE COLLECTED FROM PHILADELPHIA IN EARLY MAY 2024



EARLY DRUG PRODUCTS

DRUG MATERIALS CONTAINING MEDETOMIDINE AND OTHER SUBSTANCES

SUMMARY OF RESULTS:

- *To date, medetomidine has been commonly identified alongside fentanyl and xylazine, and the proportion of medetomidine in the drug material varies by sample.*
- *Medetomidine has been identified alongside heroin, in the absence of xylazine.*
- *Tetracaine has been identified alongside fentanyl, xylazine, and medetomidine in drug products, but not uniformly or consistently.*
- *Real-time drug material and toxicological testing are on-going to track the emergence and proliferation of medetomidine.*

PHILADELPHIA, PA

DRUG	RELATIVE PARTS
Fentanyl	1p
Xylazine	1.9p
Medetomidine	**0.8p**
Tetracaine	3.9p
Other Substances?	Caffeine

DRUG	RELATIVE PARTS
Fentanyl	1p
Xylazine	0.4p
Medetomidine	**1.9p**
para-Fluorofentanyl	0.1p
Other Substances?	No

PITTSBURGH, PA

DRUG	RELATIVE PARTS
Fentanyl	1p
Xylazine	1.5p
Medetomidine	**0.1p**
Tetracaine	0.5p
Other Substances?	*p*FF, Caffeine

CHICAGO, IL

DRUG	RELATIVE PARTS
Fentanyl	1p
Xylazine	2p
Medetomidine	**0.6p**
Diphenhydramine	0.5p
Other Substances?	pFF, Nitazenes, etc.

DRUG	RELATIVE PARTS
Heroin	1p
Fentanyl	Trace
Medetomidine	**6.3p**
Diphenhydramine	2.6p
Other Substances?	No

RESOURCES & REFERENCES

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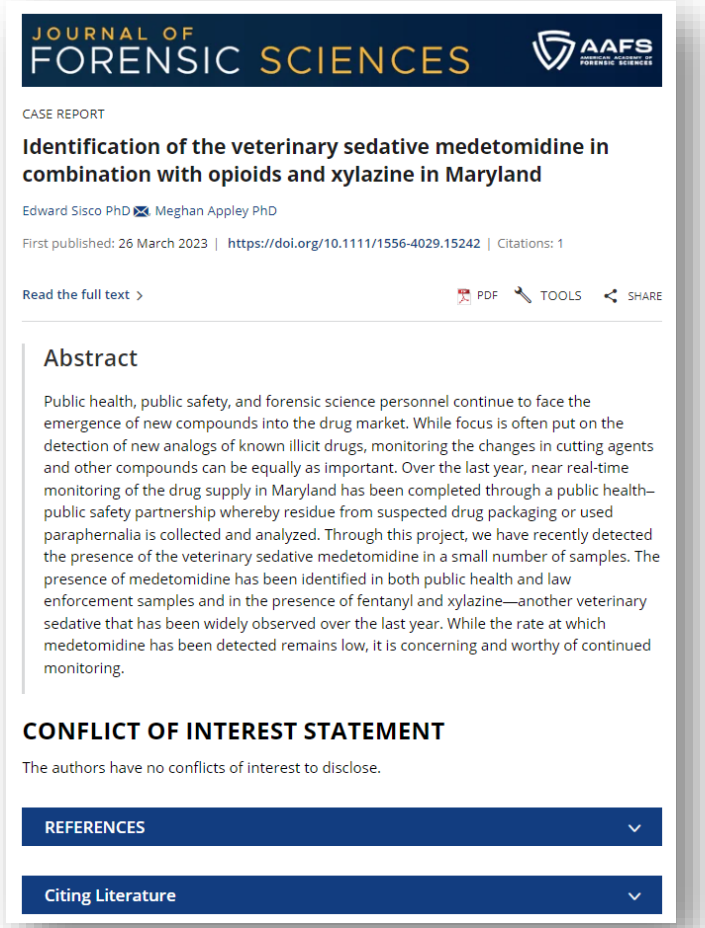
RESOURCES & REFERENCES



JOURNAL OF FORENSIC SCIENCES

CASE REPORT

Identification of the veterinary sedative medetomidine in combination with opioids and xylazine in Maryland

Edward Sisco PhD ✉ Meghan Appley PhD

First published: 26 March 2023 | https://doi.org/10.1111/1556-4029.15242 | Citations: 1

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Abstract

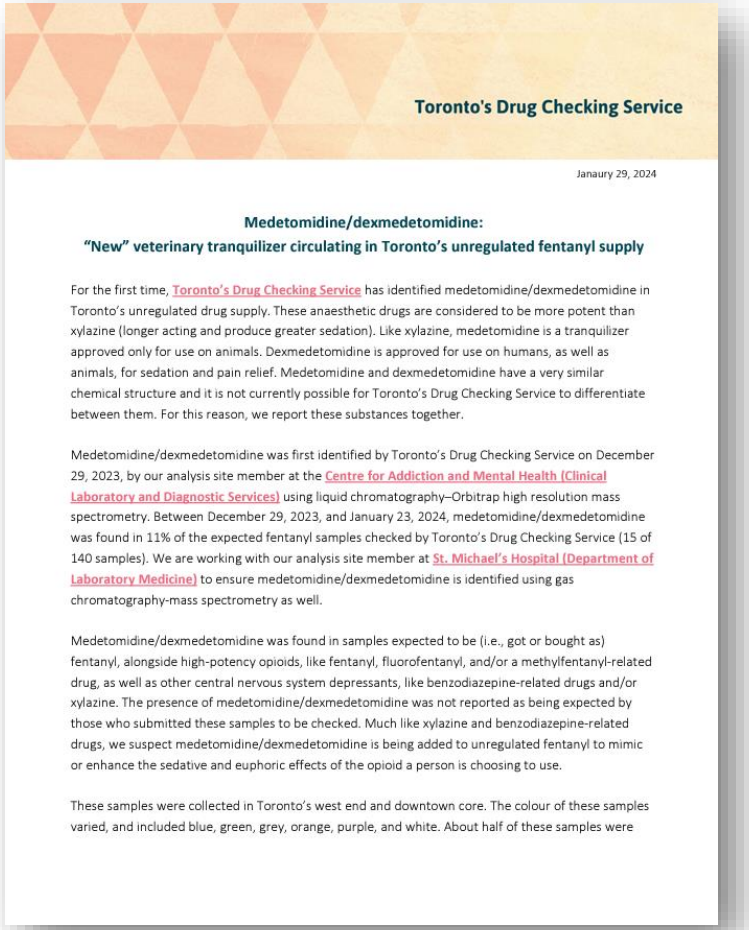
Public health, public safety, and forensic science personnel continue to face the emergence of new compounds into the drug market. While focus is often put on the detection of new analogs of known illicit drugs, monitoring the changes in cutting agents and other compounds can be equally as important. Over the last year, near real-time monitoring of the drug supply in Maryland has been completed through a public health–public safety partnership whereby residue from suspected drug packaging or used paraphernalia is collected and analyzed. Through this project, we have recently detected the presence of the veterinary sedative medetomidine in a small number of samples. The presence of medetomidine has been identified in both public health and law enforcement samples and in the presence of fentanyl and xylazine—another veterinary sedative that has been widely observed over the last year. While the rate at which medetomidine has been detected remains low, it is concerning and worthy of continued monitoring.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

REFERENCES

Citing Literature



Toronto's Drug Checking Service

Janaury 29, 2024

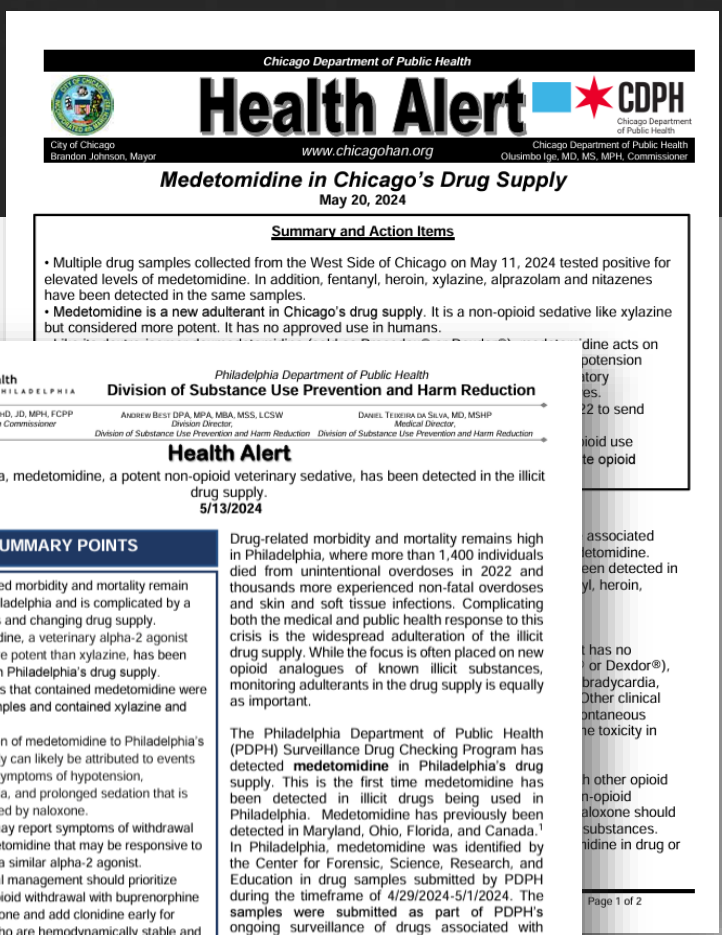
Medetomidine/dexmedetomidine:
"New" veterinary tranquilizer circulating in Toronto's unregulated fentanyl supply

For the first time, Toronto's Drug Checking Service has identified medetomidine/dexmedetomidine in Toronto's unregulated drug supply. These anaesthetic drugs are considered to be more potent than xylazine (longer acting and produce greater sedation). Like xylazine, medetomidine is a tranquilizer approved only for use on animals. Dexmedetomidine is approved for use on humans, as well as animals, for sedation and pain relief. Medetomidine and dexmedetomidine have a very similar chemical structure and it is not currently possible for Toronto's Drug Checking Service to differentiate between them. For this reason, we report these substances together.

Medetomidine/dexmedetomidine was first identified by Toronto's Drug Checking Service on December 29, 2023, by our analysis site member at the Centre for Addiction and Mental Health (Clinical Laboratory and Diagnostic Services) using liquid chromatography–Orbitrap high resolution mass spectrometry. Between December 29, 2023, and January 23, 2024, medetomidine/dexmedetomidine was found in 11% of the expected fentanyl samples checked by Toronto's Drug Checking Service (15 of 140 samples). We are working with our analysis site member at St. Michael's Hospital (Department of Laboratory Medicine) to ensure medetomidine/dexmedetomidine is identified using gas chromatography-mass spectrometry as well.

Medetomidine/dexmedetomidine was found in samples expected to be (i.e., got or bought as) fentanyl, alongside high-potency opioids, like fentanyl, fluorofentanyl, and/or a methylfentanyl-related drug, as well as other central nervous system depressants, like benzodiazepine-related drugs and/or xylazine. The presence of medetomidine/dexmedetomidine was not reported as being expected by those who submitted these samples to be checked. Much like xylazine and benzodiazepine-related drugs, we suspect medetomidine/dexmedetomidine is being added to unregulated fentanyl to mimic or enhance the sedative and euphoric effects of the opioid a person is choosing to use.

These samples were collected in Toronto's west end and downtown core. The colour of these samples varied, and included blue, green, grey, orange, purple, and white. About half of these samples were



Chicago Department of Public Health

Health Alert

CDPH Chicago Department of Public Health

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Olusimbo Ige, MD, MS, MPH, Commissioner

Medetomidine in Chicago's Drug Supply

May 20, 2024

Summary and Action Items

- Multiple drug samples collected from the West Side of Chicago on May 11, 2024 tested positive for elevated levels of medetomidine. In addition, fentanyl, heroin, xylazine, alprazolam and nitazenes have been detected in the same samples.
- **Medetomidine is a new adulterant in Chicago's drug supply.** It is a non-opioid sedative like xylazine but considered more potent. It has no approved use in humans.

Department of Public Health
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Health Alert

In Philadelphia, medetomidine, a potent non-opioid veterinary sedative, has been detected in the illicit drug supply.

5/13/2024

SUMMARY POINTS

- 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 that is more potent than xylazine, has been detected in Philadelphia's drug supply.
- All samples that contained medetomidine were 'dope' samples and contained xylazine and fentanyl.
- Introduction of medetomidine to Philadelphia's drug supply can likely be attributed to events involving symptoms of hypotension, bradycardia, and prolonged sedation that is not reversed by naloxone.
- Patients may report symptoms of withdrawal from medetomidine that may be responsive to clonidine, a similar alpha-2 agonist.
- Withdrawal management should prioritize treating opioid withdrawal with buprenorphine or methadone and add clonidine early for patients who are hemodynamically stable and have persistent symptoms.

Drug-related morbidity and mortality remains high in Philadelphia, where more than 1,400 individuals died from unintentional overdoses in 2022 and thousands more experienced non-fatal overdoses and skin and soft tissue infections. Complicating both the medical and public health response to this crisis is the widespread adulteration of the illicit drug supply. While the focus is often placed on new opioid analogues of known illicit substances, monitoring adulterants in the drug supply is equally as important.

The Philadelphia Department of Public Health (PDPH) Surveillance Drug Checking Program has detected **medetomidine** in Philadelphia's drug supply. This is the first time medetomidine has been detected in illicit drugs being used in Philadelphia. Medetomidine has previously been detected in Maryland, Ohio, Florida, and Canada.[1] In Philadelphia, medetomidine was identified by the Center for Forensic, Science, Research, and Education in drug samples submitted by PDPH during the timeframe of 4/29/2024-5/1/2024. The **samples were submitted as part of PDPH's** ongoing surveillance of drugs associated with overdose. Reports of patients presenting to hospitals during this timeframe included symptoms of prolonged sedation, bradycardia, and hypotension, which are consistent with the expected clinical effects of medetomidine. At this point, a link to these adverse drug events and the introduction of **medetomidine to Philadelphia's drug supply has** not been established. To date all samples that contained medetomidine also contained xylazine and fentanyl.

Clinical Effects of Medetomidine

Similar to xylazine, medetomidine is a synthetic alpha-2 adrenoreceptor agonist sedative used in veterinary medicine. In human medicine, medetomidine is most similar to dexmedetomidine (Precedex®) and clonidine. However, medetomidine is not approved for human use and understanding of its clinical effects is based on veterinary literature.

In the veterinary literature, the effects of medetomidine include sedation, analgesia, muscle relaxation and anxiolysis (i.e., anti-anxiety).[2] Medetomidine is more potent than xylazine and produces greater

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