

TEMPLE
UNIVERSITY



cfsre
Redefining Excellence
in Forensic Science



NPS
DISCOVERY

Data-Supported Poly-Drug Use Among Fentanyl Users: A Toxicology Perspective

**Alex J Krotulski, PhD^{1,2*}, Susan Jansen Varnum, PhD¹,
and Barry K Logan, PhD, F-ABFT^{2,3}**

¹Temple University, ²NPS Discovery at CFSRE, ³NMS Labs

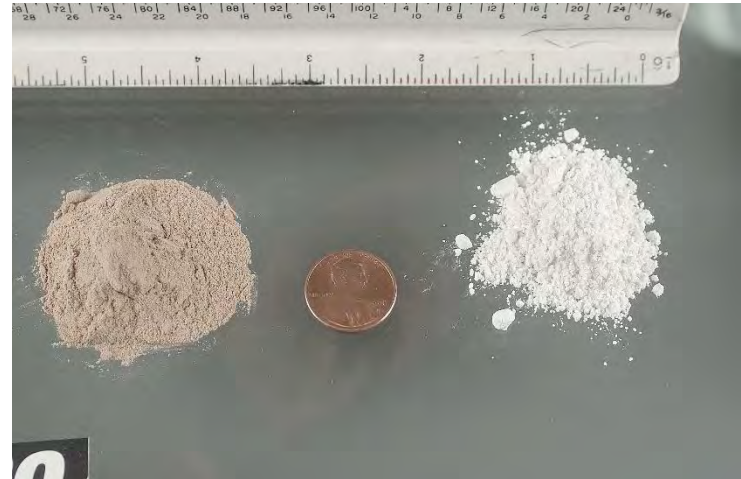
Disclosure

- This project was supported by Award Number 2017-R2-CX-0002, awarded by the National Institute of Justice, Office of Justice Programs, U.S. Department of Justice. The opinions, findings, and conclusions or recommendations expressed in this publication, program, or exhibition are those of the author(s) and do not necessarily reflect those of the Department of Justice.



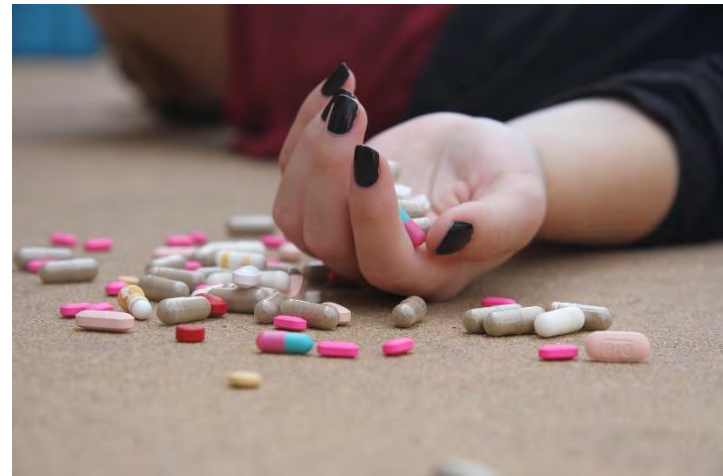
Introduction

- Poly-drug use (or poly-substance use) is defined as the use of more than one drug, at the same time or at different times
 - Concurrent vs. proximate drug use



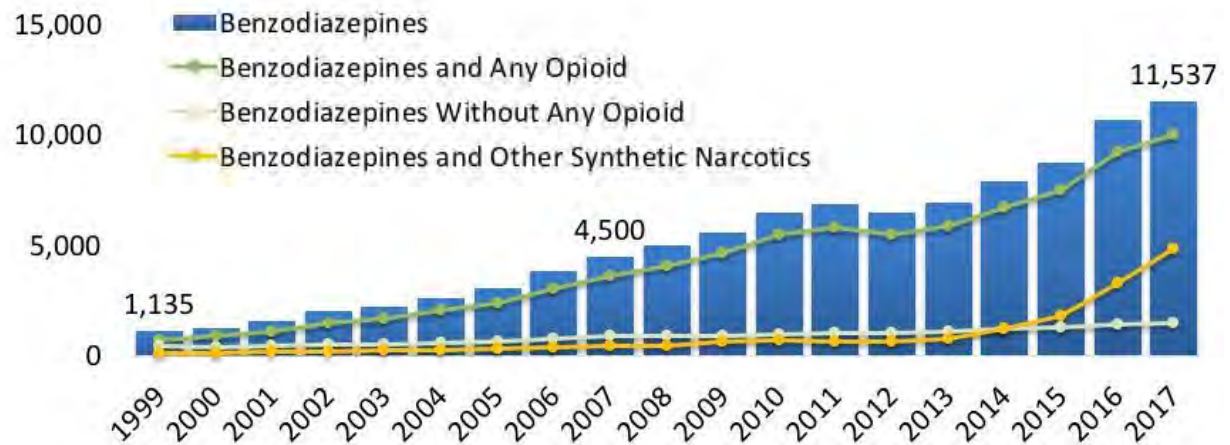
Introduction

- Poly-drug use (or poly-substance use) is defined as the use of more than one drug, at the same time or at different times
 - Concurrent vs. proximate drug use
 - Deliberate vs. unintentional



Introduction

- Poly-drug use (or poly-substance use) is defined as the use of more than one drug, at the same time or at different times
 - Concurrent vs. proximate drug use
 - Deliberate vs. unintentional
 - Common
 - Increasing

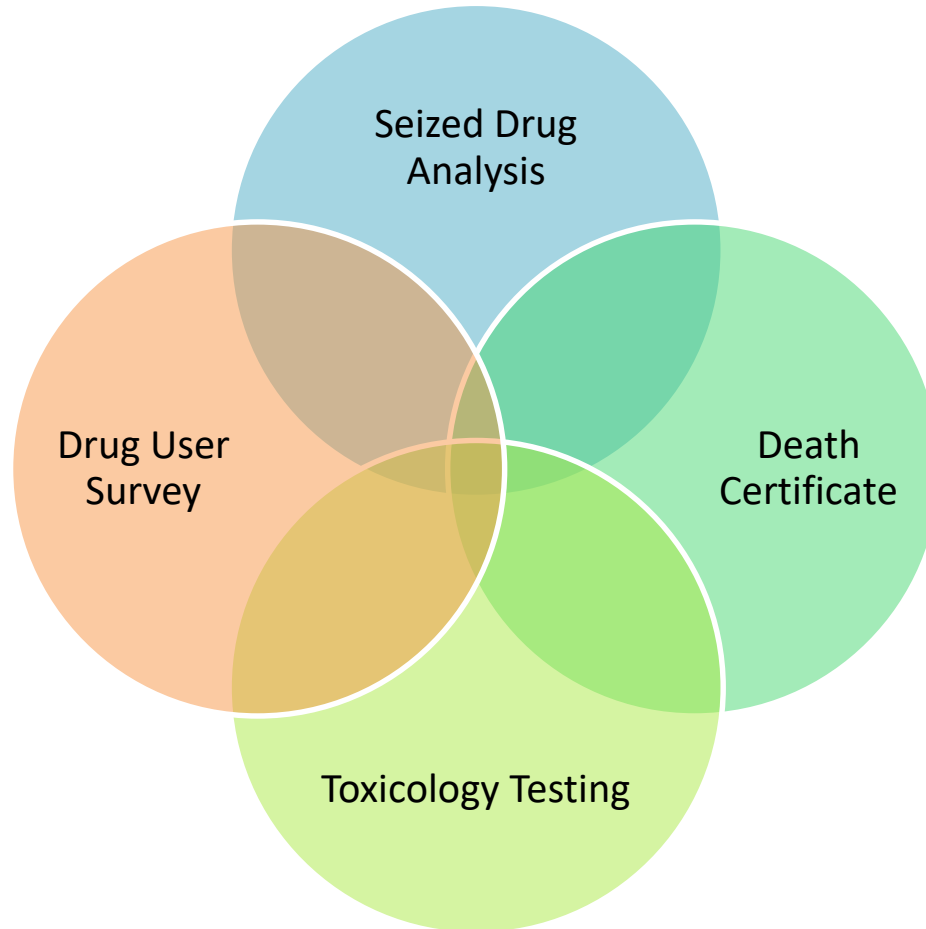


Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

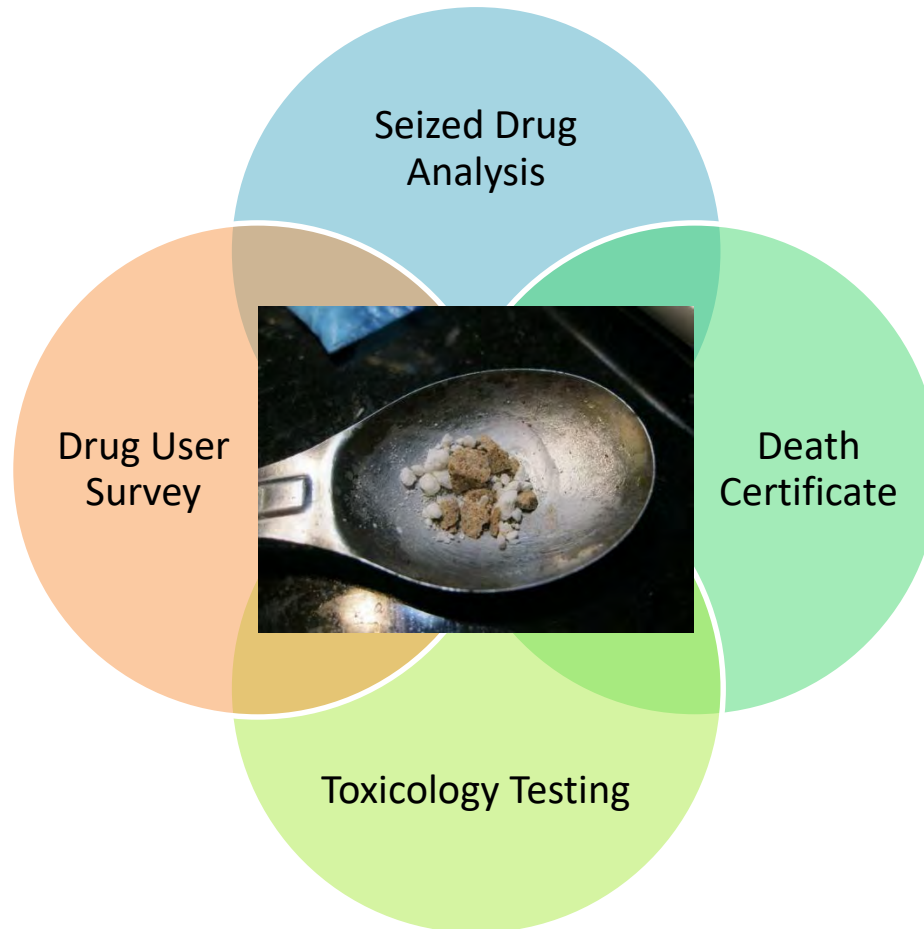
Introduction

- Poly-drug use (or poly-substance use) is defined as the use of more than one drug, at the same time or at different times
 - Concurrent vs. proximate drug use
 - Deliberate vs. unintentional
 - Common
 - Increasing
- **Poly-drug use is of great importance to public health officials, death investigators, laboratory personnel, etc.**

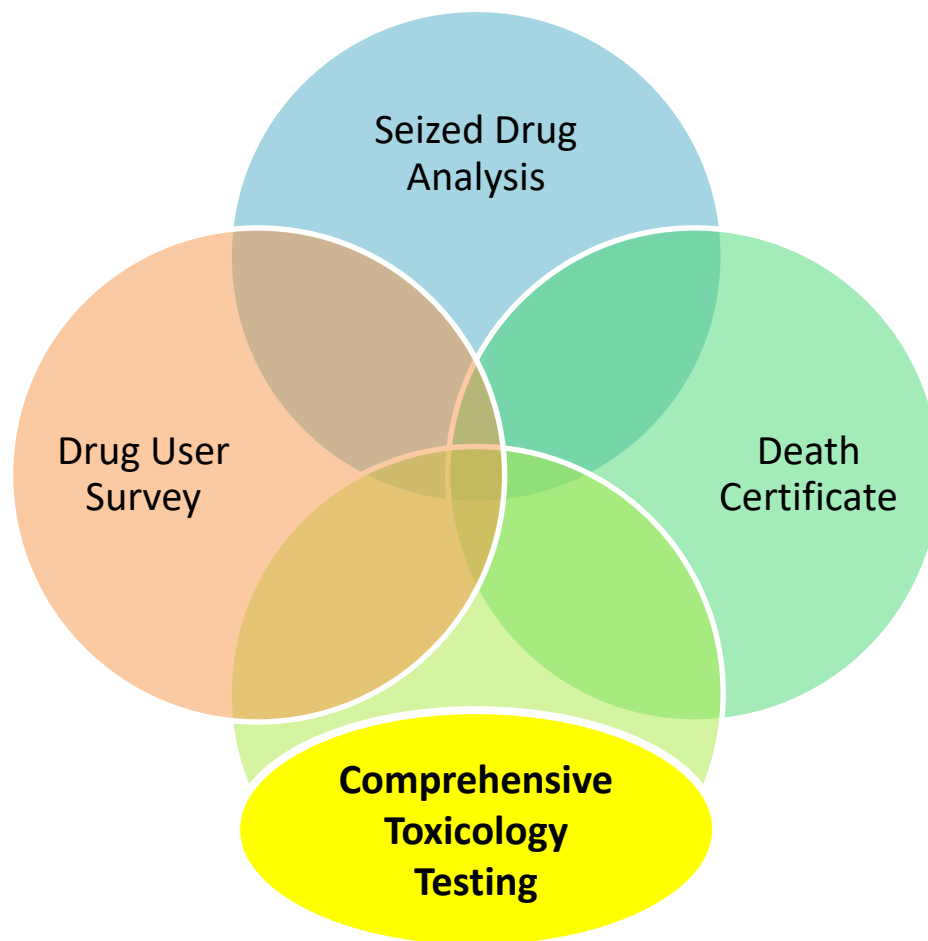
Ways to Evaluate Poly-Drug Use



Ways to Evaluate Poly-Drug Use



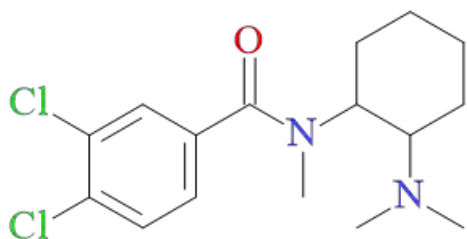
Ways to Evaluate Poly-Drug Use



Sample-Mining vs. Data-Mining

PAST:
Retrospective

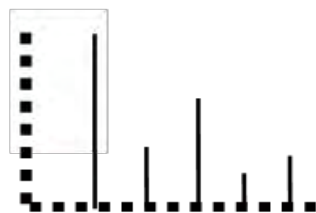
Data Mining



When was U-47700 first detected but not identified?



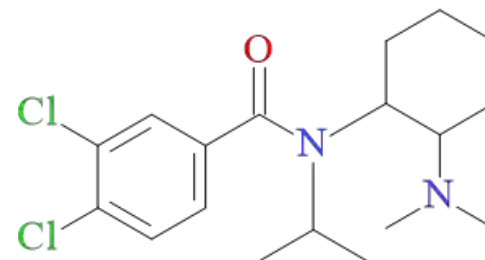
Sample Extracts



Analytical Data

PRESENT:
Real-Time

Sample Mining



When will isopropyl-U-47700 first be detected and identified?

Methods



Data Source

- Results from sample-mining and data-mining (2018 and 2019)
 - 3,543 individual samples → unique identifier
 - Processed for roughly 800 drugs (abused, novel, therapeutic, etc.)

	A	B	H	K
1	Unique ID	Sample ID	Compound	Date Submitted (NMS)
16566	EX_3533	DEB_14	Caffeine	6/17/2019
16567	EX_3533	DEB_14	Diphenhydramine	6/17/2019
16568	EX_3533	DEB_14	Flecainide	6/17/2019
16569	EX_3534	DEB_15	Benzylone	6/17/2019
16570	EX_3534	DEB_15	Etizolam	6/17/2019
16571	EX_3535	DEB_17	Fluoxetine	6/17/2019
16572	EX_3535	DEB_17	Flualprazolam	6/17/2019
16573	EX_3535	DEB_17	Fentanyl	6/17/2019
16574	EX_3535	DEB_17	Aripiprazole	6/17/2019
16575	EX_3536	DEB_19	Diphenhydramine	6/17/2019

Classification

Drug Class	Reported Drug Name	Results from LC-QTOF-MS Analysis
Opioid	Fentanyl	Fentanyl, Norfentanyl, and/or beta-Hydroxyfentanyl (excluded: 4-ANPP, Acetylfentanyl)
Opiate	Heroin	Diacetylmorphine (Heroin), 6-Monoacetylmorphine (6-MAM), Morphine, and/or Acetylcodeine (excluded: Codeine and/or Norcodeine only)
Stimulant	Cocaine	Cocaine, Benzoylcegonine (BZE), Norcocaine, and/or Cocaethylene
Stimulant	Methamphetamine	Methamphetamine and/or Amphetamine
Stimulant	MDMA	MDMA, MDA, and/or MDEA
Hallucinogen	Ketamine	Ketamine and/or Norketamine
Benzodiazepine	Diazepam	Diazepam, Nordiazepam, Oxazepam, and/or Temazepam
Opioid	Mitragynine	Mitragynine and/or 7-Hydroxymitragynine

Classification

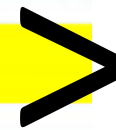
NPS Class	NPS Category	Results from LC-QTOF-MS Analysis
Opioid	Fentanyl Analogue	3-Methylfentanyl, Acrylfentanyl, Butyrylfentanyl, Carfentanil, Cyclopropylfentanyl, Fluorofentanyl, Fluoroisobutyrylfentanyl, Furanylfentanyl, Methoxyacetylfentanyl, Fluorofuranylfentanyl, Phenylfentanyl, Tetrahydrofuranylfentanyl, Valerylfentanyl (excluded: Acetylfentanyl, Sufentanil)
Opioid	Fentanyl Analogue Precursor	Benzyl Fentanyl, Benzyl Furanylfentanyl, Despropionyl 3-Methylfentanyl, Despropionyl Fluorofentanyl (F-4-ANPP), Despropionyl <i>ortho</i> -Methylfentanyl, <i>N</i> -methyl Norfentanyl, Benzyl Fluorocyclopropylfentanyl
Opioid	Non-Fentanyl Opioids [NFO]	AH-7921, Isopropyl-U-47700, 3,4-Methylenedioxy-U-47700, <i>N,N</i> -Didesmethyl-U-47700, <i>N</i> -Desmethyl-U-47700, U-47700, U-48800
Benzodiazepine	Other	Bromazepam, Clonazepam, Diclazepam, Etizolam, Flualprazolam, Flubromazolam, Flubromazepam, Phenazepam, Pyrazolam

Classification

NPS Class	NPS Category	Results from LC-QTOF-MS Analysis
Stimulant	Pyrrolidine Cathinones	4-Cl-Alpha-PVP, 4F-Alpha-PHP, Alpha-PBP, Alpha-PHP, Alpha-PVP, 3,4-Methylenedioxy-Alpha-PHP (MDPHP), Pyrovalerone
Stimulant	Methylenedioxy Cathinones	Benzyllone, Butyllone, Dibutyllone, Ethyllone, Eutyllone, Methylone, N-Ethyl Hexyllone, N-Ethyl Pentyllone, Pentyllone
Stimulant	Other Cathinones	Methcathinone, N-Ethyl Hexedrone (Hexen), 4Cl-Isopropylcathinone
Stimulant	Phenethylamines	Fluoroamphetamine (FA), Fluoroethamphetamine (FEA), Fluoromethamphetamine (FMA), Methoxyamphetamine (PMA), Methoxymethamphetamine (PMMA)
Hallucinogen	Ketamine Analogue	2F-Deschloroketamine, Deschloroketamine, N-ethyl Deschloroketamine
Hallucinogen	PCP Analogue	3/4-MeO-PCP, 3/4-OH-PCP
Hallucinogen	Other	4-HO-DiPT, N-Methyltryptamine

Examples

	A	B	H
1	Unique ID	Sample ID	Compound
1723	EX_388	OPI_18	Levamisole
1724	EX_388	OPI_18	Norfentanyl
1725	EX_388	OPI_18	Benzoylecgonine
1726	EX_388	OPI_18	Quinine
1727	EX_389	OPI_19	Norfentanyl
1728	EX_389	OPI_19	Lamotrigine
1729	EX_389	OPI_19	Nordiazepam
1730	EX_389	OPI_19	Fentanyl
1731	EX_392	OPI_23	Levamisole
1732	EX_392	OPI_23	Benzoylecgonine
1733	EX_392	OPI_23	Cocaine
1734	EX_392	OPI_23	Cocaethylene
1735	EX_392	OPI_23	Fentanyl
1736	EX_393	OPI_24	Methamphetamine
1737	EX_393	OPI_24	Morphine
1738	EX_393	OPI_24	Codeine
1739	EX_393	OPI_24	Naloxone
1740	EX_393	OPI_24	Noscapine



Fentanyl + Cocaine



Heroin + Methamp.

Results



Fentanyl Positivity

Analyte	2018				2019		Overall
	Q1	Q2	Q3	Q4	Q1	Q2	
4-ANPP	91	158	89	25	9	3	375
	14.8%	10.8%	12.0%	5.3%	6.1%	2.8%	10.6%
Acetylfentanyl	25	64	44	13	7	4	157
	4.1%	4.4%	6.0%	2.7%	4.7%	3.7%	4.4%
<i>beta</i> -Hydroxyfentanyl	7	23	43	4	1	1	79
	1.1%	1.6%	5.8%	0.8%	0.7%	0.9%	2.2%
Fentanyl	153	576	329	116	55	72	1,301
	24.8%	39.5%	44.5%	24.5%	37.2%	36.4%	36.7%
Norfentanyl	29	132	177	36	5	5	384
	4.7%	9.0%	24.0%	7.6%	3.4%	4.7%	10.8%

Fentanyl Poly-Drug Use

- **Goal:** Determine to what extent fentanyl is being used with other drugs of abuse and/or NPS (excluding therapeutic, cutting agents, etc.)
 - **Caveat:** Can not distinguish concurrent vs. alternating use

- **Fentanyl positivity:**
 - 3,543 samples
 - 1,301 “fentanyl” positives
 - 36.7% positivity
 - 79.8% poly-drug use →

Fentanyl Poly-Drug Use	# Positives	% [n=1,301]
Fentanyl + No Other Drug	263	20.2
Fentanyl + One Drug	429	33.0
Fentanyl + Two Drugs	317	24.4
Fentanyl + Three Drugs	163	12.5
Fentanyl + Four Drugs	86	6.6
Fentanyl + Five Drugs	31	2.4
Fentanyl + Six Drugs	6	0.5
Fentanyl + Seven Drugs	6	0.5

Fentanyl Poly-Drug Use

Combination by Drugs of Abuse Class	# Positives	% [n=1,301]
Fentanyl + Traditional Opiate(s)/Opioid(s)	557	42.8
Fentanyl + Heroin	368	28.3
Fentanyl + Tramadol	144	11.1
Fentanyl + Methadone	122	9.4
Fentanyl + Prescription Opioids	117	9.0
Fentanyl + Mitragynine	41	3.2
Fentanyl + Buprenorphine	38	2.9
Fentanyl + Traditional Stimulant(s)	598	46.0
Fentanyl + Cocaine	344	26.4
Fentanyl + Methamphetamine	170	13.1
Fentanyl + Cocaine + Methamphetamine	58	4.5
Fentanyl + Other Traditional Stimulant(s) [e.g. MDMA]	26	2.0

Fentanyl Poly-Drug Use

Combination by Drugs of Abuse Class	# Positives	% [n=1,301]
Fentanyl + Traditional Opiate(s)/Opioid(s)	557	42.8
Fentanyl + Heroin	368	28.3
Fentanyl + Tramadol	144	11.1
Fentanyl + Methadone	122	9.4
Fentanyl + Prescription Opioids	117	9.0
Fentanyl + Mitragynine	41	3.2
Fentanyl + Buprenorphine	38	2.9
Fentanyl + Traditional Stimulant(s)	598	46.0
Fentanyl + Cocaine	344	26.4
Fentanyl + Methamphetamine	170	13.1
Fentanyl + Cocaine + Methamphetamine	58	4.5
Fentanyl + Other Traditional Stimulant(s) [e.g. MDMA]	26	2.0
Fentanyl + Traditional Hallucinogen(s)	31	2.4
Fentanyl + Ketamine	13	1.0

Fentanyl Poly-Drug Use

Combination by Drugs of Abuse Class	# Positives	% [n=1,301]
Fentanyl + Traditional Opiate(s)/Opioid(s)	557	42.8
Fentanyl + Heroin	368	28.3
Fentanyl + Tramadol	144	11.1
Fentanyl + Methadone	122	9.4
Fentanyl + Prescription Opioids	117	9.0
Fentanyl + Mitragynine	41	3.2
Fentanyl + Buprenorphine	38	2.9
Fentanyl + Traditional Stimulant(s)	598	46.0
Fentanyl + Cocaine	344	26.4
Fentanyl + Methamphetamine	170	13.1
Fentanyl + Cocaine + Methamphetamine	58	4.5
Fentanyl + Other Traditional Stimulant(s) [e.g. MDMA]	26	2.0
Fentanyl + Traditional Hallucinogen(s)	31	2.4
Fentanyl + Ketamine	13	1.0
Fentanyl + Traditional Benzodiazepine(s)	249	19.1

Fentanyl Poly-Drug Use

Combination by Drugs of Abuse Class	# Positives	% [n=1,301]
Fentanyl + Traditional Opiate(s)/Opioid(s)	557	42.8
Fentanyl + Heroin	368	28.3
Fentanyl + Tramadol	144	11.1
Fentanyl + Methadone	122	9.4
Fentanyl + Prescription Opioids	117	9.0
Fentanyl + Mitragynine	41	3.2
Fentanyl + Buprenorphine	38	2.9
Fentanyl + Traditional Stimulant(s)	598	46.0
Fentanyl + Cocaine	344	26.4
Fentanyl + Methamphetamine	170	13.1
Fentanyl + Cocaine + Methamphetamine	58	4.5
Fentanyl + Other Traditional Stimulant(s) [e.g. MDMA]	26	2.0
Fentanyl + Traditional Hallucinogen(s)	31	2.4
Fentanyl + Ketamine	13	1.0
Fentanyl + Traditional Benzodiazepine(s)	249	19.1

Fentanyl Poly-Drug Use

Combination by NPS Class	# Positives	% [n=1,301]
Fentanyl + NPS Opioid(s)	355	27.3
Fentanyl + Fentanyl Analogue	323	24.8
Fentanyl + Non-Fentanyl Opioid (e.g. U-47700)	26	2.0
Fentanyl + Fentanyl Precursor (Other than 4-ANPP)	25	1.9
Fentanyl + NPS Stimulant(s)	55	4.2
Fentanyl + Methylenedioxy Cathinones	35	2.7
Fentanyl + Pyrrolidine Cathinones	15	1.2
Fentanyl + Other Cathinones	7	0.5
Fentanyl + Phenethylamines	3	0.2

Fentanyl Poly-Drug Use

Combination by NPS Class	# Positives	% [n=1,301]
Fentanyl + NPS Opioid(s)	355	27.3
Fentanyl + Fentanyl Analogue	323	24.8
Fentanyl + Non-Fentanyl Opioid (e.g. U-47700)	26	2.0
Fentanyl + Fentanyl Precursor (Other than 4-ANPP)	25	1.9
Fentanyl + NPS Stimulant(s)	55	4.2
Fentanyl + Methylenedioxy Cathinones	35	2.7
Fentanyl + Pyrrolidine Cathinones	15	1.2
Fentanyl + Other Cathinones	7	0.5
Fentanyl + Phenethylamines	3	0.2
Fentanyl + NPS Hallucinogen(s)	17	1.3
Fentanyl + PCP Derivatives	16	1.2
Fentanyl + Ketamine Derivatives	1	0.1

Fentanyl Poly-Drug Use

Combination by NPS Class	# Positives	% [n=1,301]
Fentanyl + NPS Opioid(s)	355	27.3
Fentanyl + Fentanyl Analogue	323	24.8
Fentanyl + Non-Fentanyl Opioid (e.g. U-47700)	26	2.0
Fentanyl + Fentanyl Precursor (Other than 4-ANPP)	25	1.9
Fentanyl + NPS Stimulant(s)	55	4.2
Fentanyl + Methylenedioxy Cathinones	35	2.7
Fentanyl + Pyrrolidine Cathinones	15	1.2
Fentanyl + Other Cathinones	7	0.5
Fentanyl + Phenethylamines	3	0.2
Fentanyl + NPS Hallucinogen(s)	17	1.3
Fentanyl + PCP Derivatives	16	1.2
Fentanyl + Ketamine Derivatives	1	0.1
Fentanyl + NPS Benzodiazepine(s)	51	3.9

Fentanyl Poly-Drug Use

Combination by Combined NPS/Drug Category	# Positives	% [n=1,301]
Fentanyl + Any Opiate(s)/Opioid(s)	771	59.3
Fentanyl + Any Stimulant(s)	625	48.0
Fentanyl + Any Hallucinogen(s)	48	3.7
Fentanyl + Any Benzodiazepine(s)	277	21.3

Fentanyl Poly-Drug Use

Fentanyl + NPS Stimulant/Hallucinogen	# Positives
<i>N</i> -Ethyl Pentylone	33
3/4-MeO-PCP	16
Alpha-PHP	10

Fentanyl + NPS Opioid	# Positives
Fluoroisobutyrylfentanyl	179
Cyclopropylfentanyl	70
Methoxyacetylfentanyl	48

Fentanyl + NPS Benzodiazepine	# Positives
Etizolam	36
Diclozepam	8
Flubromazolam	7

Bonus! ... Poly-NPS Use

- **Goal:** Determine to what extent NPS are being used with other NPS (exclude fentanyl as an NPS)
 - **Caveat:** Can not distinguish concurrent vs. alternating use

- **NPS positivity:**
 - 3,543 samples
 - 1,433 “NPS” positives
 - 40.4% positivity
 - 68.0% poly-drug use
 - 82.5% single-NPS use

NPS Poly-Drug	# Positives	% [n=1,433]
NPS + No Drugs of Abuse	459	32.0
NPS + One or More Drug	974	68.0

Poly-NPS Use with NPS	# Positives	% [n=1,433]
One NPS Substance	1182	82.5
Two+ NPS Substances	251	17.5

Conclusions



Conclusions

- Comprehensive way to monitor poly-drug use

Conclusions

- Comprehensive way to monitor poly-drug use
- Persistence of fentanyl positivity through 2019
 - Decline in NPS opioid (fentanyl analogue) positivity*

Conclusions

- Comprehensive way to monitor poly-drug use
- Persistence of fentanyl positivity through 2019
 - Decline in NPS opioid (fentanyl analogue) positivity*
- Fentanyl poly-drug use was common (nearly 80%)
 - Fentanyl with stimulant use neared 50%

Conclusions

- Comprehensive way to monitor poly-drug use
- Persistence of fentanyl positivity through 2019
 - Decline in NPS opioid (fentanyl analogue) positivity*
- Fentanyl poly-drug use was common (nearly 80%)
 - Fentanyl with stimulant use neared 50%
- Fentanyl was commonly encountered with NPS opioids
 - Trend decreasing among fentanyl analogues

Conclusions

- Comprehensive way to monitor poly-drug use
- Persistence of fentanyl positivity through 2019
 - Decline in NPS opioid (fentanyl analogue) positivity*
- Fentanyl poly-drug use was common (nearly 80%)
 - Fentanyl with stimulant use neared 50%
- Fentanyl was commonly encountered with NPS opioids
 - Trend decreasing among fentanyl analogues
- **Impact on policies and testing practices**
 - **Death investigation, forensic toxicology, public health, clinical, etc.**

Acknowledgements

- **NMS Labs**

- Donna Papsun
- Dr. Fredrick Strathmann
- Department Staff



- **National Institute of Justice**

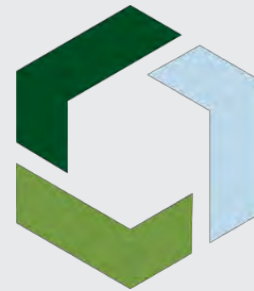




TEMPLE
UNIVERSITY



NPS
DISCOVERY



cfsre
Redefining Excellence
in Forensic Science

Questions?

www.npsdiscovery.org

alex.krotulski@cfsre.org