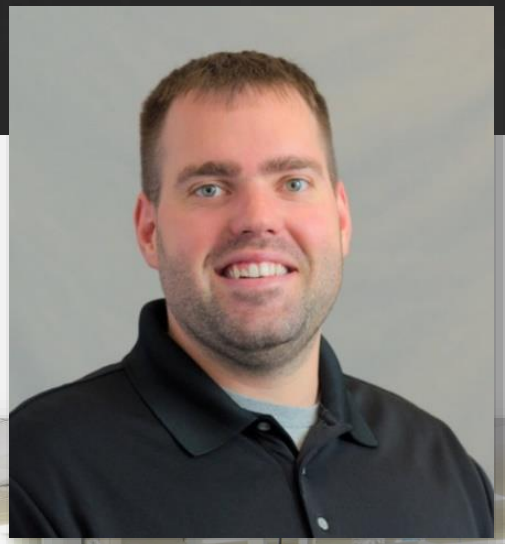
Medicolegal Death Investigations Involving Novel Psychoactive Substances (NPS)

Florida Association of Medical Examiners (FAME) Annual Education Conference

Thursday July 20, 2023 – 8:00 to 9:30 AM ET

Alex J. Krotulski, Ph.D. – Center for Forensic Science Research and Education (CFSRE)

INTRODUCTION



- **Center for Forensic Science Research & Education**
  - Associate Director
    - Toxicology & Chemistry
  - Program Manager
    - NPS Discovery

- **Thomas Jefferson University**
  - Assistant Program Director
    - MS in Forensic Toxicology
  - Faculty / Lecturer

DISCLOSURES

- I have no conflicts of interest to disclose.
- I am a scientist and employee of FRFF / CFSRE, a 501(c)(3) non-profit research and educational facility.
- CFSRE's NPS Discovery program is funded in part by the National Institute of Justice (NIJ), Office of Justice Programs (OJP), U.S. Department of Justice (DOJ).
  - Award Number: 15PNIJ-22-GG-04434-MUMU
  - The opinions, findings, conclusions and/or recommendations expressed in this publication are those of the author(s) and do not necessarily represent the official position or policies of the U.S. Department of Justice.

NIJ | National Institute of Justice

STRENGTHEN SCIENCE. ADVANCE JUSTICE.

PRESENTATION OUTLINE

- Toxicology Testing
- Interpretive Strategy
- Forensic Case Examples
  - Individual Cases
  - Case Series
  - Clinical Case*

TOXICOLOGY TESTING AND INTERPRETIVE STRATEGY

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THE CFSRE & OUR LAB

- The Center for Forensic Science Research and Education (CFSRE)
  - 501(c)(3) non-profit research and educational facility
  - Home to *NPS Discovery* and other programs

Waters Xevo® G2-S LC-QTOF-MS

Sciex X500R LC-TOF-MS

Sciex TripleTOF® 5600+ LC-TOF-MS

Agilent 6495 LC-QQQ-MS

Agilent 6430 LC-QQQ-MS

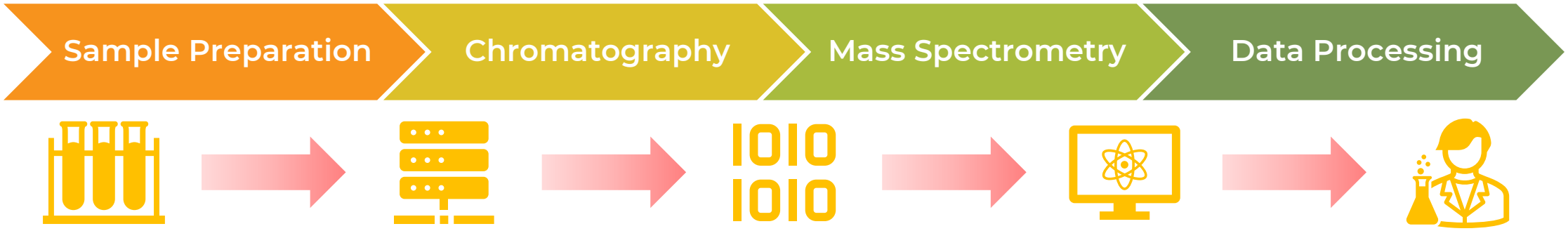
Waters TQS LC-QQQ-MS

Waters TQD LC-QQQ-MS

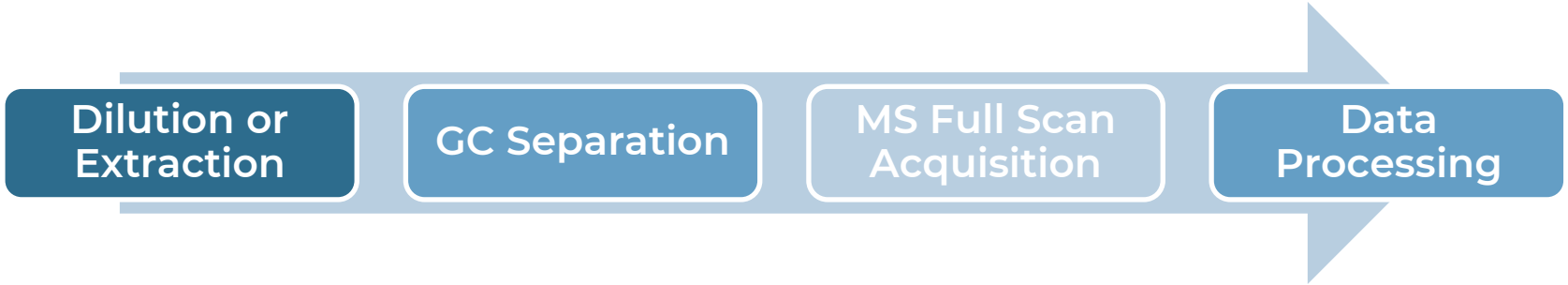
Agilent 5975 GC-MS

Agilent 5975 GC-MS

CFSRE TESTING & METHODS



- GC-MS →



- LC-QTOF-MS →

COMPARISON OF ANALYTICAL METHODS

SCRENNING ASSAYS

- Immunoassay / ELISA
  - Leveraging the benefits of cross reactivity
- GC-MS
  - Defined scope vs. vast library databases

SCRENNING ASSAYS

- LC-QTOF-MS
  - Non-targeted acquisition method
  - Targeted data processing method
  - **Library database containing >1,100 analytes**

CONFIRMATORY ASSAYS

- LC-QQQ-MS
  - Targeted acquisition methods
  - Class or subclass specific
  - Quantitative vs. qualitative

CONFIRMATORY ASSAYS

- LC-QTOF-MS
  - Qualitative confirmation
  - [Same assay as screening]
  - Library database containing >1,100 analytes

INTERPRETATION OF CASES INVOLVING NPS

MDI INFORMATION SHARED

- Case history / circumstances
- Police reports
- Death investigator report
  - Scene photos
- Autopsy report
- Medical records / prescriptions
- Crime lab results
- Other toxicology results***
- Other relevant information
  - Drug use history

TOXICOLOGY TESTING & INTERPRETATION

- Specimens available and tested
- Testing performed and scope of testing
  - Limitations of testing (e.g., sample preparation)
- Results (qualitative vs. quantitative)
  - Reference concentration ranges
  - Drug-drug interactions

NPS EVALUATION & INTERPRETATION

- What is known about the drug? Any published literature?
  - Chemistry, pharmacology, toxicity, adverse effects, etc.
- Have there been other forensic / clinical cases?
- Is the drug related to other known drugs? (e.g., analogue)
- Ultimately, is the drug the only identifiable culprit??

FORENSIC CASE EXAMPLES

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FORENSIC CASE #1

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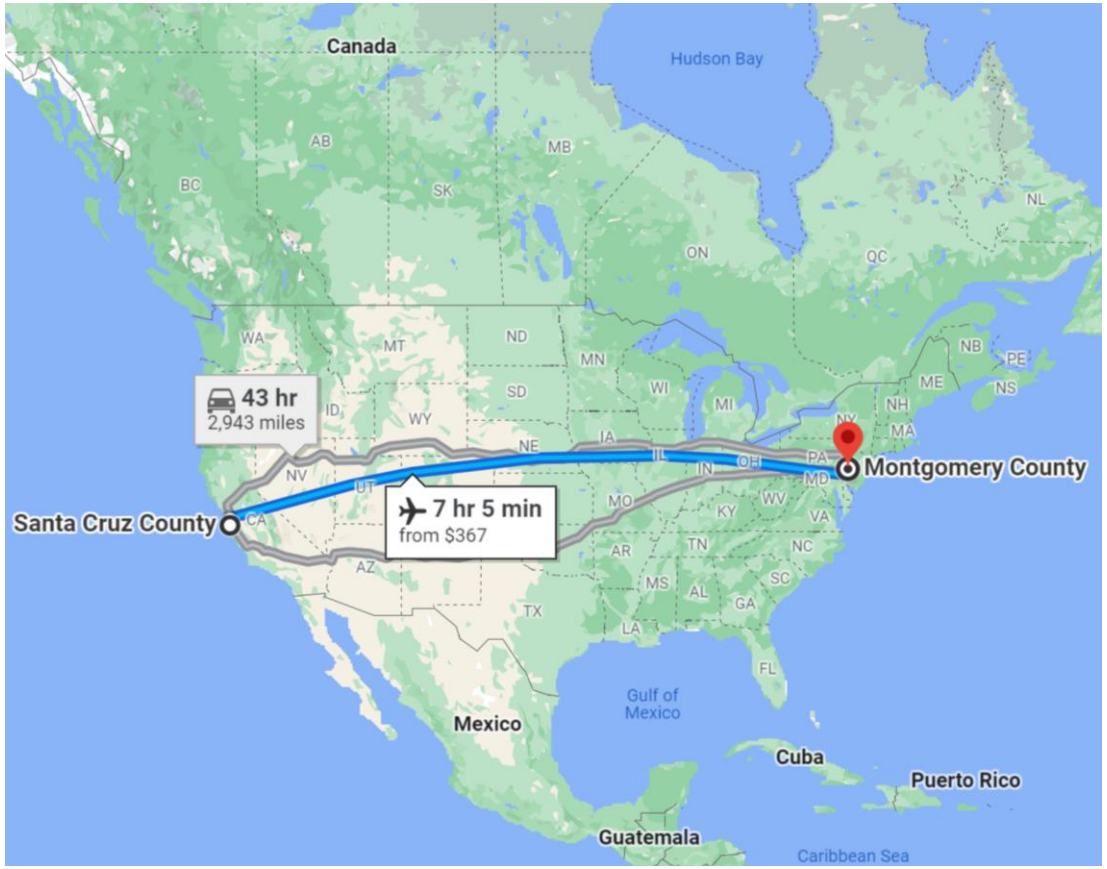
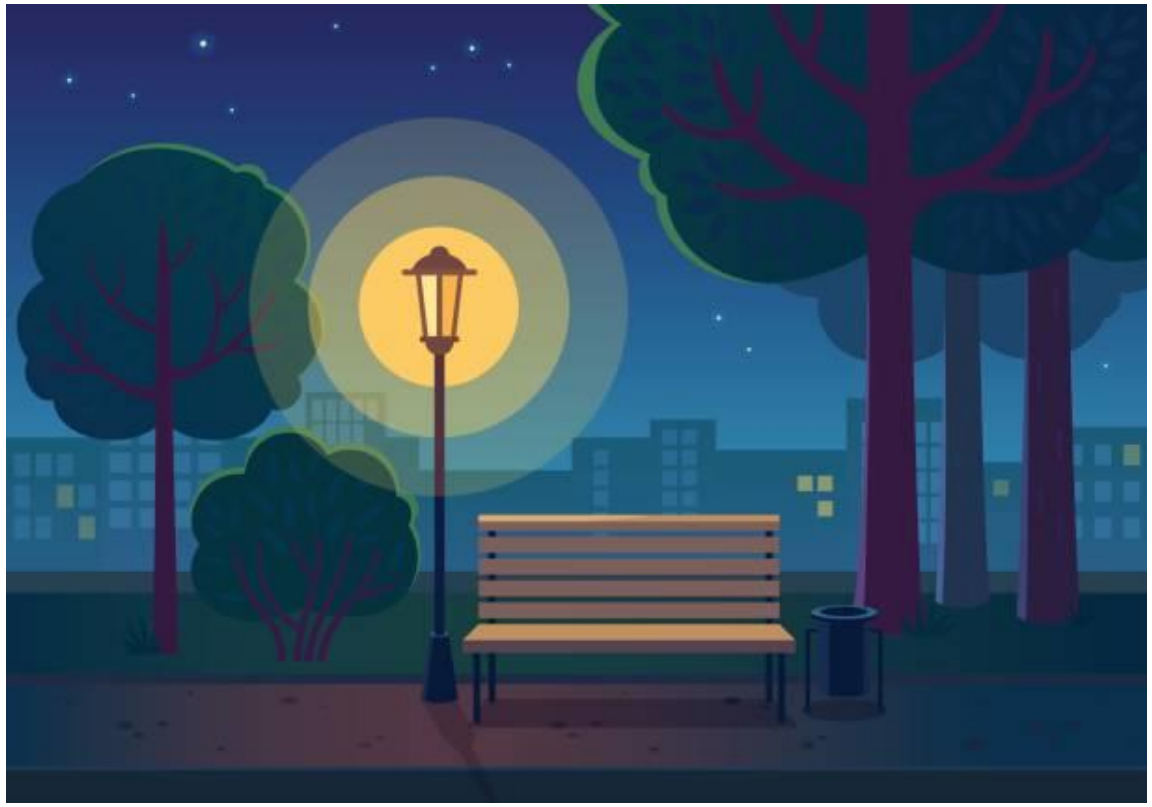
A CROSS-COUNTRY COLLABORATION

- **Santa Cruz County Sheriff-Coroner's Office**
  - On Pacific coast, south of San Jose, CA
  - Population ~300,000
- **NMS Labs**
  - Reference forensic toxicology laboratory serving clients across the U.S.
- **Center for Forensic Science Research and Education (CFSRE)**
  - Non-profit forensic laboratory specializing in the analysis of newly emerging drugs



CASE HISTORY

- October 2021 (California)
- **Three individuals unresponsive in park**
  - Snorting suspected cocaine powder
- Two women purchased cocaine from a trusted dealer who sells “untainted” drugs
  - Used drugs the night prior without incident
- Met up with a guy who purchased more cocaine from unfamiliar dealer

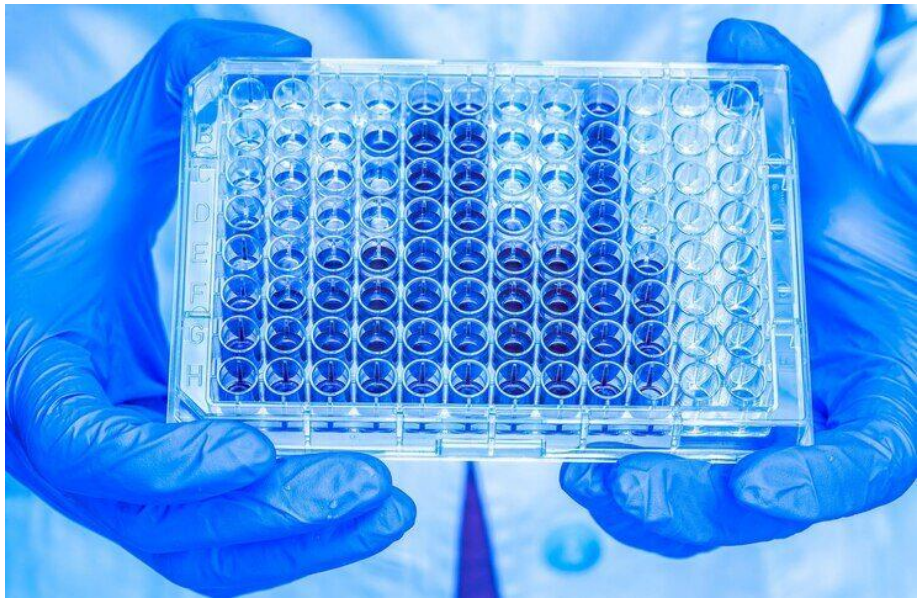


CASE HISTORY

- All were transported to the hospital
  - Two were revived with naloxone and survived
  - Third required advanced life support for persistent comatose state (suspected opioid OD)

- Hospital urine drug screen:
  - Positive → Amphetamine, cocaine, benzodiazepines
  - Negative → Opiates
  - **Not performed → Fentanyl**

- Patient died three days later
  - Body transferred to coroner's office
  - Hospital specimens transferred as well



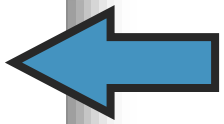
CORONER'S OFFICE

- The body of the decedent was transported to the Santa Cruz County Sheriff-Coroner's Office
- The pathologist performed an external examination
- **Hospital admission blood and urine samples were sequestered for toxicological analysis**

TOXICOLOGY TESTING

- Specimens first sent to NMS Labs (Horsham, PA)
- Analysis performed by LC-TOF-MS, LC-QQQ-MS, and GC-MS
- **Results:**

Compound	Result	Units	Matrix Source
Naloxone	Positive	ng/mL	005 - Urine
Nicotine	Positive	ng/mL	005 - Urine
1-Hydroxymidazolam	>5000	ng/mL	005 - Urine
Benzoylecgonine	14000	ng/mL	005 - Urine
Cocaine	780	ng/mL	005 - Urine
Cocaethylene	610	ng/mL	005 - Urine
Amphetamine	300	ng/mL	005 - Urine
Methamphetamine	5400	ng/mL	005 - Urine
Fentanyl	63	ng/mL	005 - Urine
Norfentanyl	17	ng/mL	005 - Urine



- *Blood: Negative for fentanyl*

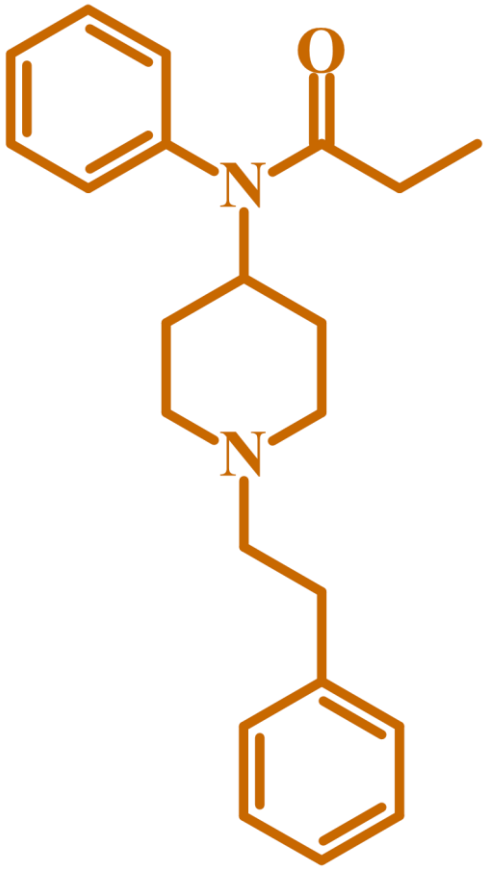
TOXICOLOGY TESTING

- Specimens first sent to NMS Labs (Horsham, PA)
- Analysis performed by LC-TOF-MS, LC-QQQ-MS, and GC-MS

- **Results:** Fentanyl, methamphetamine, and cocaine (urine)
- Review of medical records → Fentanyl administered by medical staff
  - **Was the cocaine laced with fentanyl??**
- Other toxicology results are insufficient to explain the death
  - **What's the next step??**

IS FENTANYL ALWAYS THE ANSWER?

- Fentanyl can be administered in the hospital for various reasons
  - Examples: Intubation or post-intubation sedation
- Handful of cases to date with this type of scenario
- Are there ways to distinguish hospital fentanyl vs. illicit fentanyl?
- ***Was fentanyl really the culprit in this case?***



DRUG MATERIAL TESTING

- **Three white powders** sent to the CFSRE (Willow Grove, PA)
  - Sample preparation → Methanol dilution
  - Qualitative Analysis → GC-MS and LC-QTOF-MS

- **Results:**
  - Powder #1 – Cocaine (ziplock)
  - Powder #2 – Cocaine (ziplock)

(Examples of the drug evidence)

DRUG MATERIAL TESTING

- **Three white powders** sent to the CFSRE (Willow Grove, PA)
  - Sample preparation → Methanol dilution
  - Qualitative Analysis → GC-MS and LC-QTOF-MS

- **Results:**
  - Powder #1 – Cocaine (ziplock)
  - Powder #2 – Cocaine (ziplock)
  - Powder #3 – **Etodesnitazene** (cellophane)

(Examples of the drug evidence)

TOXICOLOGY TESTING

- Secondary toxicological analysis performed at the CFSRE for **etodesnitazene**
- Blood and urine samples were submitted
  - Sample preparation → Basic liquid-liquid extraction
  - Analysis → LC-QTOF-MS and LC-QQQ-MS
  - Quantitation → Standard addition (ISTD: fentanyl-D5).
- **Results:**

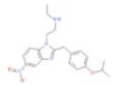
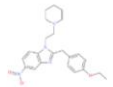
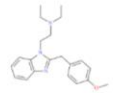
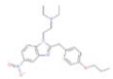
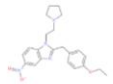
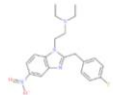
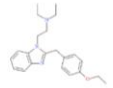
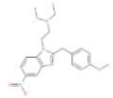
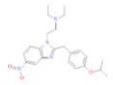
Results and Conclusions:

Exhibit #	Analyte	Concentration
1 (Blood)	Etodesnitazene	72 ng/mL
2 (Urine)	Etodesnitazene	68 ng/mL

TOXICOLOGY TESTING

- Secondary toxicological analysis performed at the CFSRE for **etodesnitazene**
- Blood and urine samples were submitted
  - Sample preparation → Basic liquid-liquid extraction
  - Analysis → LC-QTOF-MS and LC-QQQ-MS
  - Quantitation → Standard addition (ISTD: fentanyl-D5).
- **Results:** Blood = 72 ng/mL, Urine = 68 ng/mL
- **Reference Blood Concentrations:**
  - Eleven MDI cases / **Mean = 33 ng/mL**, Median = 11 ng/mL, **Range = 0.53 to 120 ng/mL**

NITAZENE ANALOGUES IDENTIFIED IN THE U.S.

Date	Class	Compound	Structure	Formula	MW	[M+]	[M+H]+
12/19/2022	Opioid	N-Desethyl Isotonitazene		C21H26N4O3	382.5	382	383.2078
11/22/2021	Opioid	N-Piperidinyl Etonitazene		C23H28N4O3	408.5	408	409.2234
09/22/2021	Opioid	Metodesnitazene		C21H27N3O	337.5	337	338.2227
05/26/2021	Opioid	Protonitazene		C23H30N4O3	410.5	410	411.2391
05/13/2021	Opioid	N-Pyrrolidino Etonitazene		C22H26N4O3	394.5	394	395.2078
03/26/2021	Opioid	Flunitazene		C20H23FN4O2	370.4	370	371.1878
02/23/2021	Opioid	Etodesnitazene		C22H29N3O	351.5	351	352.2383
01/15/2021	Opioid	Butonitazene		C24H32N4O3	424.5	424	425.2547
07/30/2020	Opioid	Metonitazene		C21H26N4O3	382.5	382	383.2078
11/19/2019	Opioid	Isotonitazene		C23H30N4O3	410.5	410	411.2391

REVIEW OF CASE FINDINGS

- **Case History:**
  - Three individuals ingested misrepresented “cocaine”
  - Two non-fatal overdoses, one fatal overdose
- **Drug Material Testing:**
  - Powder #3 → Etodesnitazene
- **Toxicology Testing:**
  - Blood & Urine → Etodesnitazene
- **Death Certification:**
  - Manner of Death – Accident
  - Cause of Death – Acute Etodesnitazene Intoxication

FORENSIC CASE #2

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CASE HISTORY

- Police and EMS respond to medical emergency
- ~30-year-old male determined to be DOA
  - Body cold to touch and no pulse
- No medical history or medication
- Prior leg injury → opioid use disorder
- Oxycodone and marijuana found at scene

MEDICAL EXAMINER'S OFFICE

- Full autopsy performed
- No signs of visible wounds
- Rigor mortis and livor mortis present
- Body cavities were unremarkable
- Heart was free of abnormalities
- Upper airway contained foam
- Other organs mostly unremarkable

TOXICOLOGY RESULTS

- Comprehensive toxicology testing performed
- Results (Peripheral Blood):

Drug	Concentration
Fentanyl	19 ng/mL
Norfentanyl	1.1 ng/mL
4-ANPP	Positive
Mitragynine	33 ng/mL
Hydroxy-THC	1.1 ng/mL

TOXICOLOGY RESULTS

- Comprehensive toxicology testing performed
- Results (Peripheral Blood):

Drug	Concentration
Fentanyl	19 ng/mL
Norfentanyl	1.1 ng/mL
4-ANPP	Positive
Mitragynine	33 ng/mL
Hydroxy-THC	1.1 ng/mL

- Secondary toxicology testing performed
- Results (Peripheral Blood):

Drug	Concentration
ortho-Chloro-Fentanyl	4.4 ng/mL

- **Combined effects of opioids**

NEXT STEPS FOR THE CASE

- Death Certification:
  - Manner: Accident
  - Cause: Fentanyl, ortho-chlorofentanyl, and mitragynine intoxication

- Further case details:
  - Crime lab testing → counterfeit oxycodone tablets
    - 4-ANPP, acetaminophen, despropionyl ortho-chlorofentanyl, fentanyl, and ortho-chlorofentanyl
  - Police investigation → text messages

FORENSIC CASE #3

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CASE HISTORY

- Homeowner calls 911 to report a deceased individual in basement
- Police respond to residence:
  - Discover decedent
  - **Recover drug paraphernalia near the body**
- History of drug use:
  - Heroin, cocaine, marijuana
- MEO takes custody of the body

MEDICAL EXAMINER'S OFFICE

- Full autopsy performed
- Autopsy findings:
  - Needle puncture marks
  - Pulmonary edema
  - More signs point to drug overdose death
- Blood, urine and vitreous collected and sent for toxicological analysis

TOXICOLOGY RESULTS

- Initial toxicology testing performed:
  - Comprehensive drug screening by LC-TOF-MS and ELISA, blood alcohol analysis, LC-QQQ-MS quantitative confirmations

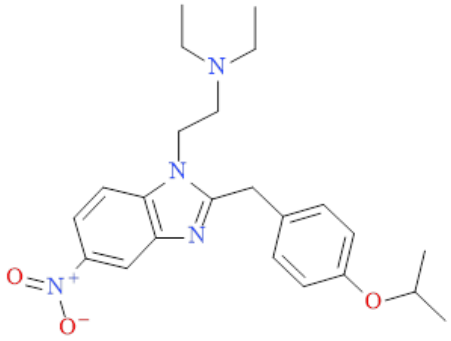
- Initial toxicology results:
  - Ethanol, caffeine, alprazolam, lamotrigine, amphetamine

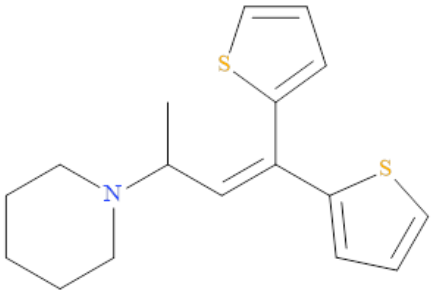
TOXICOLOGY RESULTS

- Initial toxicology testing performed:
  - Comprehensive drug screening by LC-TOF-MS and ELISA, blood alcohol analysis, LC-QQQ-MS quantitative confirmations

- Initial toxicology results:
  - Ethanol, caffeine, alprazolam, lamotrigine, amphetamine

- Additional toxicology testing results:
  - **Isotonitazene (0.9 ng/mL)**
  - **Piperidylthiambutene (0.5 ng/mL)**





TOXICOLOGY RESULTS

- Initial toxicology testing performed:
  - Comprehensive drug screening by LC-TOF-MS and ELISA, blood alcohol analysis, LC-QQQ-MS quantitative confirmations

- Initial toxicology results:
  - Ethanol, caffeine, alprazolam, lamotrigine, amphetamine

- Additional toxicology testing results:
  - **Isotonitazene (0.9 ng/mL)**
  - **Piperidylthiambutene (0.5 ng/mL)**

- Crime labs results:
  - **Syringe:**
    - **Isotonitazene**
  - **Spoon:**
    - **Isotonitazene, Piperidylthiambutene**

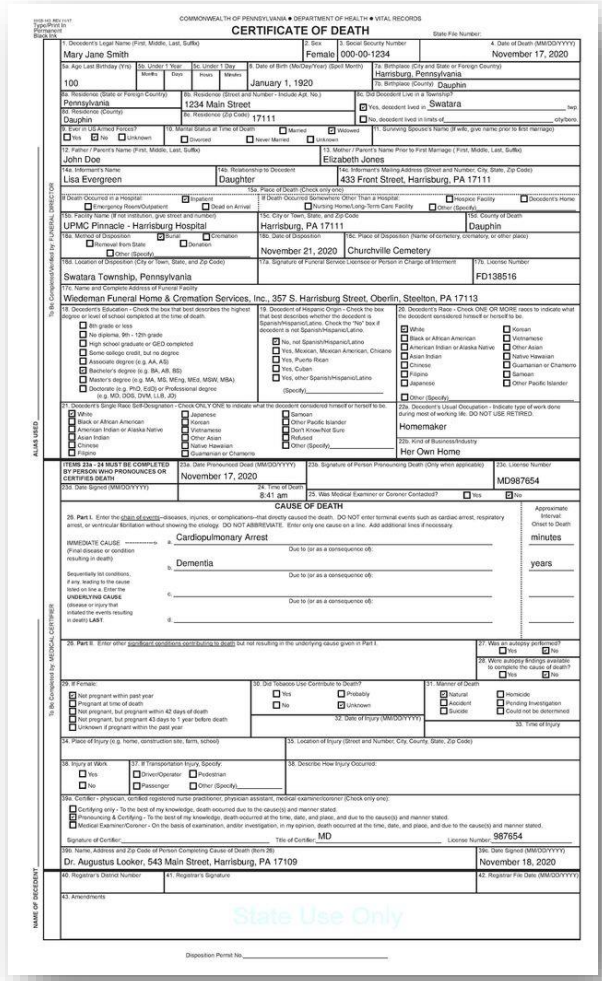
INTERPRETATION & CONSULTATION

- **Medical Examiner Interpretation:**
  - No anatomical cause of death
  - Other drugs largely unremarkable on their own

- **Forensic Toxicologist Interpretation:**
  - Combined effects of opioids, benzodiazepines, and alcohol
  - First case involving isotonitazene and piperidylthiambutene
  - Link with death investigation and crime lab

DEATH CERTIFICATION

- Manner of Death:
  - Accident
- Cause of Death:
  - **Acute isotonitazene and piperidylthiambutene intoxication**
- Other Significant Conditions:
  - Ethanol, alprazolam, and lamotrigine ingestion



COMMONWEALTH OF PENNSYLVANIA ● DEPARTMENT OF HEALTH ● VITAL RECORDS

CERTIFICATE OF DEATH

1. Decedent's Legal Name (First, Middle, Last, Suffix)	Mary Jane Smith
2. Sex	Female
3. Social Security Number	000-00-1234
4. Date of Death (MM/DD/YYYY)	November 17, 2020
5a. Age Last Birthday (Yrs)	100
6. Date of Birth (Mo/Day/Year) (Spell Month)	January 1, 1920
7a. Birthplace (City and State or Foreign Country)	Harrisburg, Pennsylvania
7b. Birthplace (County)	Dauphin
8a. Residence (State or Foreign Country)	Pennsylvania
8b. Residence (Street and Number - Include Apt. No.)	1234 Main Street
8c. Did Decedent Live in a Township?	Yes, decedent lived in Swatara twp
8d. Residence (County)	Dauphin
8e. Residence (Zip Code)	17111
9. Ever in US Armed Forces?	No
10. Marital Status at Time of Death	Widowed
11. Surviving Spouse's Name (If wife, give name prior to first marriage)	
12. Father / Parent's Name (First, Middle, Last, Suffix)	John Doe
13. Mother / Parent's Name Prior to First Marriage (First, Middle, Last, Suffix)	Elizabeth Jones
14a. Informant's Name	Lisa Evergreen
14b. Relationship to Decedent	Daughter
14c. Informant's Mailing Address (Street and Number, City, State, Zip Code)	433 Front Street, Harrisburg, PA 17111
15a. Place of Death (Check only one)	Inpatient
15b. Facility Name (If not institution, give street and number)	UPMC Pinnacle - Harrisburg Hospital
15c. City or Town, State, and Zip Code	Harrisburg, PA 17111
15d. County of Death	Dauphin
16a. Method of Disposition	Burial
16b. Date of Disposition	November 21, 2020
16c. Place of Disposition (Name of cemetery, crematory, or other place)	Churchville Cemetery
16d. Location of Disposition (City or Town, State, and Zip Code)	Swatara Township, Pennsylvania
17a. Signature of Funeral Service Licensee or Person in Charge of Interment	
17b. License Number	FD138516
17c. Name and Complete Address of Funeral Facility	Wiedeman Funeral Home & Cremation Services, Inc., 357 S. Harrisburg Street, Oberlin, Steelton, PA 17113
18. Decedent's Education	12th grade, no diploma
19. Decedent of Hispanic Origin	No, not Spanish/Hispanic/Latino
20. Decedent's Race	White
21. Decedent's Single Race Self-Designation	White
22a. Decedent's Usual Occupation	Homemaker
22b. Kind of Business/Industry	Her Own Home
23a. Date Pronounced Dead (MM/DD/YYYY)	November 17, 2020
23b. Signature of Person Pronouncing Death (Only when applicable)	
23c. License Number	MD987654
23d. Date Signed (MM/DD/YYYY)	
24. Time of Death	8:41 am
25. Was Medical Examiner or Coroner Contacted?	No

CAUSE OF DEATH

IMMEDIATE CAUSE (Final disease or condition resulting in death)	a. Cardiopulmonary Arrest	minutes
Sequentially list conditions, if any, leading to the cause listed on line a. Enter the UNDERLYING CAUSE disease or injury that initiated the events resulting in death LAST.	b. Dementia	years
	c.	
	d.	

29. Part I. Enter the chain of events—diseases, injuries, or complications—that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Part II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in Part I.

27. Was an autopsy performed? No

28. Were autopsy findings available to complete the cause of death? No

29. If Female: Not pregnant within past year

30. Did Tobacco Use Contribute to Death? Unknown

31. Manner of Death: Natural

32. Date of Injury (MM/DD/YYYY)

33. Time of Injury

34. Place of Injury (e.g. home, construction site, farm, school)

35. Location of Injury (Street and Number, City, County, State, Zip Code)

36. Injury at Work: No

37. If Transportation Injury, Specify: Driver/Operator

38. Describe How Injury Occurred:

39a. Certifier - physician, certified registered nurse practitioner, physician assistant, medical examiner/coroner (Check only one): Certifying only - To the best of my knowledge, death occurred due to the cause(s) and manner stated.

Signature of Certifier: Title of Certifier: MD License Number: 987654

39b. Name, Address and Zip Code of Person Completing Cause of Death (Item 39): Dr. Augustus Looker, 543 Main Street, Harrisburg, PA 17109

39c. Date Signed (MM/DD/YYYY): November 18, 2020

40. Registrar's District Number

41. Registrar's Signature

42. Registrar File Date (MM/DD/YYYY)

43. Amendments

State Use Only

Disposition Permit No.

FORENSIC CASE #4

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CASE HISTORY

- Male in 20s found dead on friend's deck
- Suspected drug overdose
- Drug paraphernalia found on scene
  - White oval shaped "IP204" pill
- Reported history of polydrug abuse
- No additional information provided

MEDICAL EXAMINER'S OFFICE

- Full autopsy performed

- Autopsy findings:
  - External examination – unremarkable
    - No evidence of injury
  - Respiratory system:
    - Dried frothy fluid on face
    - Mild amount of aspirated vomitus
  - Other organs → no abnormalities noted

- Femoral blood, urine, and vitreous fluid collected and sent for toxicological analysis

INITIAL TOXICOLOGY TESTING

DRUG SCREENING

- **Ethanol and Volatiles (Blood):**
  - None detected
- **ELISA (Blood and Urine):**
  - Opioids – Present
  - Oxycodone – Present
  - Cannabinoids / THC – Present
- **GC-MS Screen (Urine):**
  - Cotinine – Present
  - Acetaminophen – Present
  - Oxycodone – Present

DRUG CONFIRMATION

- **LC-MS (Blood):**
  - Opioids – None detected
- **LC-MS (Blood):**
  - **Oxycodone – 41 ng/mL**
  - Fatal Reference – 100-8,000 ng/mL (Baselt)
    - Average: ~400 ng/mL
- **LC-MS (Blood):**
  - Acetaminophen – Present (<10 ug/mL)
- **LC-MS (Blood):**
  - THC-COOH – Present

SECONDARY FORENSIC TESTING

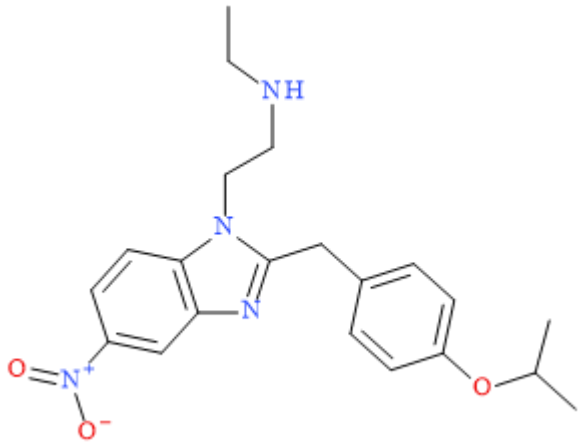
TOXICOLOGY RESULTS

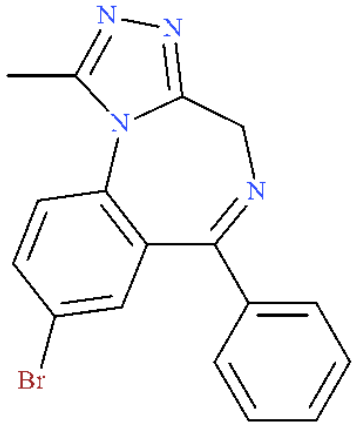
- **LC-QQQ-MS (Blood):**
  - *N*-Desethyl Isotonitazene – 5.0 ng/mL
  - Bromazolam – Positive (<5.0 ng/mL)
  - Oxycodone – Positive *(@ 41 ng/mL)*
  - Acetaminophen – Positive

- **LC-QQQ-MS (Urine):**
  - *N*-Desethyl Isotonitazene – 1.7 ng/mL
  - Bromazolam – Positive (<5.0 ng/mL)
  - Oxycodone – Positive
  - Noroxycodone – Positive
  - Acetaminophen – Positive

CHEMISTRY RESULTS

- **GC-MS (Pills):**
  - *N*-Desethyl Isotonitazene – Positive
  - Bromazolam – Identified
  - Acetaminophen – Positive
  - ***[Counterfeit oxycodone tablets]***





INTERPRETATION & DEATH CERTIFICATION

- **Toxicology Results:**
  - *N*-Desethyl Isotonitazene → novel opioid that is ~20 times more potent than fentanyl
  - Bromazolam → novel benzodiazepine suggested to be more potent than alprazolam
  - Polydrug use → Combined effects of opioids and benzodiazepines

- **Death Certification:**
  - Manner of Death:
    - Accident
  - Cause of Death:
    - Probable mixed drug intoxication (see toxicology)

Results and Conclusions:

Exhibit #	Analyte	Concentration
1 *(Blood)*	*N*-Desethyl Isotonitazene	5.0 ng/mL
1	Bromazolam	Positive (<5.0 ng/mL)
1	Oxycodone	Positive
1	Acetaminophen	Positive
2 *(Urine)*	*N*-Desethyl Isotonitazene	1.7 ng/mL
2	Bromazolam	Positive (<5.0 ng/mL)
2	Oxycodone	Positive
2	Noroxycodone	Positive
2	Acetaminophen	Positive
3 *(Pill)*	*N*-Desethyl Isotonitazene	Positive
3	Bromazolam	Identified
3	Acetaminophen	Positive

PUBLIC ALERT: N-DESETHYL ISOTONITAZENE

New potent synthetic opioid proliferating among recreational drug supply in USA

- One of the latest nitazene analogues to emerge
- Approximately 20x more potent than fentanyl
- States: Florida, Pennsylvania, New Jersey, Colorado, etc.
- Various sample types: pills, powders, blood, oral fluid, etc.

"DOPE" SAMPLES CONTAINING *N*-DESETHYL ISOTONITAZENE

LOCATION: Philadelphia, PA, USA

NUMBER OF SAMPLES: 7+

CONTENTS (PURITY RANGE):

- Xylazine (49% to 76%)
- Fentanyl (1.1% to 5.1%)
- *N*-Desethyl Isotonitazene (0.05% to 0.4%)
- Bromazolam (trace to 2.5%)
- Flubromazepam (trace)
- *para*-Fluorofentanyl (trace)

TIMELINE — *N*-DESETHYL ISOTONITAZENE ...

- **September 2022:** Identified in urine samples from a drug treatment program (PA).
- **October:** Identified in oral fluid samples collected from people who use drugs (PA).
- **November:** Identified in a counterfeit "A215" (oxycodone) round blue tablet (FL).
- **December:** Identified in "dope" samples alongside fentanyl, xylazine, and bromazolam (PA).
- **January 2023:** Continues to be identified in "dope" samples among Philadelphia drug supply (PA).

FORENSIC CASE SERIES

cfsre | NPS DISCOVERY

DIMETHYLPENTYLONE

cfsre | NPS DISCOVERY

DIMETHYLPENTYLONE CASE REPORT (2023)

Journal of Analytical Toxicology, 2023, **00**, 1–9
DOI: https://doi.org/10.1093/jat/bkad037
Advance Access Publication Date: 17 June 2023
Special Issue

OXFORD

N,N-Dimethylpentylone (dipentylone)—A new synthetic cathinone identified in a postmortem forensic toxicology case series

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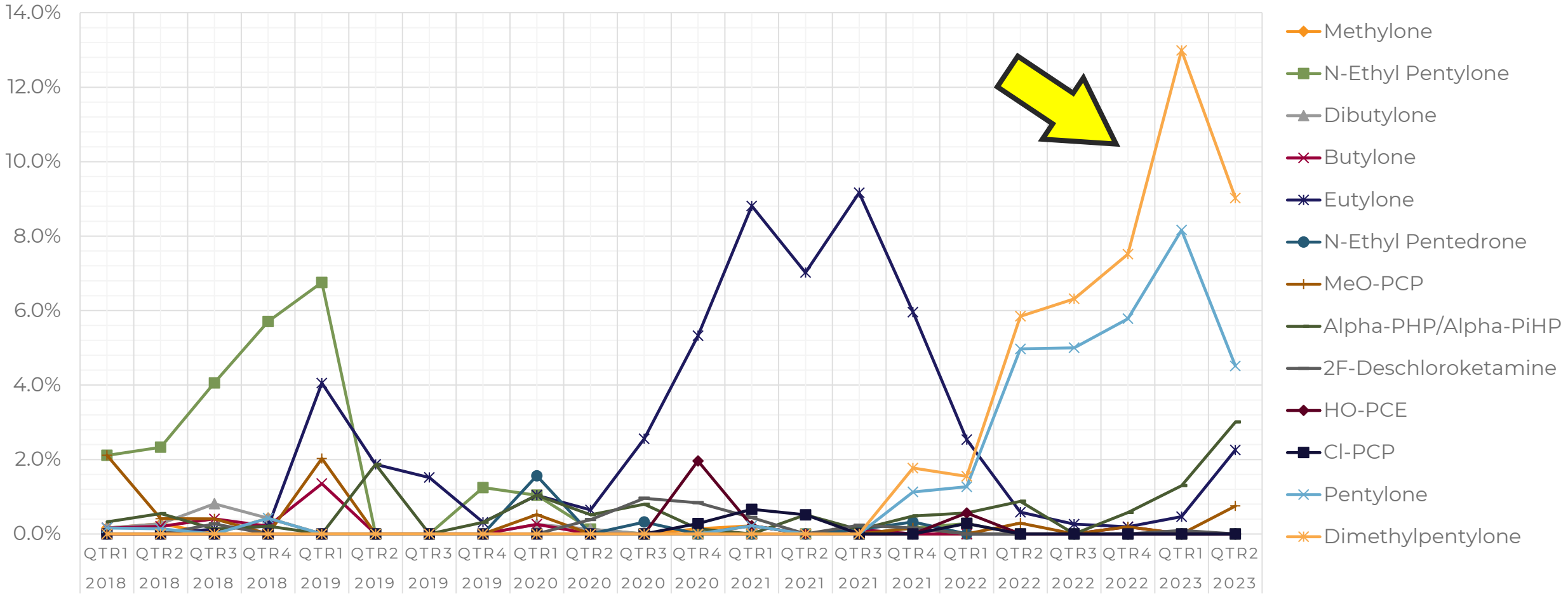
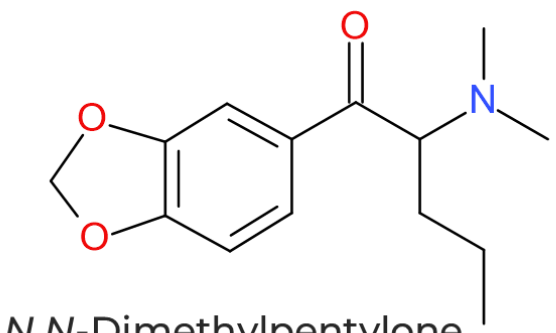
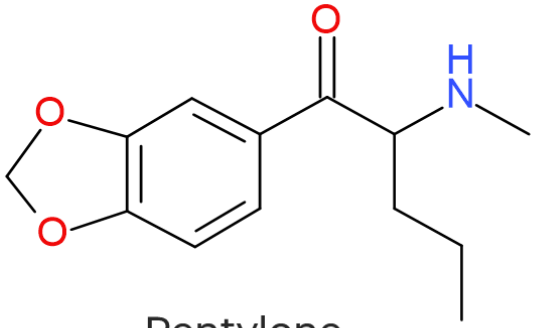
DIMETHYLPENTYLONE IN THE U.S.



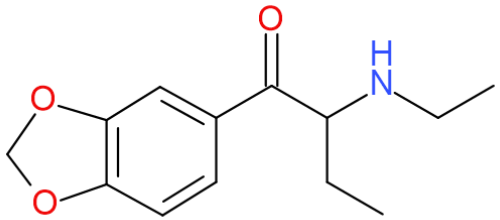
ISOMERS / SCOPE OF TESTING



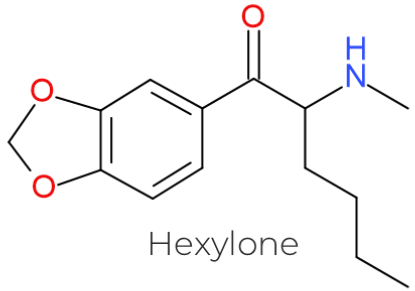
N,N-Dimethylpentylone



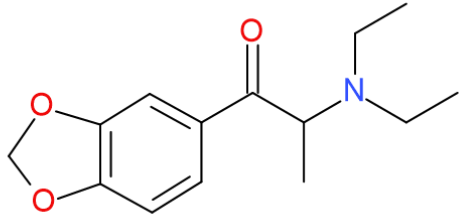
Pentylone



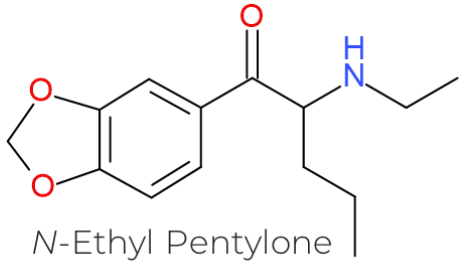
Eutylone



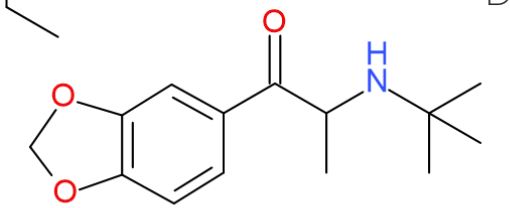
Hexylone



Diethylone



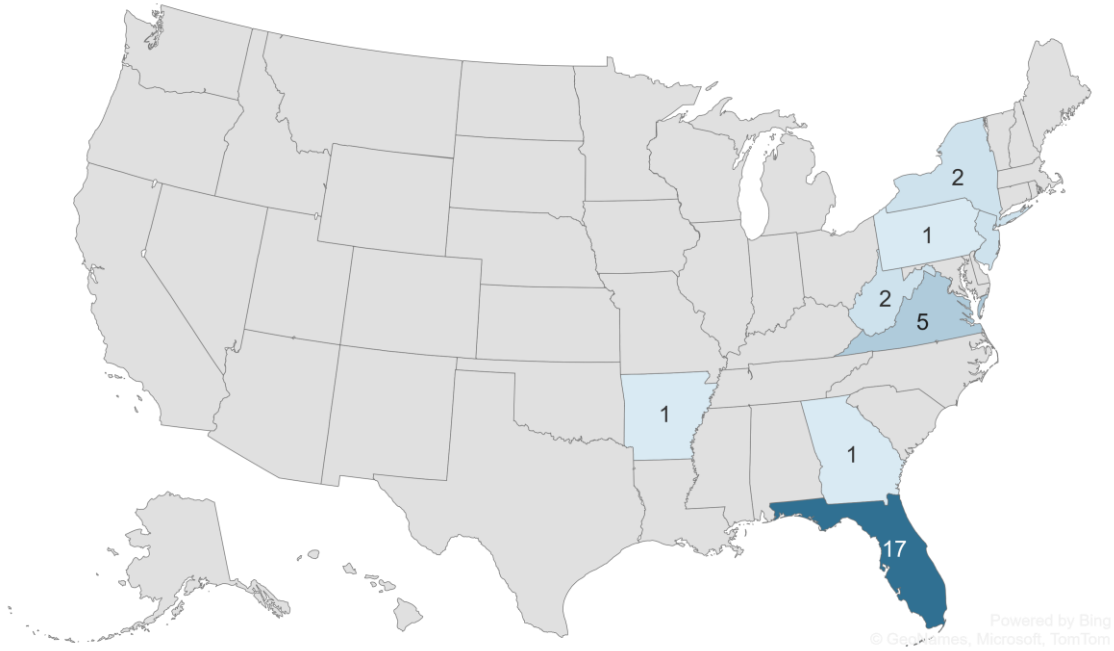
N-Ethyl Pentylone

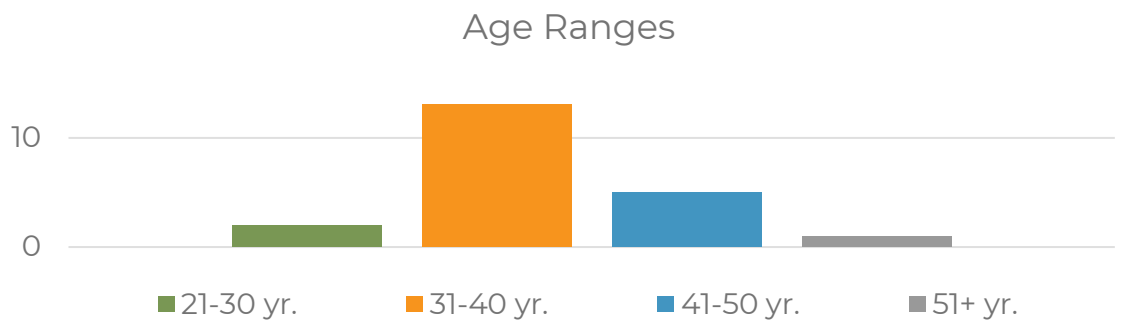


Tertylone

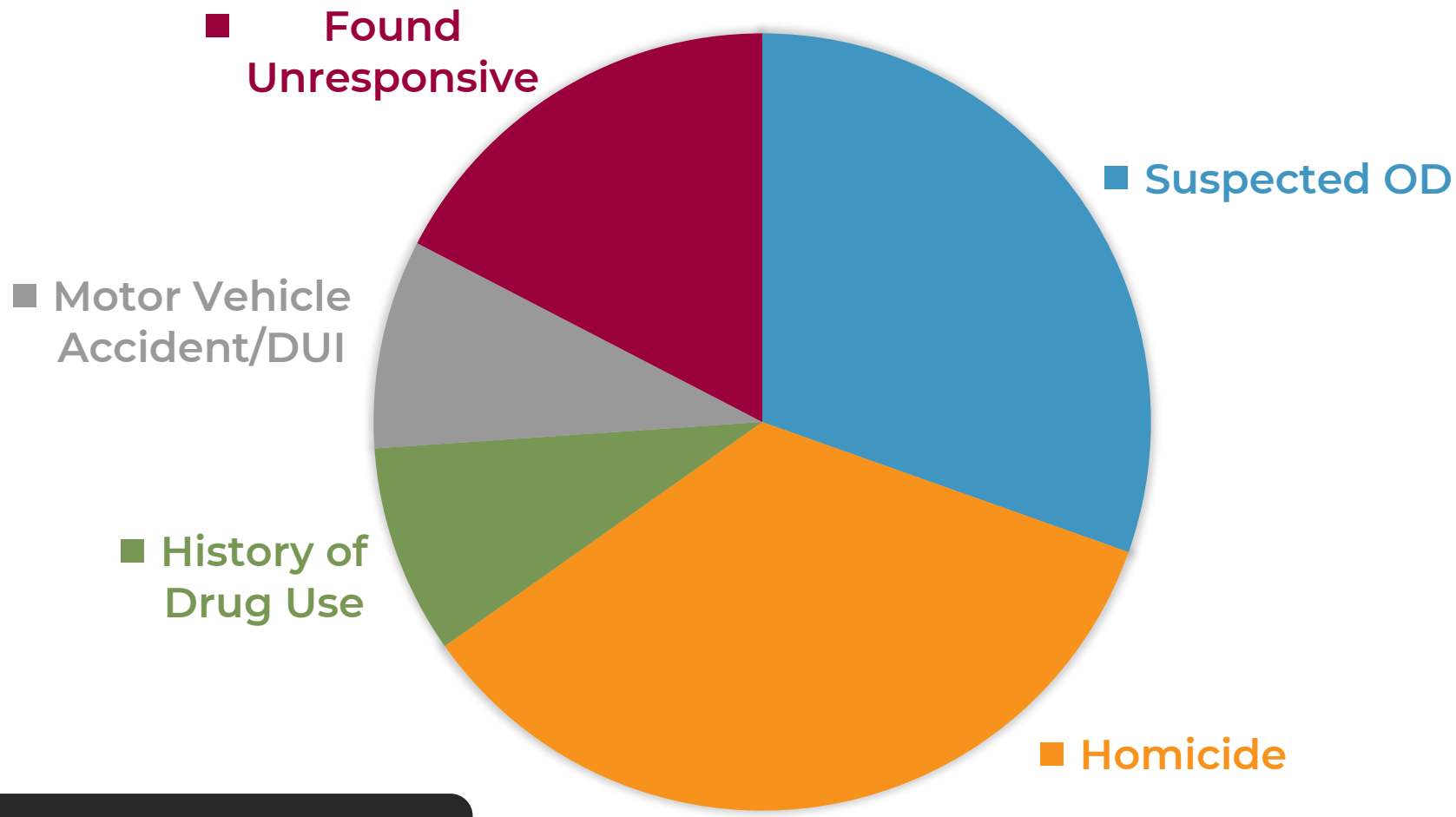
AUTHENTIC CASES RECEIVED (CASE REPORT)

- Cases originated primarily from medical examiner and coroner offices
- 32 cases collected between August 2021 and March 2022
  - Postmortem: 26
  - DUID : 1
  - Unknown: 5
- Cases originated from 9 states
- Male (62%), Female (13%), Unknown (25%)

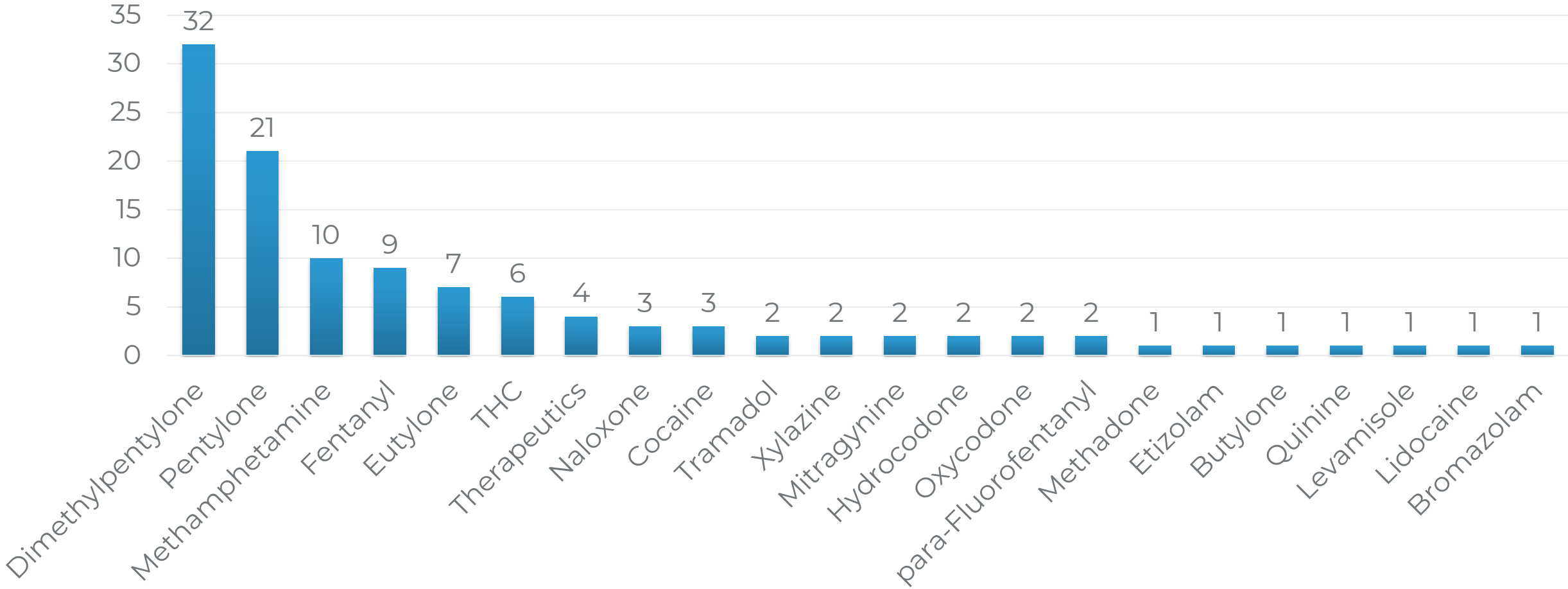




CASE HISTORIES



TOXICOLOGY RESULTS BREAKDOWN



QUANTITATIVE RESULTS

Drug	Mean (±SD) (ng/mL)	Median (ng/mL)	Range (ng/mL)
Dimethylpentylone	283±308	137	10-1200
Pentylone	120±146	47	2-550

DIMETHYLPENTYLONE CASE REPORT (2023)

Case #	[DMP] (Blood)	Manner of Death	Cause of Death
1	970 ng/mL	Suicide	Gunshot wound of head
2	33 ng/mL	Accident	Mixed drug toxicity (fentanyl, pentylone, eutylone, methadone, methamp...)
3	87 ng/mL	Accident	Injuries sustained in motor vehicle crash
4	57 ng/mL	Accident	Intoxication with fentanyl and N,N-dimethylpentylone
5	200 ng/mL	Homicide	Gunshot wound to chest with perforation of heart and lung
6	20 ng/mL	Homicide	Multiple gunshot wounds
7	650 ng/mL	Homicide	Multiple gunshot wounds
8	150 ng/mL	Homicide	Multiple gunshot wounds
9	140 ng/mL	Homicide	Gunshot wound of head
10	620 ng/mL	Homicide	Gunshot wounds of torso
12	450 ng/mL	Accident	Mixed drug intoxication due to cocaine, fentanyl, and N,N-dimethylpentylone
13	10 ng/mL	Accident	Intoxication with cocaine, fentanyl, methamp., pentylone, and N,N-dimethylpentylone
14	330 ng/mL	Accident	Mixed drug intoxication with fentanyl and N,N-dimethylpentylone
15	125 ng/mL	Accident	N,N-Dimethylpentylone intoxication
18	600 ng/mL	Accident	N,N-Dimethylpentylone toxicity (Other significant conditions: Obesity)

SYNTHETIC CANNABINOIDS

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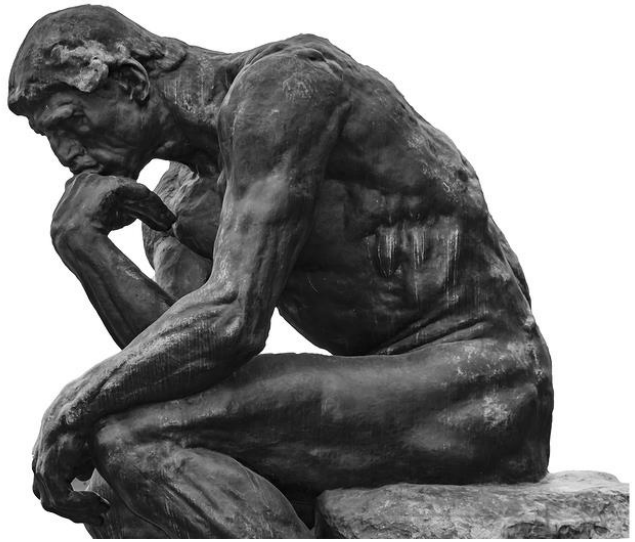
NALOXONE IN ABSENCE OF OPIOIDS

- Around 2018 and 2019, we began noticing death cases where naloxone was detected on drug screen, but **no opioids were detected** (nor confirmed, when pursued)
- Began investigating these cases to find new NPS opioids
  - **No NPS opioids were found**, however, we did find **synthetic cannabinoids**



Case #	Date	Circumstances	Sex	Age	State	Initial Toxicology Results	Expanded Syn. Cann. Testing
1	6/2/2018	Suspected drug OD					
2	7/28/2018	Suspected drug OD					
3	9/28/2018	Suspected drug OD					
4	12/31/2018	Suspected drug OD					
5	2/5/2019	Suspected drug OD					
6	5/2/2019	Suspected drug OD					
7	5/11/2019	Suspected drug OD					
8	6/20/2019	Suspected drug OD					
9	7/18/2019	Suspected drug OD					
10	9/12/2019	Suspected drug OD					
11	8/29/2020	Suspected drug OD					
12	7/24/2021	Suspected drug OD					
13	9/18/2020	Suspected drug OD					
14	9/16/2020	Suspected drug OD					
15	1/15/2021	Suspected drug OD					

Case #	Date	Circumstances	Sex	Age	State	Initial Toxicology Results	Expanded Syn. Cann. Testing
1	6/2/2018	Suspected drug OD	F	38	IN		
2	7/28/2018	Suspected drug OD	M	42	LA		
3	9/28/2018	Suspected drug OD	M	27	UT		
4	12/31/2018	Suspected drug OD	M	44	IN		
5	2/5/2019	Suspected drug OD	M	28	IL		
6	5/2/2019	Suspected drug OD	M	36	FL		
7	5/11/2019	Suspected drug OD	M	N/A	IN		
8	6/20/2019	Suspected drug OD	M	55	IN		
9	7/18/2019	Suspected drug OD	M	21	VA		
10	9/12/2019	Suspected drug OD	M	29	LA		
11	8/29/2020	Suspected drug OD	M	60	LA		
12	7/24/2021	Suspected drug OD	M	29	TX		
13	9/18/2020	Suspected drug OD	M	29	IN		
14	9/16/2020	Suspected drug OD	M	N/A	TX		
15	1/15/2021	Suspected drug OD	M	22	TX		

Case #	Date	Circumstances	Sex	Age	State	Initial Toxicology Results	Expanded Syn. Cann. Testing
1	6/2/2018	Suspected drug OD	F	38	IN	Ethanol, Cotinine, **Naloxone**	
2	7/28/2018	Suspected drug OD	M	42	LA	Caffeine, Cotinine, **Naloxone**, Quetiapine	
3	9/28/2018	Suspected drug OD	M	27	UT	Caffeine, **Naloxone**	
4	12/31/2018	Suspected drug OD	M	44	IN	Caffeine, Cotinine, **Naloxone**	
5	2/5/2019	Suspected drug OD	M	28	IL	**Naloxone**, Sertraline	
6	5/2/2019	Suspected drug OD	M	36	FL	Caffeine, **Naloxone**, Olanzapine, Fluoxetine	
7	5/11/2019	Suspected drug OD	M	N/A	IN	Cotinine, **Naloxone**	
8	6/20/2019	Suspected drug OD	M	55	IN	Ethanol, Cotinine, **Naloxone**	
9	7/18/2019	Suspected drug OD	M	21	VA	Ethanol, **Naloxone**	
10	9/12/2019	Suspected drug OD	M	29	LA	Cotinine, **Naloxone**	
11	8/29/2020	Suspected drug OD	M	60	LA	Cotinine, **Naloxone**	
12	7/24/2021	Suspected drug OD	M	29	TX	**Naloxone**, Carbamazepine, THC	
13	9/18/2020	Suspected drug OD	M	29	IN	Cotinine, **Naloxone**	
14	9/16/2020	Suspected drug OD	M	N/A	TX	Caffeine, **Naloxone**, Levetiracetam, Sertraline	
15	1/15/2021	Suspected drug OD	M	22	TX	**Naloxone**	

Case #	Date	Circumstances	Sex	Age	State	Initial Toxicology Results	Expanded Syn. Cann. Testing
1	6/2/2018	Suspected drug OD	F	38	IN	Ethanol, Cotinine, **Naloxone**	5F-ADB
2	7/28/2018	Suspected drug OD	M	42	LA	Caffeine, Cotinine, **Naloxone**, Quetiapine	5F-ADB
3	9/28/2018	Suspected drug OD	M	27	UT	Caffeine, **Naloxone**	FUB-AMB
4	12/31/2018	Suspected drug OD	M	44	IN	Caffeine, Cotinine, **Naloxone**	5F-MDMB-PICA
5	2/5/2019	Suspected drug OD	M	28	IL	**Naloxone**, Sertraline	5F-MDMB-PICA
6	5/2/2019	Suspected drug OD	M	36	FL	Caffeine, **Naloxone**, Olanzapine, Fluoxetine	4F-MDMB-BINACA
7	5/11/2019	Suspected drug OD	M	N/A	IN	Cotinine, **Naloxone**	5F-MDMB-PICA
8	6/20/2019	Suspected drug OD	M	55	IN	Ethanol, Cotinine, **Naloxone**	5F-MDMB-PICA
9	7/18/2019	Suspected drug OD	M	21	VA	Ethanol, **Naloxone**	4F-MDMB-BINACA
10	9/12/2019	Suspected drug OD	M	29	LA	Cotinine, **Naloxone**	4F-MDMB-BINACA
11	8/29/2020	Suspected drug OD	M	60	LA	Cotinine, **Naloxone**	4F-MDMB-BINACA
12	7/24/2021	Suspected drug OD	M	29	TX	**Naloxone**, Carbamazepine, THC	4F-MDMB-BICA
13	9/18/2020	Suspected drug OD	M	29	IN	Cotinine, **Naloxone**	MDMB-4en-PINACA
14	9/16/2020	Suspected drug OD	M	N/A	TX	Caffeine, **Naloxone**, Levetiracetam, Sertraline	MDMB-4en-PINACA
15	1/15/2021	Suspected drug OD	M	22	TX	**Naloxone**	4F-MDMB-BICA

SYNTHETIC CANNABINOIDS AND NALOXONE

- Clinical study underway at the time examining **opioids in emergency department populations**
  - Link between synthetic cannabinoids & respiratory failure
  - **"Respiratory depression is a potentially lethal adverse effect of synthetic cannabinoid overdose" →**

- **Discussion:**
  - Synthetic cannabinoids and naloxone are a peculiar finding
  - Adverse effects of synthetic cannabinoids can present like opioids, both antemortem and postmortem
  - Testing for synthetic cannabinoids should be considered in cases where these NPS could be toxicologically significant
    - E.g., naloxone without opioids

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2021.1975734

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Taylor & Francis Group

SHORT COMMUNICATION

Check for updates

Respiratory failure in confirmed synthetic cannabinoid overdose

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ABSTRACT

Context: Synthetic cannabinoids (SCs) are a structurally heterogenous synthetic class of drugs of abuse. The objective was to describe the incidence of acute respiratory failure in Emergency Department (ED) patients with confirmed SC exposure, and to investigate the association between SC overdose with respiratory failure compared to non-SC overdose.

Methods: This was an observational cohort of ED patients ≥18 years with suspected cannabinoid overdose between 2015 and 2020 at two tertiary-care hospitals. Patient serum was analyzed *via* liquid chromatography/quadrupole time-of-flight mass spectrometry using a library with >800 drugs including novel psychoactive substances. The primary outcome was acute respiratory failure.

Discussion: Of 83 patients with suspected cannabinoid overdose, there were 29 confirmed SC overdoses: 5 F-MDMB-PICA ($n = 18$) and its metabolite 5OH-MDMB-PICA ($n = 16$), ADB-FUBINACA ($n = 4$), AB-CHMINACA ($n = 4$), AB-FUBINACA ($n = 1$), AB-PINACA ($n = 1$), MDMB-4en-PINACA ($n = 1$), and 4 F-MDMB-BINACA ($n = 1$). Overall, incidence of acute respiratory failure was 31.3% (95%CI 21.6–42.4). Compared to non-SC overdose, confirmed SC overdose was significantly associated with respiratory failure (25.0% SC vs. 4.2% non-SC, $p = 0.05$).

Conclusion: This study demonstrates that SCs are associated with respiratory failure. Since respiratory depression is a potentially lethal adverse effect of SC overdose, future research is warranted.

ARTICLE HISTORY
Received 4 June 2021
Revised 16 August 2021
Accepted 28 August 2021

KEYWORDS
Synthetic cannabinoids; synthetic cannabinoid receptor agonists; SCRAs; respiratory failure; naloxone

Introduction

Synthetic cannabinoids (SCs) are a structurally heterogenous synthetic class of drugs of abuse. While the United States has used legislative and regulatory methods to ban specific compounds and their analogues, this drug class remains widely-available. SCs are also known as Synthetic Cannabinoid Receptor Agonists (SCRAs), and have brand names such as 'Spice' and 'K2.' SCs differ from cannabis in several ways; SC binding affinity for the CB1 receptor ranges from similar to 90 times higher than Δ9-tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis, with full receptor activation [1]. SC's lack phytocannabinoids that modulate effects at CB1, such as cannabidiol, and binding of non-CB1 receptors varies among SCs.

Various clinical effects have been attributed to SCs, and respiratory depression has been suggested but poorly described. Previous accounts are limited to case reports or uncontrolled case series, some of which have analytical confirmation [2]. The objective was to describe the incidence of acute respiratory failure in Emergency Department (ED) patients with confirmed SC exposure, and to investigate the association between SC overdose with respiratory failure compared to non-SC overdose.

Methods

This was a prospective observational cohort of ED patients ≥18 years with suspected cannabinoid overdose between 2015 and 2020 at two tertiary-care hospitals. All overdoses were prospectively screened, and were excluded if cannabinoid drugs were not suspected based on chart review, or if waste serum was unavailable. Samples were stored at −80 °C prior to analysis, and serum was analyzed *via* liquid chromatography/quadrupole time-of-flight mass spectrometry using a library with >800 drugs including novel psychoactive substances, 258 parent SC drugs, and 30 SC metabolites. Trained abstractors performed chart review using a standardized tool.

The primary outcome was acute respiratory failure, defined as a composite of (A) intubation, (B) non-invasive positive pressure ventilation, or (C) naloxone administration. Secondary outcomes were adverse cardiovascular events, ED

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CLINICAL CASE EXAMPLE

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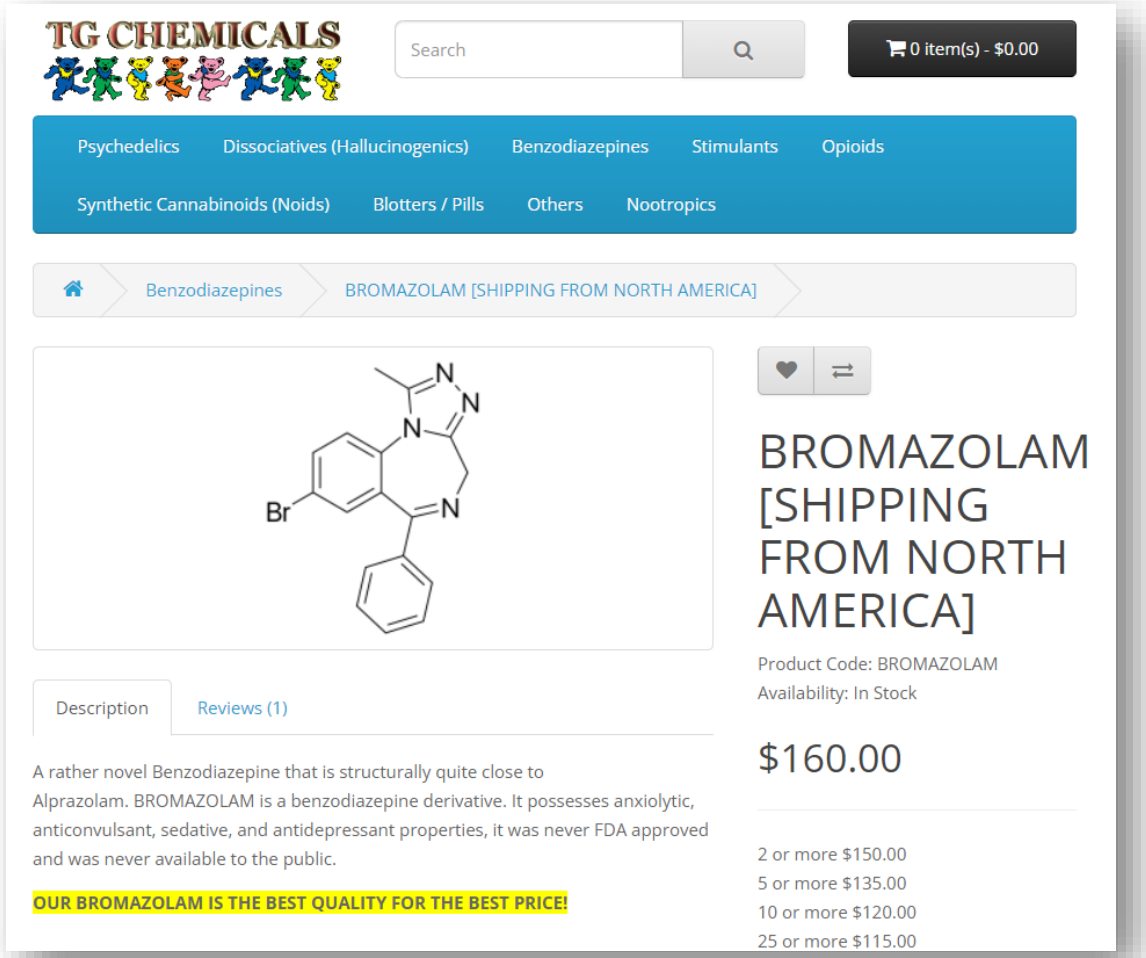
CASE HISTORY

- 29-year-old male with polysubstance dependence (opioids and benzos)
- Presents to ED with laceration to butt after fall
  - Standing on toilet searching for "stash" in ceiling
- Initially discharged after repair but progression of delirium
- Significant other calls police after he attempted to strangle her while driving back to hospital
- **Symptoms started after cessation of a new dark web supply of benzos**



CLINICAL CARE AND MEDICATIONS

- Delirium symptoms progressed despite initial treatments with haloperidol, midazolam, and lorazepam
- Phenobarbital (5 mg/kg) and methadone were administered IV
  - Transiently calmed
- Admitted to ICU for suspected benzo withdrawal

Day	Medications
1	Haloperidol 17.5 mg, lorazepam 1 mg, methadone 30 mg, midazolam 9 mg, phenobarbital 520 mg
2	Dexmedetomidine 0.4 mcg/kg/hr, haloperidol 10 mg, hydromorphone 1 mg, methadone 100 mg, phenobarbital 826.8
3	Dexmedetomidine 1 mcg/kg/hr, haloperidol 15 mg, methadone 100 mg, phenobarbital 826.8 mg, quetiapine 100 mg
4	Dexmedetomidine 1.5 mcg/kg/hr, haloperidol 10 mg, hydromorphone 1 mg, methadone 100 mg, phenobarbital 1430 mg, valproate 500 mg q12h
5	Clonidine 0.1 mg q6h, dexmedetomidine 0.5 mcg/kg/hr, methadone 110 mg, phenobarbital 453.6 mg, quetiapine 100 mg, valproate 500 mg q12h
6	Clonidine 0.1 mg q6h, dexmedetomidine 1.5 mcg/kg/hr, haloperidol 5 mg, methadone 55 mg, phenobarbital 779.2 mg, valproate 500 mg q12h
7	Clonidine 0.2 mg patch, dexmedetomidine 1.5 mcg/kg/hr, diphenhydramine 50 mg, methadone 55 mg, phenobarbital 519.8 mg, quetiapine 100 mg, valproate 500 mg q12h
8	Alprazolam 1 mg, clonidine 0.2 mg q8h, dexmedetomidine 1.1 mcg/kg/hr, diphenhydramine 100 mg, lorazepam 4 mg, methadone 110 mg, olanzapine 10 mg, phenobarbital 389.7 mg, quetiapine 400 mg, valproate 500 mg q12h
9	Alprazolam 6 mg, clonidine 0.2 mg q8h, methadone 110 mg, phenobarbital 259.9 mg, quetiapine 400 mg, valproate 500 mg q12h
10	Alprazolam 2 mg q6h, clonidine 0.2 mg q8h, diphenhydramine 100 mg, methadone 110 mg, phenobarbital 195 mg, valproate 500 mg q12h

TESTING & DISCUSSION

- **Chemistry Testing:**
  - GC-MS and LC-QTOF-MS
  - Bromazolam – Estimated at 3 mg/tablet
- Patient off phenobarbital and dexmedetomidine, tapering off alprazolam before leaving AMA on day 9
- **Effects and withdrawal from novel benzos are not well understood**
  - Complicated to manage due to the unknown drug present and pharmacology
  - Unknown dosage and drug combinations

DISCUSSION & CONCLUSIONS

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DISCUSSION

- Recreational drug supply in the U.S. remains **dynamic**, **volatile**, and (overall) increasingly **toxic**
- **NPS continue to appear** in medicolegal death investigations and forensic toxicology specimens
- Fentanyl is the primary driver of drug related deaths in the U.S., but its not always the answer
- **MAC-D** → Misrepresentation, Adulteration, Cutting, and/or Dilution of drug materials
  - Why? → Increase profits, produce better effects or highs, reduce potential unwanted side effects, etc.

DISCUSSION

- Importance of the forensic toxicologist's perspective(s)
  - Workflow for interpretation of challenging cases involving NPS

- **Case example outcomes:**
  - NPS as the cause of death
  - Other drug levels don’t explain the death – NPS of interest
  - NPS providing investigational information
  - The need for chemistry and toxicology reports to match with respect to NPS
  - Labs need to be on top of the most recent NPS trends – most useful scope of testing

CONCLUSIONS

- **New drugs continue to appear in fatal overdose** scenarios, albeit at lower occurrence than fentanyl and other drugs
  - New synthetic opioids (e.g., nitazene analogues, cathinones) are causing increased mortality across the country
- These cases stress the **importance of thorough medicolegal death investigation and forensic collaboration**
  - Forensic pathologists, forensic toxicologists, forensic chemists and others working together
- **Comprehensive toxicology testing** is preferred in cases of suspected overdose
  - Especially in the absence of fentanyl

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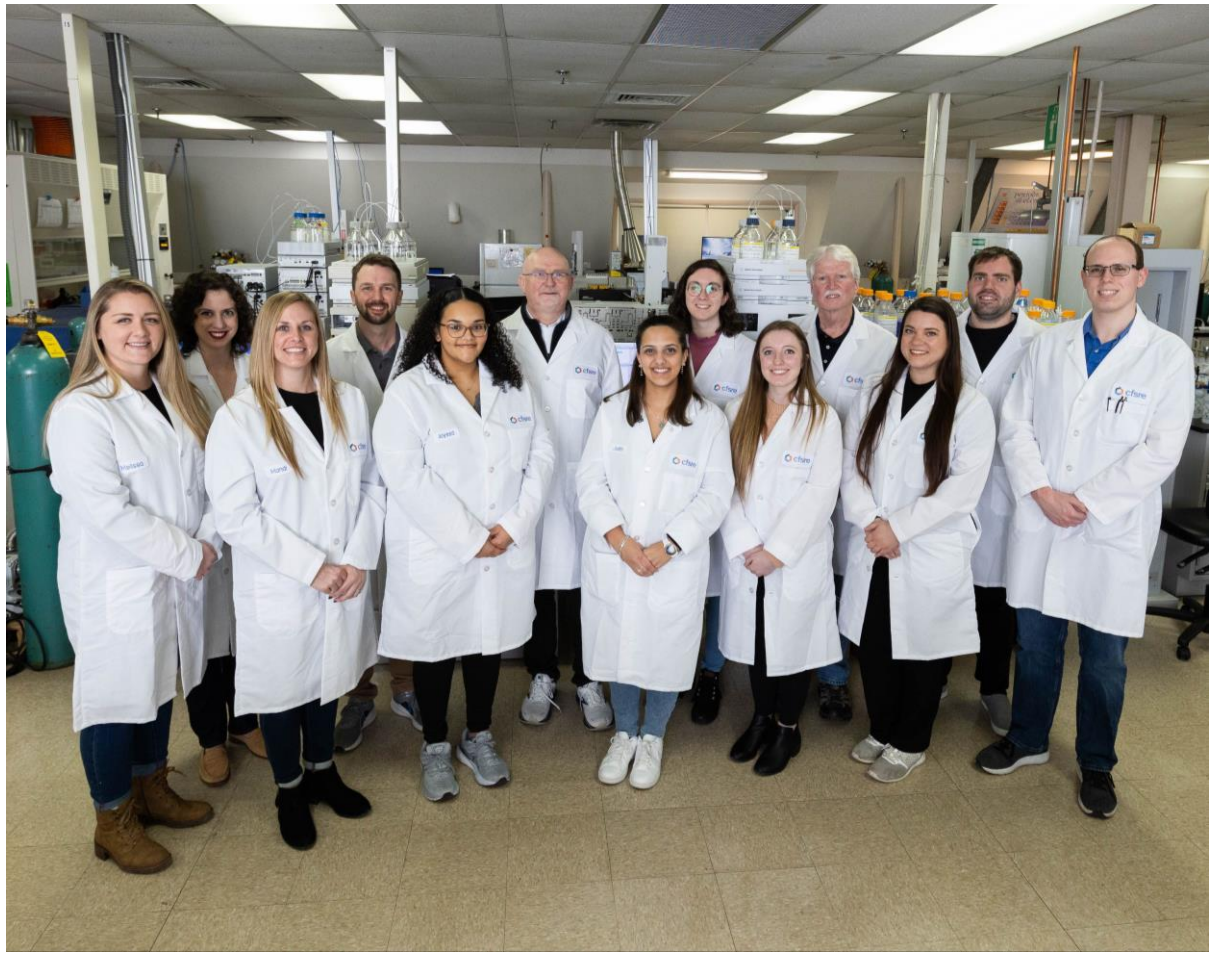

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THANK YOU! QUESTIONS?

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