America's Decades-Long Opioid Epidemic and the Synthetic Transformation of Illicit Drug Markets:

Implications for Public Health and Community Response

Jon E. Zibbell, PhD

Senior Scientist

Center for Health Behavior & Implementation Science

RTI International, Atlanta, GA

Kentucky Harm Reduction Summit

Lexington

June 16-17, 2025

Disclosures

I have no actual or potential conflict of interest in relation to this presentation.

RISE IN OPIOID OVERDOSE DEATHS IN AMERICA

MORE THAN

564,000

PEOPLE DIED FROM AN OPIOID OVERDOSE

(1999-2020)

A Multi-Layered Problem in Three Distinct Waves

1990s

mark a rise in prescription opioid overdose deaths

Rx OPIOIDS

Includes natural, semi-synthetic, and methadone and can be prescribed by doctors

2010

marks a rise in heroin overdose deaths

HEROIN

An illegal opioid

2013

marks a rise in synthetic opioid overdose deaths

SYNTHETIC OPIOIDS

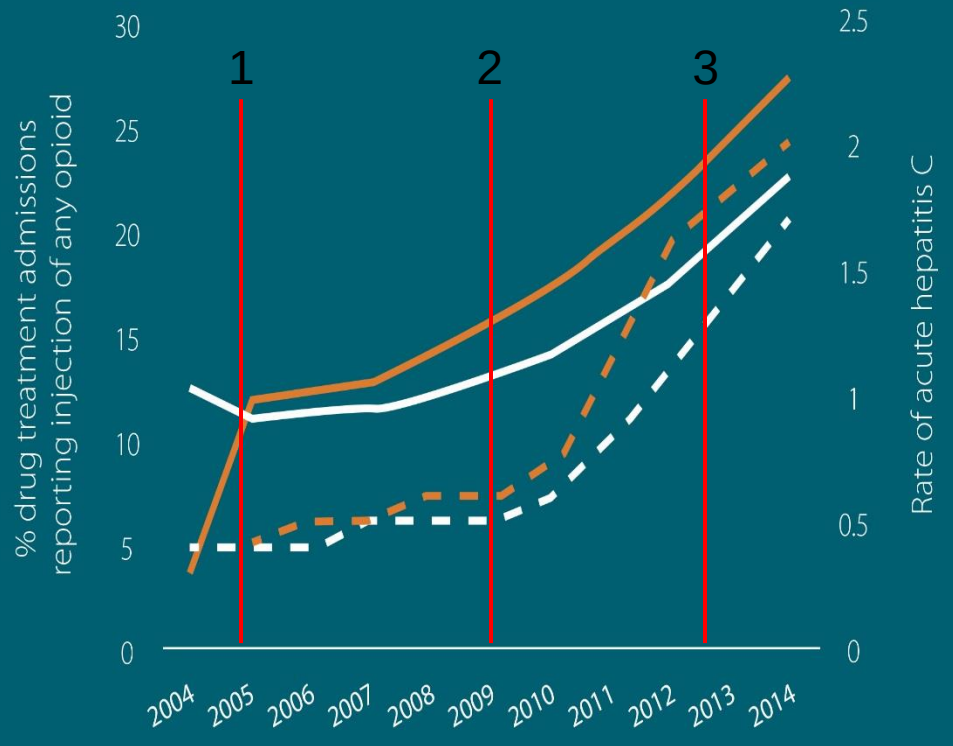
Includes illicitly made fentanyl

Estimated number of people who inject drugs in the United States

- The first update to the number of people who inject drugs in the U.S. in nearly ten years.
- There were an estimated **3,694,500 PWID in the U.S. in 2018**
  - (95% CI: 1,872,700–7,273,300)
  - 1.46% of the adult population (95% CI: 0.74% – 2.87%)
- From 1.5 million in 2012 to more than 3.5 million in 2018
- Findings suggest the population size of PWID has substantially grown in the past decade
- The estimated prevalence of injection drug use was highest among:
  - male persons (2.1%; 95% CI: 1.1–4.2%)
  - non-Hispanic White persons (1.8%; 95% CI: 0.9–3.6%)
  - adults aged 18–39 years (1.8%; 0.9–3.6%)

CDC Report on Hepatitis C and Opioid Injecting

HEPATITIS C AND OPIOID INJECTION ROSE DRAMATICALLY IN YOUNGER AMERICANS FROM 2004-2014



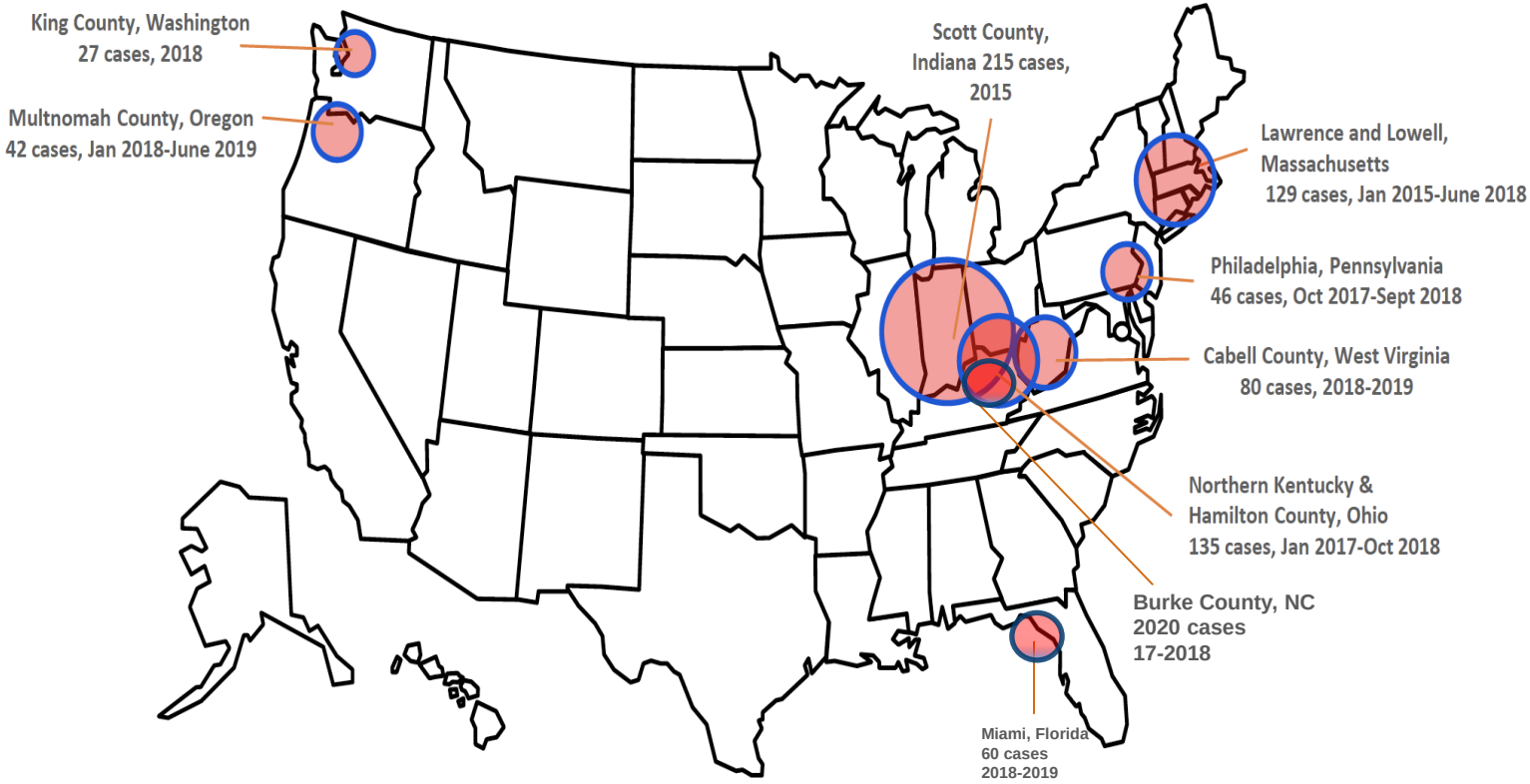
- Among people aged 18-29, HCV increased by 400% and admission for opioid injection by 622%
- Among people aged 30-39, HCV increased by 325% and admission for opioid injection by 83%

Any Opioid Injection (18-29)
Any Opioid Injection (30-39)
HCV Rate (18-29)
HCV Rate (30-39)

Source: Centers for Disease Control and Prevention and Substance Abuse and Mental Health Services Administration

Zibbell et al., 2018, *Am Jour Pub Hth*

HIV Cluster Outbreaks Increasing Among PWID, United States, 2015-?



Data adapted from Volkow *et al.*, 2019, publications, presentations, and health alerts.

A New Fentanyl Risk Environment:

Highlights from Interviews with People who Inject Drugs (PWID) in NC

Respondents detected rapid changes to the illicit opioid market using physical and physiological indicators.

PWID reported that, compared to heroin, fentanyl causes a stronger rush, a shorter high, and heavier sedation

Extreme sedation

"Fentanyl makes you nod out real bad. Regular heroin does that too, but the fentanyl is a lot stronger"

"Fentanyl hits you right away, but it doesn't last . . . If you got something that lasts for more than 10 minutes, you found some really amazing shit"

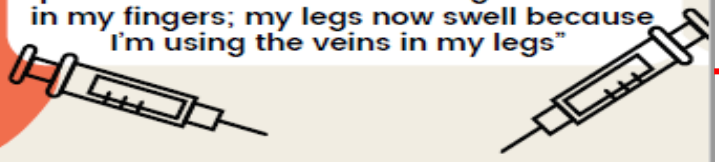
Fentanyl saturation of the illicit opioid market directly contributed to changes in drug use behavior

Because of fentanyl's shorter high, PWID are injecting more frequently to maintain the opioid effects

Foreshadowing of population-level transitions to smoking fentanyl

Many respondents reported modifying their method of consumption from injecting to smoking or snorting

"The fact that I have to inject more is tearing my veins up. It's harder to find places to shoot and I'm losing sensation in my fingers; my legs now swell because I'm using the veins in my legs"



Foreshadowing of increased bacterial infections and novel wounds

PWID reported increasingly using illicit stimulants to combat the unwanted heavy sedation of fentanyl

"These days the meth I do to counteract the sedation of fentanyl"

72% of respondents reported co-using crack/cocaine with opioids

44% reported co-using methamphetamine and opioids

4th wave of opioid epidemic involving illicit stimulants

Duhart Clarke, 2022, *IJDP*

Recent Research on HIV Risk Behaviors in Rural America

Original Investigation Substance Use and Addiction

August 21, 2023

Variation in HIV Transmission Behaviors Among People Who Use Drugs in Rural US Communities

Wiley D. Jenkins, PhD, MPH[1]; Samuel R. Friedman, PhD[2]; Christopher B. Hurt, MD[3]; et al

Author Affiliations Article Information

JAMA Netw Open. 2023;6(8):e2330225. doi:10.1001/jamanetworkopen.2023.30225

Key Points

Question What are the frequency and distribution of HIV transmission behaviors among people who use drugs (PWUD) who live in rural areas?

Findings In this cross-sectional study of 3048 PWUD living in rural areas of the US, substantial proportions of individuals reported drug injection (84.9%), sharing syringes (41.8%), condomless sex (80.0%), and transactional sex (7.5%). Study sites had significant variation in participant characteristics (eg, race and sexual orientation) and HIV transmission behaviors, and some participant characteristics (eg, age and sexual orientation) were more frequently associated with transmission behaviors.

Growing Syphilis Infections Among Rural PWID

The Journal of Infectious Diseases

Issues More Content ▾ Publish ▾ Purchase Advertise ▾ About ▾ The Journal of Infectious D ▾

Volume 222, Issue
Supplement_5
1 October 2020

JOURNAL ARTICLE

The Emerging Intersection Between Injection Drug Use and Early Syphilis in Nonurban Areas of Missouri, 2012–2018 FREE

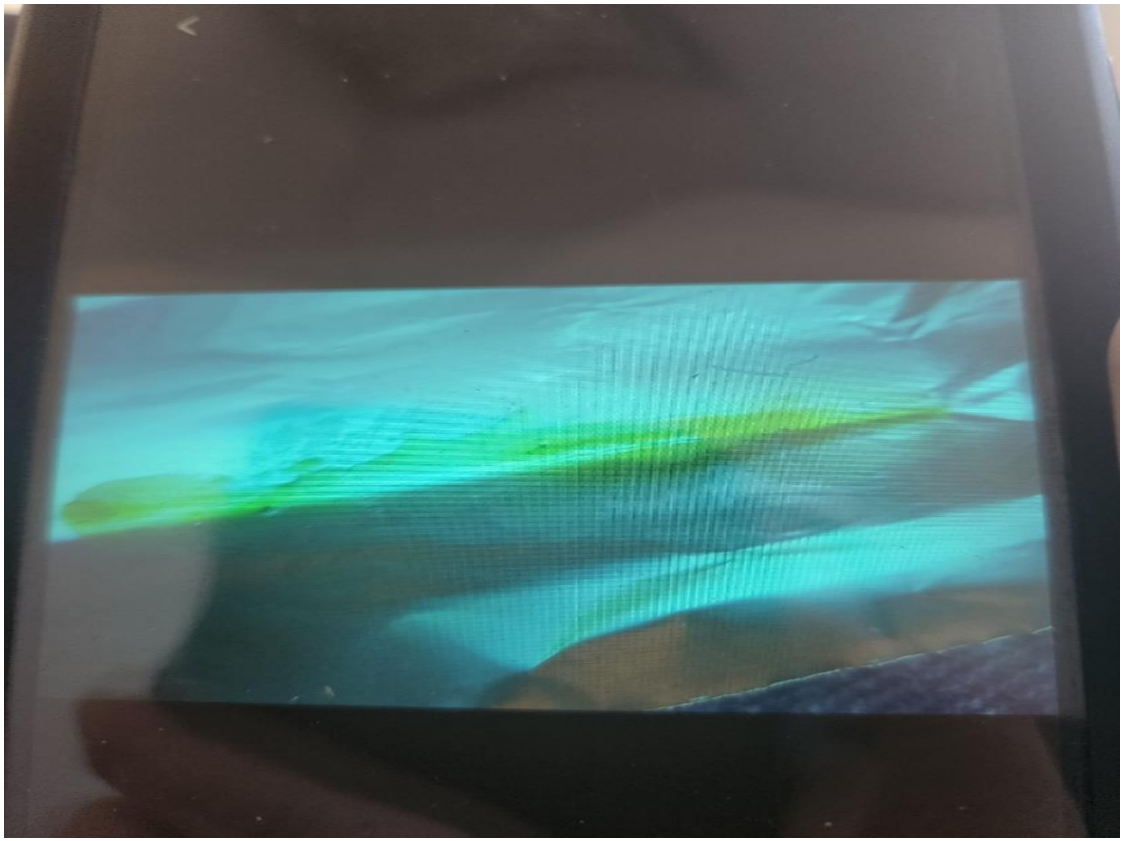
Hilary Reno ✉, Branson Fox, Craig Highfill, Angela McKee, Anne Trolard, Stephen Y Liang, Bradley P Stoner, Beth E Meyerson

The Journal of Infectious Diseases, Volume 222, Issue Supplement_5, 1 October 2020, Pages S465–S470, https://doi.org/10.1093/infdis/jiaa056
Published: 02 September 2020

SYPHILIS AND HIV

Having syphilis can increase your chances of getting or transmitting HIV.

Emerging research show population-level increases in fentanyl smoking among persons who Inject drugs



Fentanyl under black light on foil after heat has been applied and the oil has run

Photo: Zibbell

Published in final edited form as:
Drug Alcohol Depend. 2021 October 01; 227: 109003. doi:10.1016/j.drugalcdep.2021.109003.

Transition from Injecting Opioids to Smoking Fentanyl in San Francisco, California

Alex H. Kral[1], **Barrot H. Lambdin**[1],[2],[3], **Erica N. Browne**[1], **Lynn D. Wenger**[1], **Ricky N. Bluthenthal**[4], **Jon E. Zibbell**[1], **Peter J. Davidson**[5]

[1]RTI International, Research Triangle Park, NC

[2]University of California San Francisco, CA

[3]University of Washington, Seattle WA

[4]University of Southern California

[5]University of California San Diego, CA

Abstract

Background: The introduction of illicitly made fentanyl in the United States has slowly replaced heroin. New illicit drugs are often associated with changes in frequency and modes of administration. We assessed changes in injection frequency and smoking fentanyl in the new era of fentanyl availability in San Francisco.

Methods: We used targeted sampling to recruit 395 people who inject drugs (PWID) into an observational cohort study in San Francisco 2018–2020. We assessed changes in injection frequency, opioid injection frequency and fentanyl smoking frequency in four six-month periods. We also conducted qualitative interviews with PWID asking about motivations for injecting and smoking opioids.

Results: The median number of past-month injections steadily decreased by semi-annual calendar year from 92 injections in July to December 2018 to 17 injections in January to June 2020. The rate of opioid injections reduced by half (Adjusted Incidence Rate Ratio=0.41; 95% Confidence Interval=0.25, 0.70; $p<0.01$). The number of days smoking fentanyl was associated with fewer number of injections ($X^2(2) = 11.0$; $p<0.01$). Qualitative interviews revealed that PWID's motivation for switching from injecting tar heroin to smoking fentanyl was related to difficulties accessing veins. After switching to smoking fentanyl, they noticed many benefits including how the drug felt, improved health, fewer financial constraints, and reduced stigma.

Conclusion: Between 2018 and 2020, there was a shift from injecting tar heroin to smoking fentanyl in San Francisco. Reductions in injection of illicit drugs may offer public health benefit if it reduces risk of blood-borne viruses, abscesses and soft-tissue infections, and infective endocarditis.

Drug and Alcohol Dependence
Available online 9 June 2025, 112749
In Press, Journal Pre-proof What's this?

Longitudinal Patterns of Opioid and Stimulant Use by Route of Administration among People Who Inject Drugs in the South Atlantic Fentanyl Test Strip Study: A Latent Transition Analysis

Nicholas Peiper [a], Arnie Aldridge [b], Stephen Tueller [b], Judith Feinberg [c], Jon E. Zibbell [b]

Show more

+ Add to Mendeley Share Cite

https://doi.org/10.1016/j.drugalcdep.2025.112749 ↗

Highlights

- There is a growing population of PWID in the U.S. who are smoking fentanyl as a strategy to better manage heavy sedation and reduce injection-related harm.
- The smoking of fentanyl by itself or in combination with illicit stimulants is a common practice among PWID in the South Atlantic region.
- Experiencing an abscess was associated with PWID injecting fentanyl less frequently.
- There was no evidence that the population of PWID in the South Atlantic region of the U.S. are transitioning to smoking as their primary route of administration.

Prior to Fentanyl, Illicit Opioids Were Not Smoked in the US

Photos: Zibbell

What are the public health implications of the shift to smoking fentanyl?

- **Potential for significant reduction injection-related harm**
  - A population-level shift from injecting to insufflation will sharply reduce infectious disease from parenteral exposure of drugs and bacteria
- **Yet…pipes are inhabited with fentanyl 'resin'**
  - Smoking equipment is shared more frequently than syringes due to the former's reduced risk for infectious disease
  - New research shows fentanyl collecting in pipes or on heating coils in vaping devices
  - Fentanyl resin can contribute to larger doses being unwittingly/unintentionally consumed
  - This is evidence for including safer smoking supplies in harm reduction services (rather than for reducing infectious disease risk)
- **Holding in smoke can increase OD risk substantially**
  - Blow out smoke immediately to prevent OD
- **More frequent consumption events compared with injecting**
  - Smoking attributable to higher daily costs and delays in treating fentanyl withdrawal
- **Harm from smoking fentanyl with store-bought *aluminum* foil**
  - A cerebral consequence of foil smoking is *leukoencephalopathy*, a spongiform degeneration of the white matter. This is likely triggered by the *pyrolysate* [decomposing compounds due to heat] generated during the heating process (Hagel et al., 2005, *Can Assoc Redio J*).

Emerging Synthetic Drug Crisis Involving Sharp Increases in Novel Psychoactive Substances in the Illicit Opioid Market

The Nation.

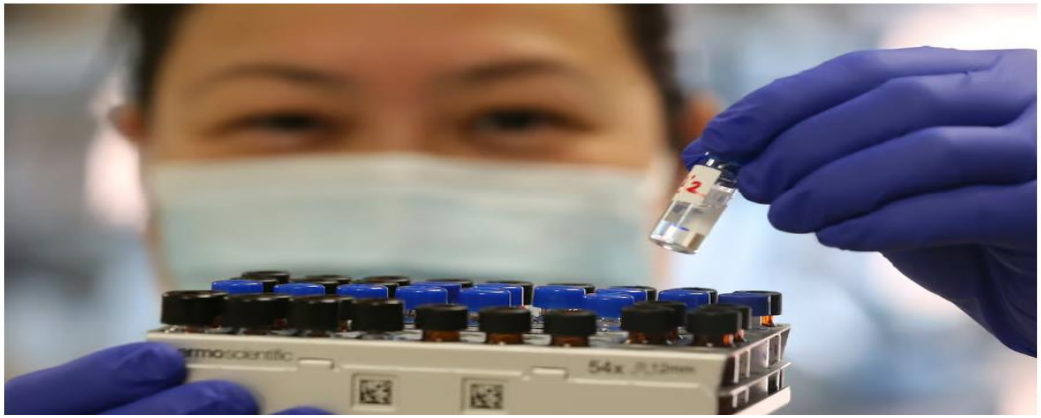
DRUG WAR AND DRUG POLICY DRUG TESTING ILLICIT DRUGS

Synthetic Drugs Are Sending the Overdose Crisis Into Overdrive

US policy is keeping public health officials, scientists, and emergency-room doctors in the dark about a growing manufactured plague.

By Joseph Friedman and Eric Reinhart

AUGUST 9, 2022



Surging Supply of Novel Psychoactive Substances in the US

EMERGENCE OF NPS IN THE U.S.

- Since 2018, NPS Discovery has reported **154** newly discovered NPS in the United States (Figure 1). **NPS opioids** remain the largest subclass (Figure 2).
- In 2023, NPS Discovery reported the discovery of **17** NPS for the first time.

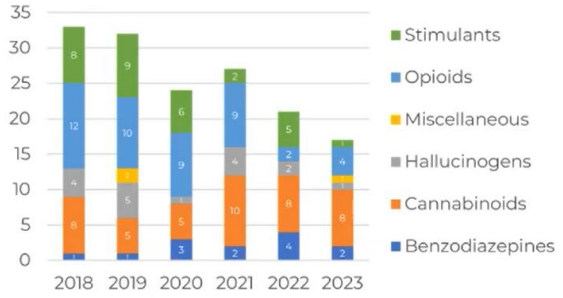


Figure 1: Newly discovered NPS reported for the first time since 2018.

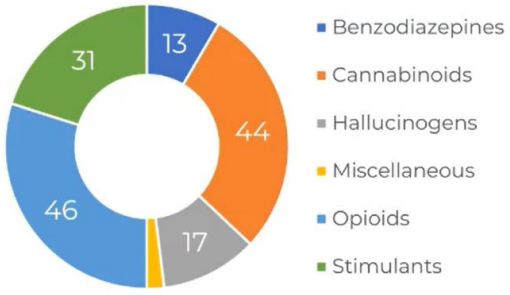


Figure 2: Breakdown by subclass of newly discovered NPS, 2018-2023.

cfsre | NPS DISCOVERY

Source: Alex Krotulski, NPS Discovery

Fentanyl and Fentanyl-Related Compounds (FFRC)

3',4'-Dimethoxy fentanyl	Fluorofentanyl
3-Fluorofentanyl	Fluoroisobutyryl fentanyl
3-Fluoroisobutyryl fentanyl	Furanyl benzyl fentanyl
3-Furanyl fentanyl	Furanyl fentanyl
3-Methylfentanyl	Furanyl/3-Furanyl fentanyl
3-Methylthiofentanyl	Isobutyryl fentanyl
3-Phenylpropanoyl fentanyl	Isovaleryl fentanyl
4-Fluoroisobutyryl fentanyl	Lofentanil
4'-Methyl Acetyl Fentanyl	meta-fluoro Furanyl fentanyl
Acetyl fentanyl	Methoxyacetyl fentanyl
Acetyl norfentanyl	Methoxybutyryl fentanyl
Acetyl-alpha-methylfentanyl	Methyl Acetyl Fentanyl
Acryl fentanyl	Methyl cyclopropyl fentanyl
Acryl-alpha-methylfentanyl	Methylfentanyl
Alfentanil	N-Benzyl Fluoro Norfentanyl
Alpha-methylfentanyl	N-methyl Norfentanyl
Alpha-methylthiofentanyl	Norfentanyl
alpha'-methyl Butyryl fentanyl	o-FBF
ANPP	o-FIBF
Benzodioxole fentanyl	o-fluoro Acrylfentanyl
Benzoylbenzyl fentanyl	o-fluoro Furanyl fentanyl
Benzylfentanyl	o-Fluorofentanyl
Beta-hydroxy-3-methylfentanyl	o-methoxybutyryl fentanyl
Beta-hydroxyfentanyl	o-Methyl acetyl fentanyl
Beta-hydroxythiofentanyl	ortho-methoxy Furanyl fentanyl
beta-Methylfentanyl	p-fluoro Acrylfentanyl
Butyryl fentanyl	p-fluoro Benzyl Fentanyl
Carfentanil	p-fluoro Cyclopropyl benzyl fentanyl
Chlorofentanyl	p-Fluorobutyryl fentanyl
cis-3-methylfentanyl	p-Fluorofentanyl
Crotonyl fentanyl	p-methoxybutyryl fentanyl
Cyclopentyl fentanyl	para-Chlorofentanyl
Cyclopropyl fentanyl	para-fluoro Furanyl fentanyl
Cyclopropyl/Crotonyl Fentanyl	para-Methoxy furanyl fentanyl
Despropionyl Fluorofentanyl	para-Methylfentanyl
Despropionyl m-Fluorofentanyl	Phenethyl 4-ANPP
Despropionyl o-Fluorofentanyl	Phenyl fentanyl
Despropionyl o-Methylfentanyl	Remifentanil
Despropionyl p-Fluorofentanyl	Sufentanil
Fentanyl	Tetrahydrofuran fentanyl
Fentanyl carbamate	Thenyl fentanyl
Fentanyl-related substance (unspecified)	Thio fentanyl
fluoro Furanyl fentanyl	Thiofuranyl fentanyl
Fluorobutyryl fentanyl	trans-3-Methylfentanyl
Fluorobutyryl/fluoroisobutyryl fentanyl	Valeryl fentanyl

Source: Drug Enforcement Administration (DEA)

New, Dangerous Synthetic Opioid in D.C., Emerging in Tri-State Area

DEA Washington, DC Division - Public Information Office

The DEA Washington Division is warning area residents of a new drug, emerging in the D.C. metropolitan area that is as dangerous and deadly as fentanyl.

This week, the DEA Washington Division brought local news outlets into their regional laboratory to see and discuss a dangerous class of drugs they are seeing emerge in the region (-nitazenes). A drug that was never approved for medical use, nitazines are being sourced from China and being mixed into other drugs.

Isotonitazene (aka nitazene or "ISO") is a particular synthetic opioid the DEA is seeing move into the area.

Medetomidine: An Emerging Toxic Adulterant in the Illicit Drug Supply

059

Kari M. Midthun, PhD[1]; Sherri L. Kacinko, PhD[1]; Sara E. Walton, MS[2]; Alex J. Krotulski, PhD[2]; and Barry K. Logan, PhD[1,2]

[1]NMS Labs, Pennsylvania, United States, [2]Center for Forensic Science Research & Education (CFSRE), Pennsylvania, United States

Background

Medetomidine, an alpha-2-agonist like xylazine & clonidine, is the latest adulterant identified in the illicit drug supply. Medetomidine exists in two enantiomeric forms: potent, **active dexmedetomidine** and largely **inactive levomedetomidine**. Dexmedetomidine is approved for surgical and anesthetic use in humans (e.g., Precedex®, while veterinary medicine utilizes a racemic mixture of the two forms (e.g., Domitor®, Sedin®, Placadine®). Notably, levomedetomidine is not prepared or used alone.

Medetomidine in the Drug Supply

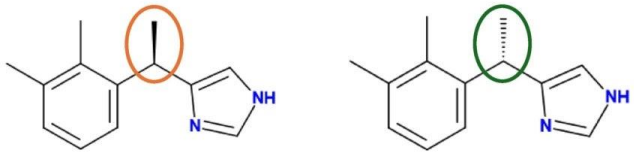
- **July 2022:** First identified in drug samples from Maryland.
- **March 2025:** Detected across U.S., parts of Canada, & U.K.
- **Commonly found with opioids, primarily fentanyl, and with or without other drugs, such as:**
  - Fentanyl (& analogs)
  - Heroin
  - Novel synthetic opioids
  - Cocaine
  - Xylazine
  - Designer benzodiazepines

Figure 1: Distribution of Medetomidine Toxicology Cases

+ Canada & U.K.

Medetomidine (particularly the dex- isomer) is a **more potent, selective, and specific agonist in the PNS and CNS than xylazine** and has a longer duration of action.

Figure 2: Structural Isomers



Dexmedetomidine **Levomedetomidine**

Table 1: Summary of Quantitative Findings in Authentic Blood Samples (n=36)

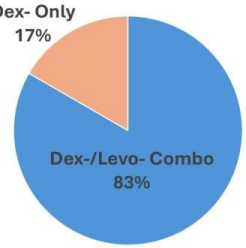
	N	Median	Mean ± S.D.	Min	Max
Fentanyl	33	7.5	11 ± 12	<0.1	48
Norfentanyl	32	14	17 ± 20	0.57	100
Xylazine	31	3.5	11 ± 15	0.23	60
Medetomidine	36	1.2	3.1 ± 4.0	<0.1	16

**Note: All concentration units reported in ng/mL*

Figure 3: Medetomidine Differentiation

Majority of medetomidine-positive samples (n=30, 83%) contain both dex- and levo-medetomidine.

Racemic drug presence indicates source not from human pharmaceutical origin.



Indicators of Medetomidine Toxicity

- Sedation & analgesia (dose-dependent)
- Respiratory depression
- Hypnotic/anesthetic effects
- Mydriasis
- Hypothermia
- Spontaneous muscle contractions
- Bradycardia
- Initial hypertension, followed by prolonged hypotension

Clinical Case Example

- Male, 40s; EMS dispatched for suspected OD
  - 4 mg IM naloxone → incr. resp. rate; irreg. breathing
  - 1 mg IV naloxone → no immediate response
  - Ventilated with mask
  - Mental status improved, became agitated
- Taken to ED, somnolent with moments of agitation
  - 3 mg IV naloxone (1 mg, followed by 2 mg)
  - Intubated with ketamine & rocuronium
  - Serial blood samples collected (7 total in 4 hrs)
  - Treated for polysubstance OD, hypertension, encephalopathy, resp. depression, & elevated troponin
- Patient left against medical advice
- Toxicology positive for Fentanyl, Xylazine, Cocaine, Medetomidine, Ketamine & Naloxone

Table 2: Serial Blood Sample Toxicology Results

Time (hr)	Fentanyl	Norfentanyl	Xylazine	Medetomidine
0	9.8	44	37	57
0.5	9.7	42	37	53
1	8.4	37	32	45
1.5	7.8	36	31	39
2	7.1	36	29	34
3	6.5	32	26	27
4	5.9	30	25	23

**Note: All concentration units reported in ng/mL*

References: Scheinin M, et al. (1987) *Br J Clin Pharmac*, 24: 443-451 o Virtanen R, et al. (1988) *Eur J Pharmacol*, 150 (1-2): 9-14. o Jorden VSB, et al. (2004) *Ann Pharmacother*, 38(5): 803-807. o Bardhi A, et al. (2021) *Drug Test Anal*, 13(7): 1249-1255. o Connell AR, et al. (2022) *J Ocul Pharmacol Ther*, 38(2): 156-166. o Sisco E & Appley M. (2023) *J Forens Sci*, 68: 1708-1712. o *CFSRE NPS Discovery publications* (https://www.cfsre.org/nps-discovery)

Funding: CFSRE's NPS Discovery Program receives funding from the National Institute of Justice, the National Institutes of Health, the Centers for Disease Control and Prevention, and others.

Illicit Benzodiazepines

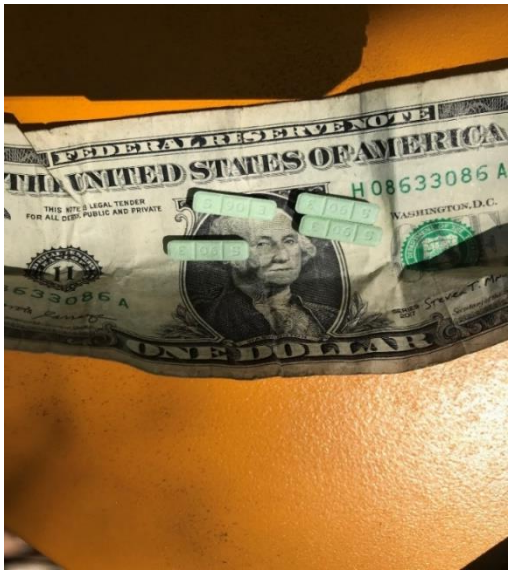
CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

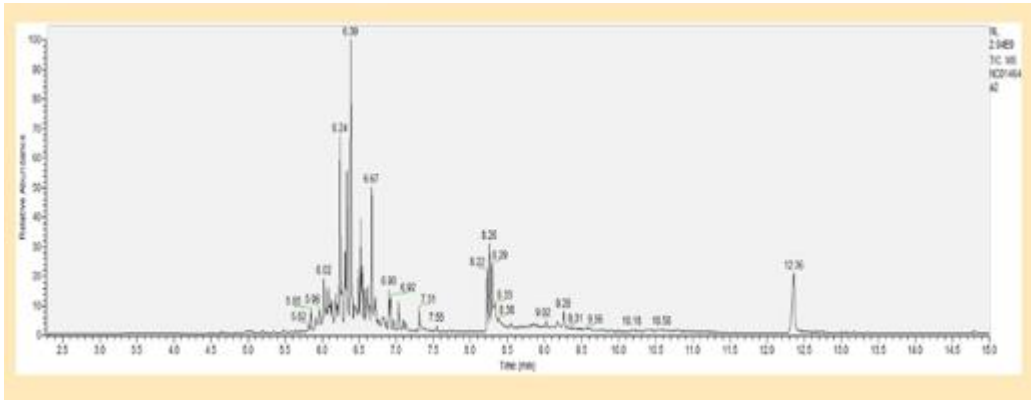
Morbidity and Mortality Weekly Report (*MMWR*)

Notes from the Field: Illicit Benzodiazepines Detected in Patients Evaluated in Emergency Departments for Suspected Opioid Overdose — Four States, October 6, 2020–March 9, 2021

Weekly / August 27, 2021 / 70(34);1177–1179

Kim Aldy, DO[1,2]; Desiree Mustaquim, PhD[3]; Sharan Campleman, PhD[1]; Alison Meyn, MPH[1]; Stephanie Abston[1]; Alex Krotulski, PhD[4]; Barry Logan, PhD[4,5]; Matthew R. Gladden, PhD[3]; Adrienne Hughes, MD[6]; Alexandra Amaducci, DO[7]; Joshua Shulman, MD[8]; Evan Schwarz, MD[9]; Paul Wax, MD[1,2]; Jeffrey Brent, MD, PhD[10]; Alex Manini, MD[11]; the Toxicology Investigators Consortium Fentalog Study Group (VIEW AUTHOR AFFILIATIONS)





Major substances in graph:

- Peak 12.36 = clonazolam

Photo: Zibbell

CDC: Xylazine Detection & Involvement in OD Deaths, US, 2019

Morbidity and Mortality Weekly Report

Notes from the Field

Xylazine Detection and Involvement in Drug Overdose Deaths — United States, 2019

Mbabazi Kariisa, PhD[1]; Priyam Patel, MSPH[1,2]; Herschel Smith, MPH[1,2]; Jessica Bitting, MS[1,3]

Xylazine is a drug used in veterinary medicine as an animal sedative with muscle relaxant and analgesic properties (*1*). It is not approved by the Food and Drug Administration for use in humans, in whom it acts as a central nervous system depressant and can cause respiratory depression, slowed heart rate, and hypotension (*2*). When used as a toxic adulterant in illicitly produced opioids such as fentanyl or heroin (*3*), xylazine might potentiate sedation and respiratory depression, increasing the risk for fatal overdose. In addition, because xylazine is not an opioid, it does not respond to opioid reversal agents such as naloxone; therefore, if illicit opioid products containing xylazine are used, naloxone might be less effective in fully reversing an overdose. Several states have reported increases in xylazine-involved overdose deaths; however, the prevalence of xylazine involvement in drug overdose deaths (overdose deaths) has not been extensively studied, particularly in the United States (*4*). To better understand the impact of xylazine adulteration on the evolving drug overdose epidemic in the United States, CDC analyzed unintentional and undetermined intent overdose death data from the State Unintentional Drug Overdose Reporting System (SUDORS) in 38 states and the District of Columbia (DC).*,†

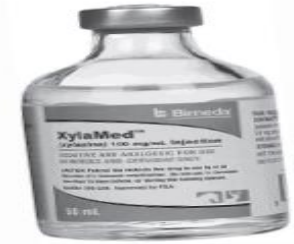
A SUDORS case was defined as xylazine-positive if xylazine was detected on postmortem toxicology or if xylazine was listed on the death certificate as a contributing cause of death by the medical examiner or coroner based on postmortem toxicology detection, evidence of drug use at the scene, or witness reports of drug use. SUDORS cases in which xylazine is listed on the death certificate as a contributing cause of death by the medical examiner or coroner were defined as xylazine-involved. Thus, a xylazine-involved case would also be considered to be xylazine-positive by definition; however, a xylazine-positive case would not always mean that xylazine contributed to the death (i.e., xylazine-involved). Using data from 38 states and DC, CDC examined xylazine-positive and xylazine-involved overdose deaths that occurred during 2019. In addition, detailed narrative text for each case was reviewed for information about xylazine use or presence among drug products or paraphernalia found at the scene.

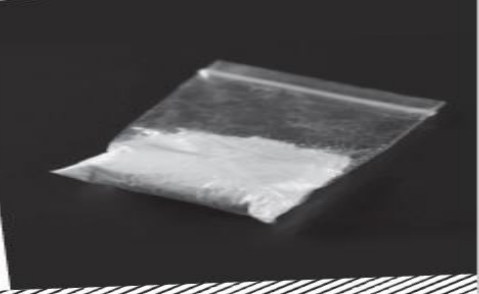
Among 45,676 overdose deaths reported to SUDORS during January–December 2019, xylazine-positive (826; 1.8%), and xylazine-involved (531; 1.2%) deaths were identified in 25 and 23 states, respectively. Xylazine was listed as a cause of death in 64.3% of deaths in which it was detected. The majority of xylazine-involved deaths were among males (73.1%), non-Hispanic White persons (75.4%), and from states in the Northeast Census region (67.0%).§ Among all xylazine-involved deaths, one or more other drugs, particularly illicit drugs, were also listed as a cause of death, and 98.7% of xylazine-positive deaths and 99.1% of xylazine-involved deaths had fentanyl (including analogs) listed as a cause of death. Cocaine and heroin were listed as a cause of death in 32.1% and 26.0% of xylazine-positive deaths respectively and in 29.6% and 28.4% of xylazine-involved deaths respectively (Table).

The findings in this report are subject to at least one limitation. Estimates of xylazine detection in overdose deaths might be underestimated. Data reviews revealed instances where

*SUDORS captures data on fatal unintentional and undetermined intent

WHAT'S THE DEAL WITH XYLAZINE ('TRANQ')?





- Xylazine is a potent *Alpha 2 Adrenergic Receptor* agonist; an analog of clonidine
- Very strong sedative effects, with opioid activity at the Kappa receptor (in mice)
- Discovered as an antihypertensive agent in 1962 by Bayer in Germany
- Not approved for human consumption
- Due to hazardous side effects—including *hypotension* and *bradycardia*—xylazine was not approved by the FDA for human use.
- Used as a veterinary anesthetic and the recommended dose varies between species.
- Increased prevalence of xylazine and other novel substances (e.g., nitazenes) as both *adulterants* and *stand-alone products* seem to be contributing to an illicit drug supply that is increasingly more toxic but seemingly less lethal
  - This market-level change in the illicit opioid supply may be responsible for declining OD deaths
  - Inflection point in opioid epidemic: increasing morbidity & decreasing mortality

Source: Prevention Point, Philadelphia

Surging Prevalence of Xylazine in Illicit Opioid Markets and Opioid OD Deaths

DEA NFLIS-Drug Identifications of Xylazine by Region			
Region	**2020**	**2021**	**% Increase**
Northeast	346	556	61%
South	198	580	193%
Midwest	110	118	7%
West	77	163	112%

Number of Xylazine-Positive OD Deaths by Region			
Region	**2020**	**2021**	**% Increase**
Northeast	631	1281	103%
South	116	1423	1,127%
Midwest	57	351	516%
West	4	34	750%

Source: DEA, Joint Intelligence Report, October 2022

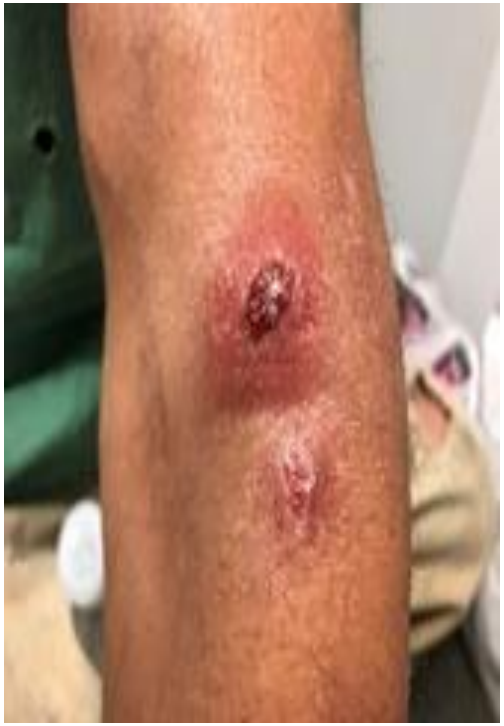
Drugs Identified in Samples by Expected vs. Lab-tested Results, North Carolina, 3/2021-12/2023, (N=1144)

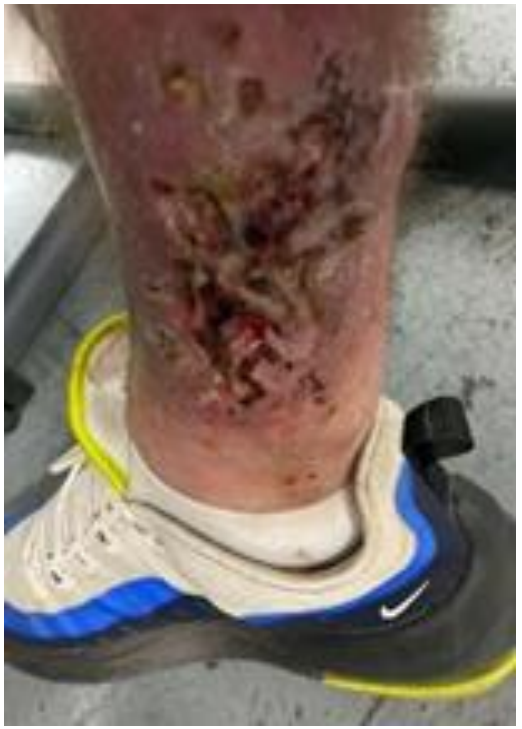
Drug Expected	N	Heroin		Fentanyl		Xylazine		Cocaine		Meth-amphetamine	
		Primary	Trace	Primary	Trace	Primary	Trace	Primary	Trace	Primary	Trace
Heroin	238	4.2	0.8	79.0	5.9	28.6	10.1	15.1	15.5	10.1	7.6
Fentanyl	409	0.5	0.7	85.6	4.6	26.2	11.7	7.3	12.5	10.5	6.6
Heroin and Fentanyl	114	0.9	1.8	83.3	5.3	31.6	10.5	9.6	15.8	11.4	9.6
Xylazine	77	1.3	2.6	89.6	1.3	50.6	11.7	6.5	7.8	10.4	7.8
Xylazine and Fentanyl	73	1.4	2.7	93.2	1.4	52.1	12.3	5.5	8.2	9.6	6.8
Cocaine	48	0.0	0.0	10.4	4.2	2.1	2.1	89.6	2.1	2.1	2.1
Cocaine and Fentanyl	1	0.0	0.0	100.0	0.0	0.0	0.0	0.0	0.0	100.0	0.0
Meth-amphetamine	171	0.0	0.0	7.6	1.8	0.6	1.2	1.2	4.7	90.6	2.9
Meth-amphetamine and Fentanyl	13	0.0	0.0	53.8	7.7	7.7	7.7	0.0	23.1	61.5	23.1

Growing incidence of novel and severe wounds is an **emerging public health crisis**

- Lost among skyrocketing OD deaths is an alarming burden of novel wounds, skin and soft-tissue infections, and invasive bacterial infections among PWID
- Abscesses and bacterial infections have been a concern for PWID for decades, but factors driving recent increases in prevalence and change in characteristics are poorly understood
- In this era of increasing contamination of the illicit drug supply with novel and synthetic drugs, a new public health crisis is emerging.

Growing Crisis: Novel Wounds & Skin/Soft Tissue Infections





Photos: Zibbell

X(ylazine) Wounds: What We Know

- Can occur in areas not injected
  - On different limbs, and mainly lower extremeties
  - Not common on trunk (unless at injection sites)

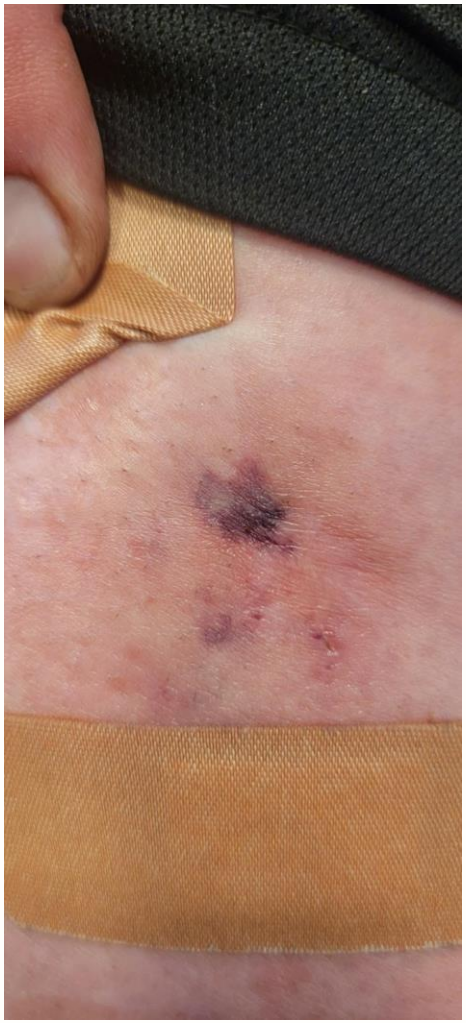
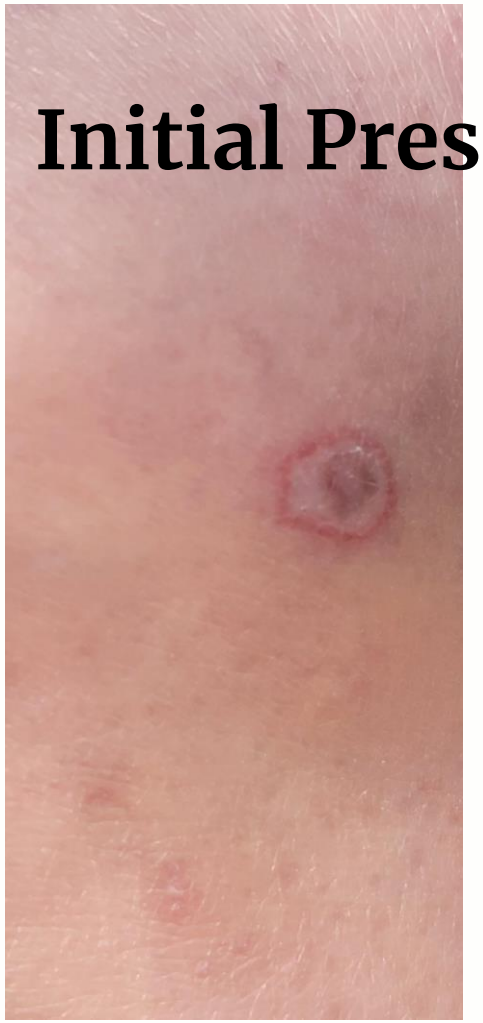
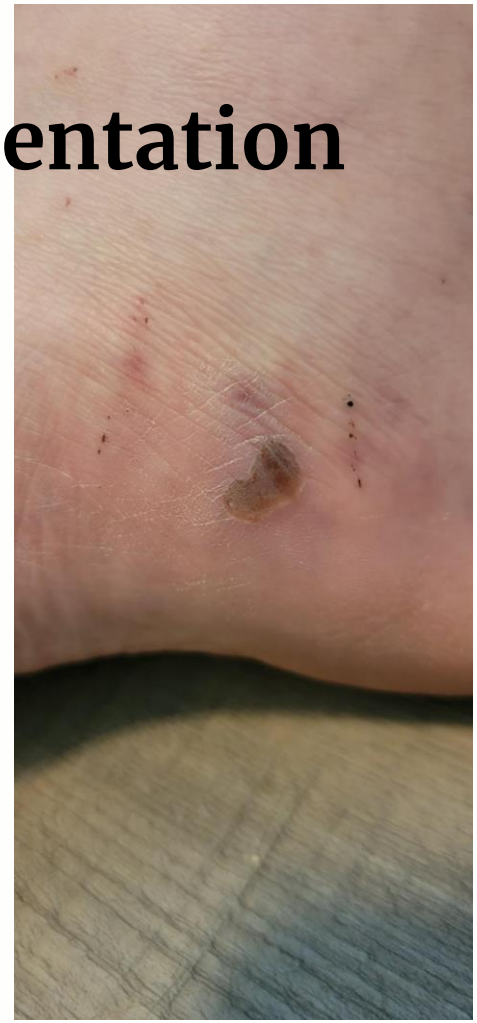
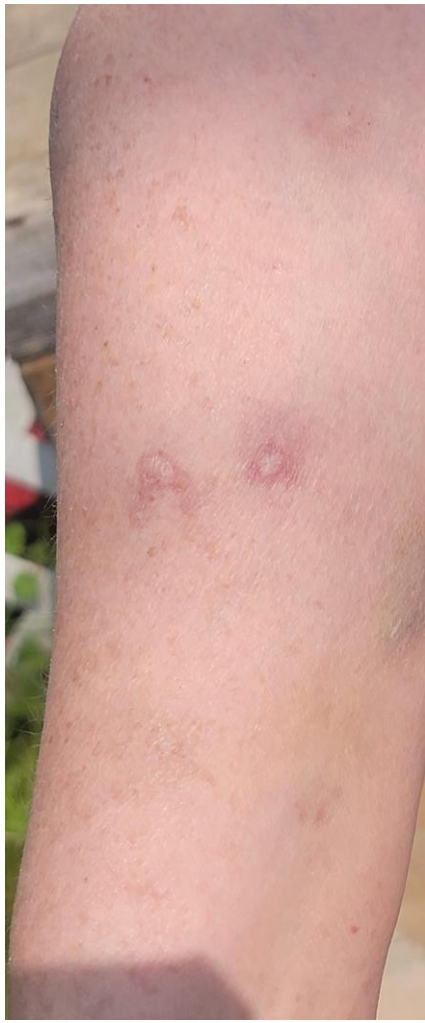
- Putting it up your nose can cause nasal sores
  - Rectal and vaginal administration was reported to cause soft-tissue issues.

- Starts as a small spot that may be:
  - Darkened area with odd round border.
  - Purple or red blister.

Warning: The next several slides are *graphic* and could cause discomfort

Source: Jason Bienert

Initial Presentation

Source: Jason Bienert

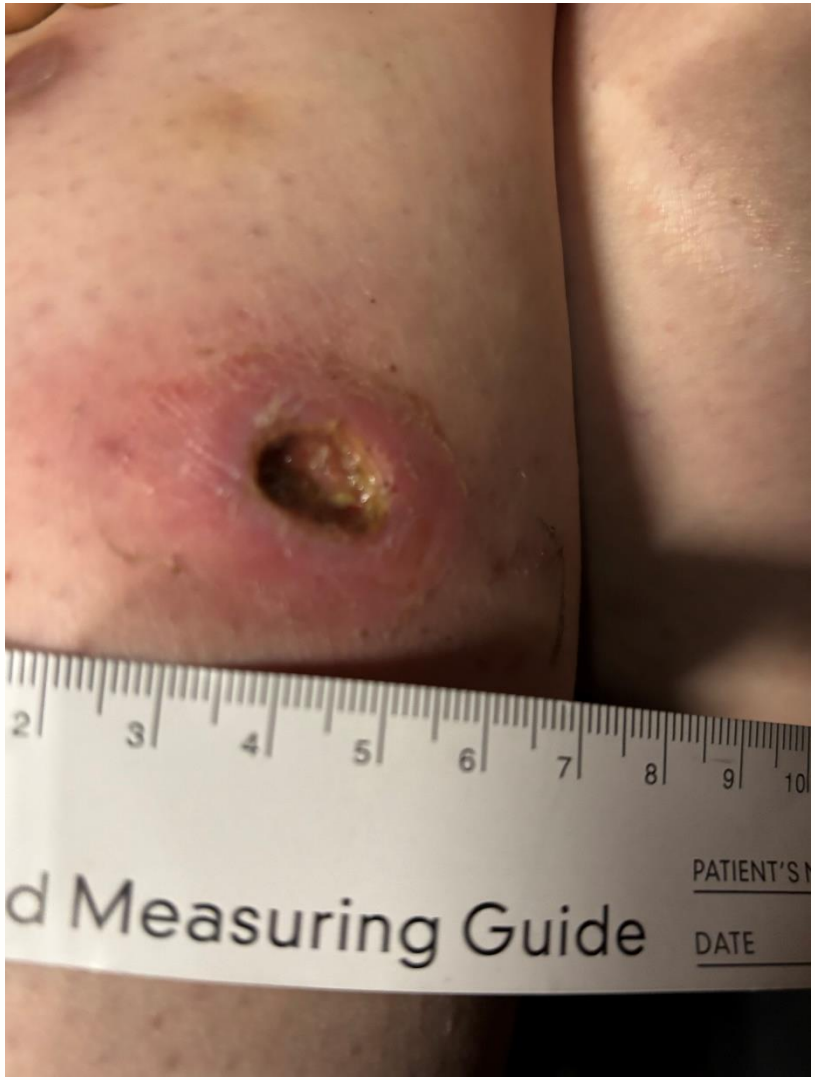
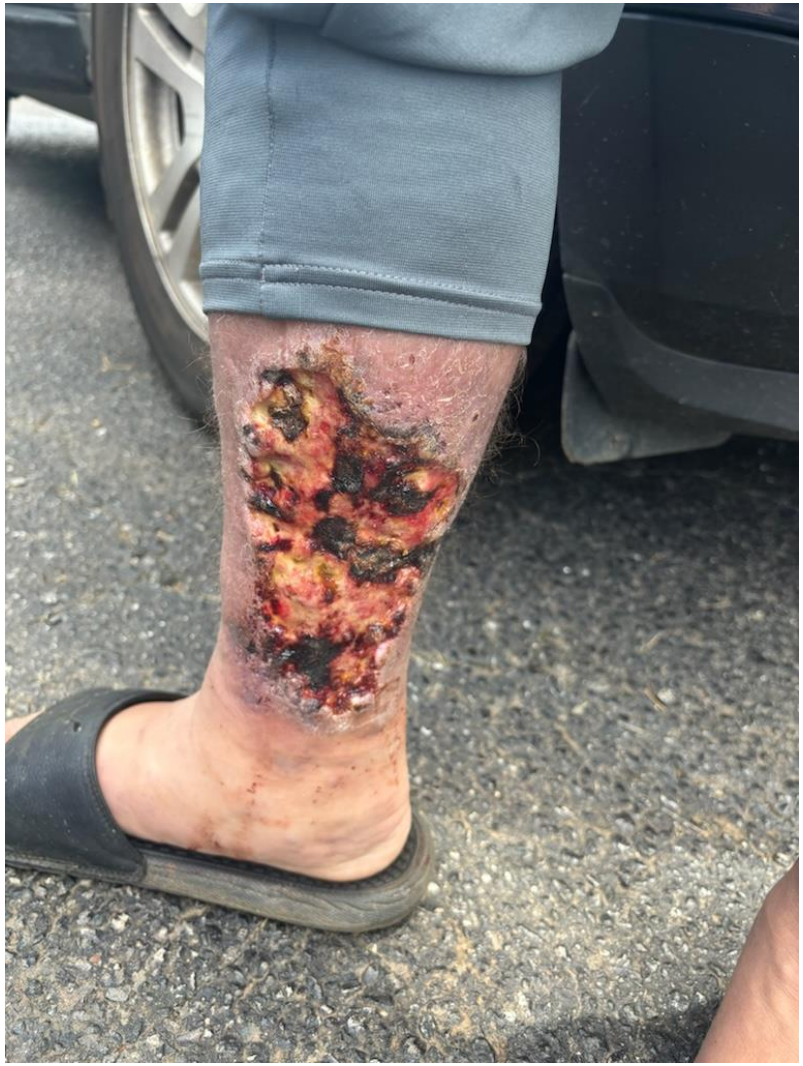


Photo: Zibbell



Source: Michelle Mathis

X Wounds: What We're Beginning to Understand

- Initially not infected
  - Typically, do not need antibiotic intervention throughout healing
- Sores can be healed. **Early care is key**
- Large deep wounds don't start as big sores
- Simple wound care can make a big difference
  - Does not need to be aired out
  - Do not inject into wound or edges
  - If possible, let the limb "cool down" (i.e., rotate injection sites)

Source: Jason Bienert

Modifying Harm Reduction for the Synthetic Drug Crisis

- Illicit synthetic opioids like Fentanyl and Nitazenes and novel sedatives like Xylazine and Medetomidine have become the primary purveyors of drug-related harm.

- So, if adverse health outcomes are stemming mainly from the drug supply, how should harm reduction be modified to respond to supply-side risk factors?

- The radical transformation of the illicit opioid supply requires a drastic renovation for how we deliver harm reduction services and how we respond to an increasingly toxic illicit drug supply.

States need local, community-based, illicit drug surveillance

- Infectious /Communicable Disease
- Food Based pathogens
  - (e.g., E-Coli; Hepatitis A)
- Testing the Lettuce
- Disseminating Information to People, Communities, Regions
  - Feedback information loops
  - Tailor messaging based on geography, race, culture, etc.
- To investigate associations between adverse health outcomes and specific drugs
- Partner with people who use street drugs
- Localities need to have point-of-use, portable, and lab-based drug checking capacity

Types of Drug Checking: Point-of-Use; Field; and Lab

Types of Testing	Examples	Time	$$$	Accuracy	Ease of Use
"Field" Testing	Test Strips, Reagents	5 mins	Low Cost	Low Accuracy	Easy
Point-of-Use	FTIR, Raman, MS*	5-10 mins	Mid Cost	Mid Accuracy	Medium
Lab – Qual	GC-MS, LC-MS	20+ mins	High Cost	High Accuracy	Hard
Lab – Quant	GC-MS, LC-MS	20+ mins	Higher Cost	High Accuracy	Extra Hard

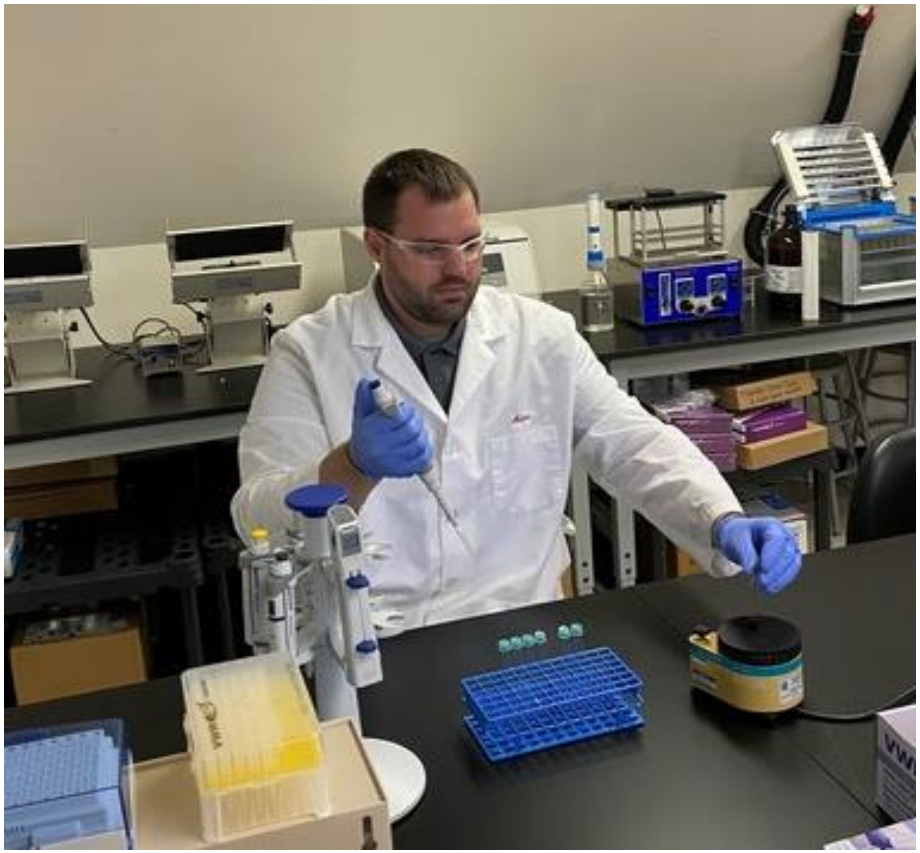
Source: Alex Krotulski, NPS Discovery

Community-Based Drug Checking with Portable* platforms

*Fourier-Transform Infrared Spectroscopy

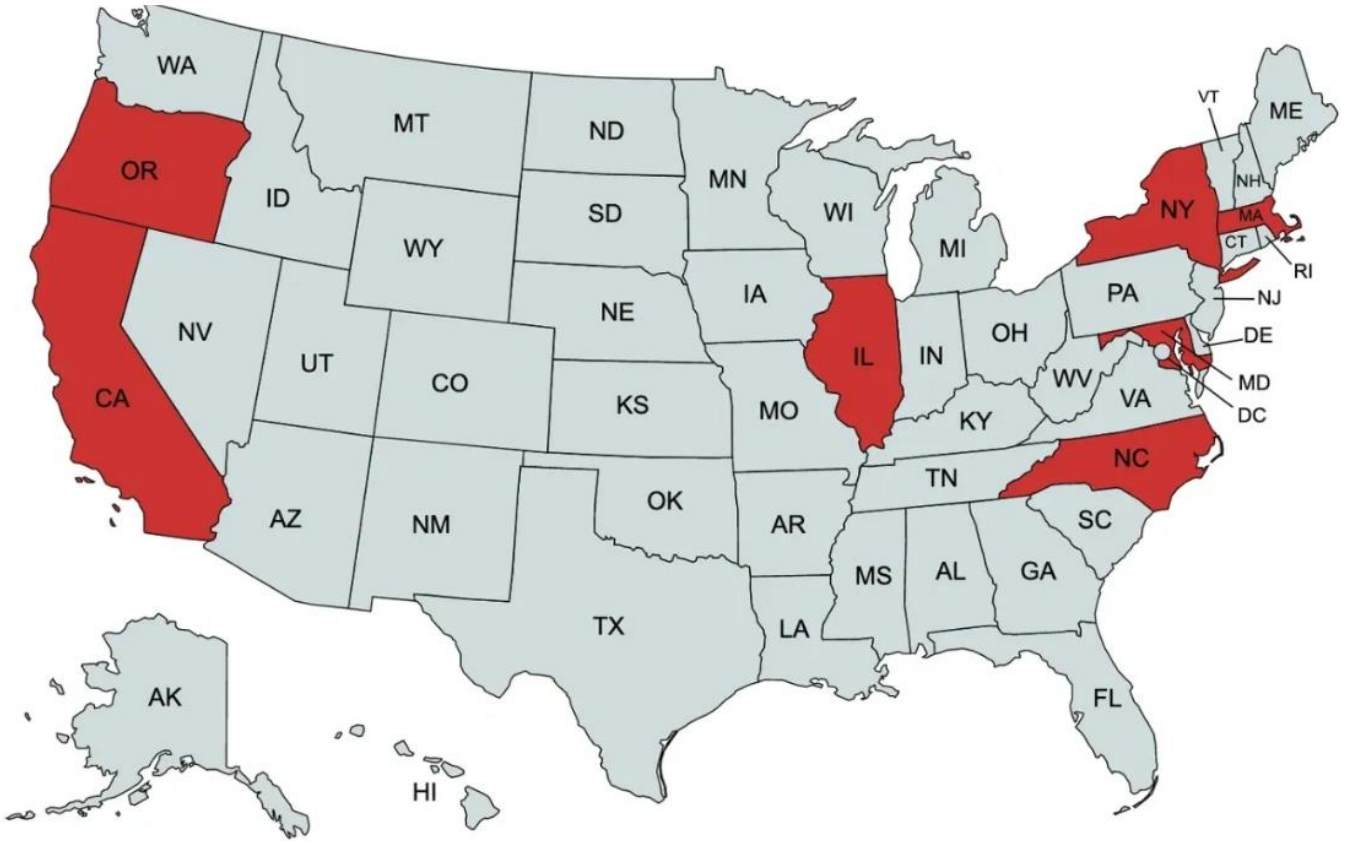
Source: UNC-SDAL; Zibbell

Laboratory-based Qual and Quant Testing:
Center for Forensic Science Research and Education (CFSRE)



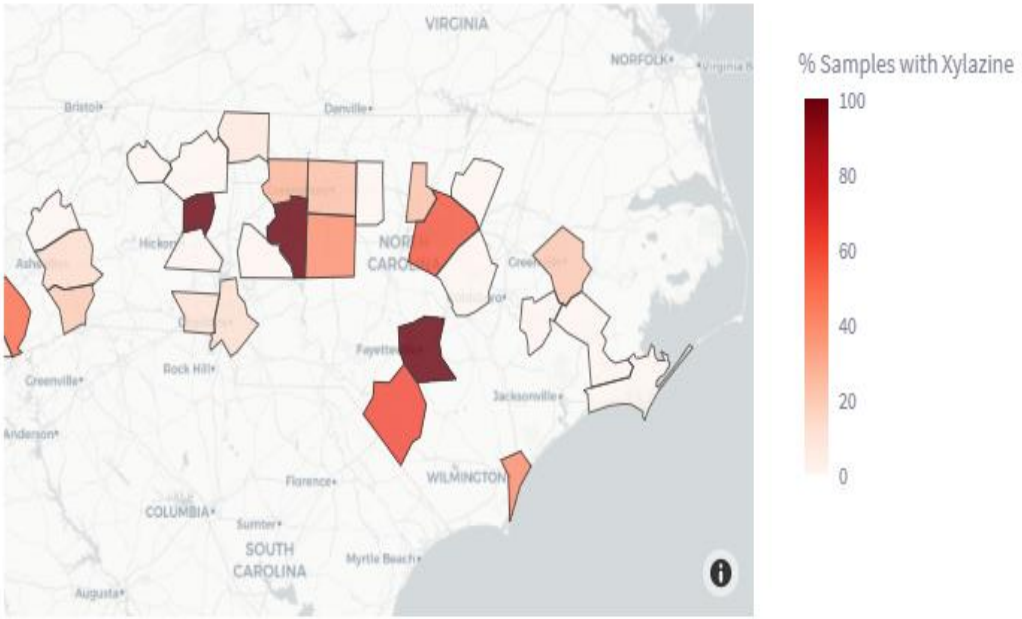
Featured: Alex Krotulski, CFSRE

DIRECTORY OF NORTH AMERICAN DRUG CHECKING PROGRAMS



Percentage of Samples Testing Positive for Xylazine, NC, 2022

Percent of Samples Testing Positive for Xylazine



Latest xylazine detection dates by location

	Most_Recent
Alexander County	November 28, 2022
Buncombe County	April 07, 2023
Cumberland County	June 17, 2022
Davidson County	August 30, 2022
Durham County	March 21, 2023
Forsyth County	March 31, 2023
Gaston County	September 14, 2022
Guilford County	December 08, 2022
Henderson County	July 17, 2022
Macon County	February 08, 2023
Mecklenburg County	August 25, 2022
New Hanover County	January 05, 2023
Pitt County	March 31, 2023
Randolph County	November 29, 2022
Robeson County	March 22, 2023
Surry County	March 16, 2023
Wake County	April 07, 2023

PWUD as Subject Matter Experts

- Participants demonstrated ability to understand rapid changes in illicit opioid market by employing **sensory strategies** to identify drugs.
- The capacity to **discern market changes** illustrates the benefits of including people who use drugs in local, community-based drug checking efforts.
- PWUD can serve as subject matter experts and **interface with illicit markets** to provide drug samples and sentinel information on new and emerging drugs.

Sensory Strategies used by consumers to discern psychoactive drugs

Sight, Smell, Touch, & Taste

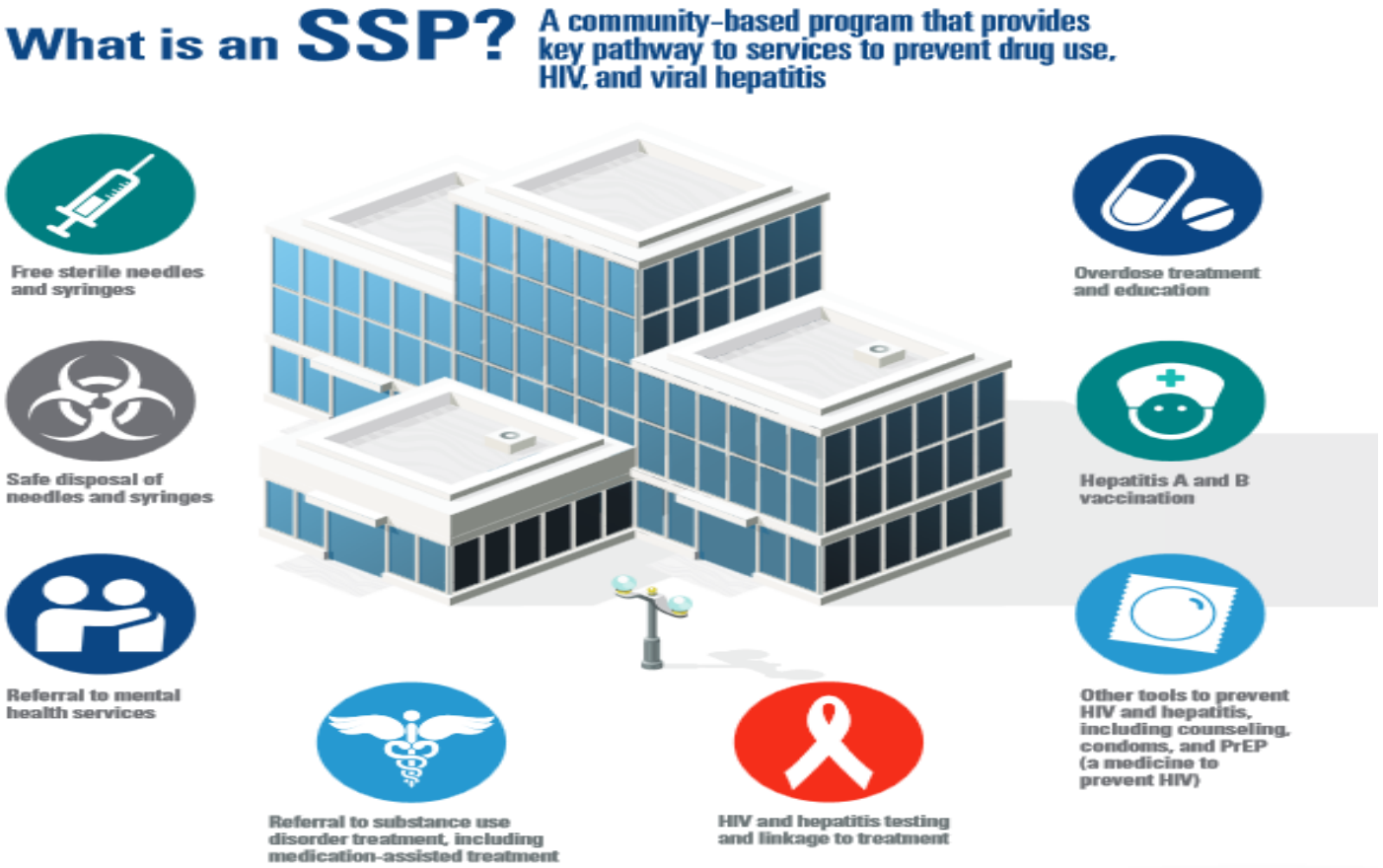
- Color (of drug & drug solution)
- Texture (chunky, rocky, fine powder)
- Taste (raw drug & post-injection flavor)
- Smell (as raw product or when heated)
- Behavior (in water, when heated, etc.)

Physical Effects

- Onset (the 'rush')
  - rapid, creeping, delayed, pins/needles, hot flashes, dizziness
- Duration (the 'high')
  - Short/lengthy; legs/no legs; euphoria/no effect
- Opioid Energy vs. Heavy Sedation

Duhart Clarke et al., 2020

Syringe Services Programs as Medical Homes for PWUD



CDC, Vital Signs, 2016

Harm Reduction is a Patient-Centered Philosophy

Defining the Medical Home

A patient-centered philosophy that drives primary care excellence

The medical home is best described as a model or philosophy of primary care that is patient-centered, comprehensive, team-based, coordinated, accessible, and focused on quality and safety. It has become a widely accepted model for how primary care should be organized and delivered throughout the health care system, and is a philosophy of health care delivery that encourages providers and care teams to meet patients where they are, from the most simple to the most complex conditions. It is a place where patients are treated with respect, dignity, and compassion, and enable strong and trusting relationships with providers and staff. Above all, the medical home is not a final destination. Instead, it is a model for achieving primary care excellence so that care is received in the right place, at the right time, and in the manner that best suits a patient's needs.

In 2007, the major primary care physician associations developed and endorsed the Joint Principles of the Patient-Centered Medical Home. The model has since evolved, and today PCC actively promotes the medical home as defined by the Agency for Healthcare Research and Quality (AHRQ).

Features of the Medical Home

Adapted from the AHRQ definition, PCC describes the medical home as an approach to the delivery of primary care that is:

- **Patient-centered:** A partnership among practitioners, patients, and their families ensures that decisions respect patients' wants, needs, and preferences, and that patients have the education and support they need to make decisions and participate in their own care.
- **Comprehensive:** A team of care providers is wholly accountable for a patient's physical and mental health care needs, including prevention and wellness, acute care, and chronic care.
- **Coordinated:** Care is organized across all elements of the broader health care system, including specialty care, hospitals, home health care, community services and supports.
- **Accessible:** Patients are able to access services with shorter waiting times, "after hours" care, 24/7 electronic or telephone access, and strong communication through health IT innovations.
- **Committed to quality and safety:** Clinicians and staff enhance quality improvement to ensure that patients and families make informed decisions about their health.

Source: Primary Care Collaborative; www.thepcc.org

Integrating Harm Reduction into Clinical Practice

1

Assess and refine practice policies to promote harm reduction.

2

Ask your patients for input and ideas.

3

Implement changes to policies to align more closely with harm reduction principles.

4

Identify community-based harm reduction resources for your patients.

Photo: Zibbell

The Need for Health Care Delivery in America's Hinterland

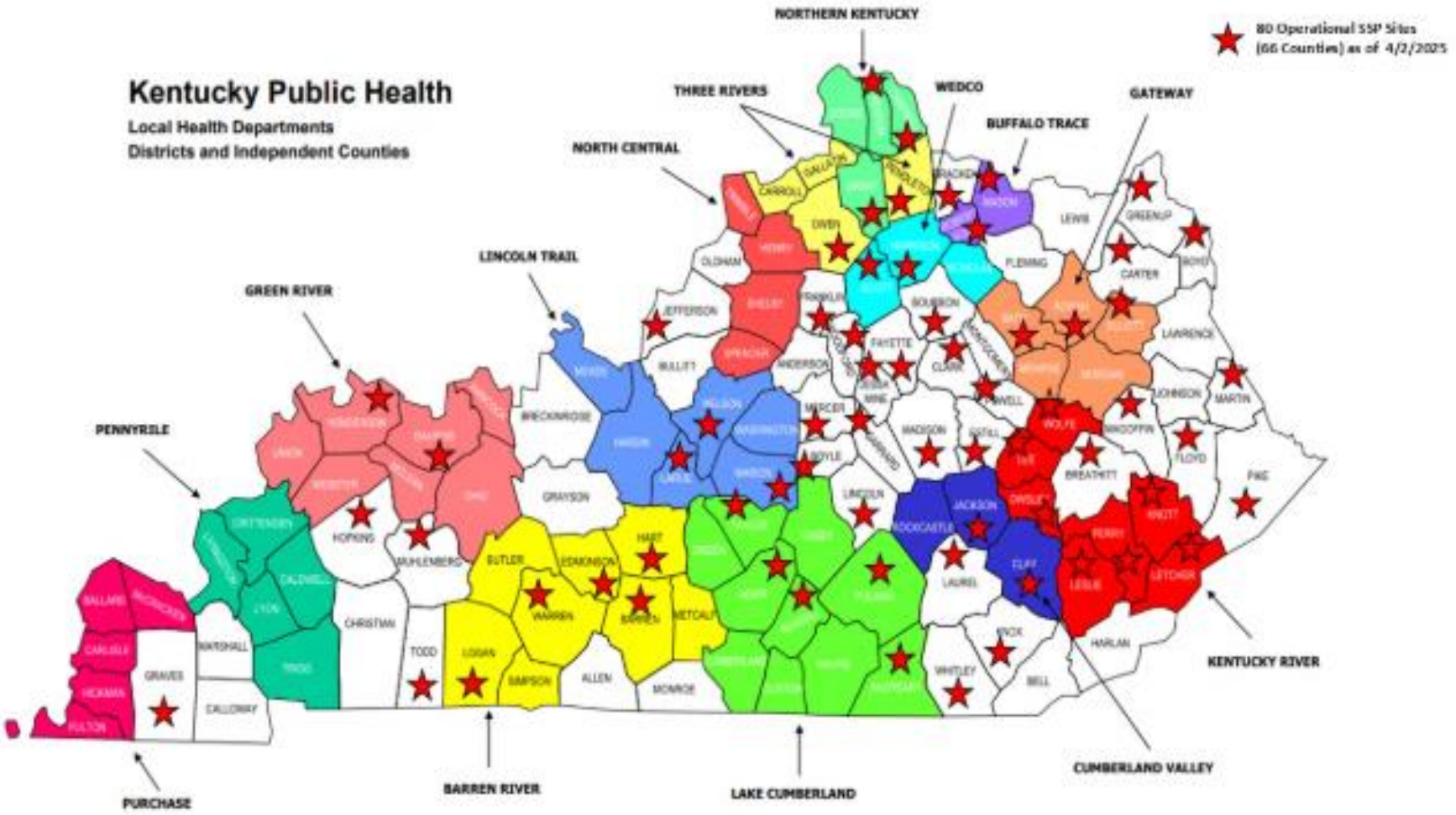
Photo: Jon Zibbell

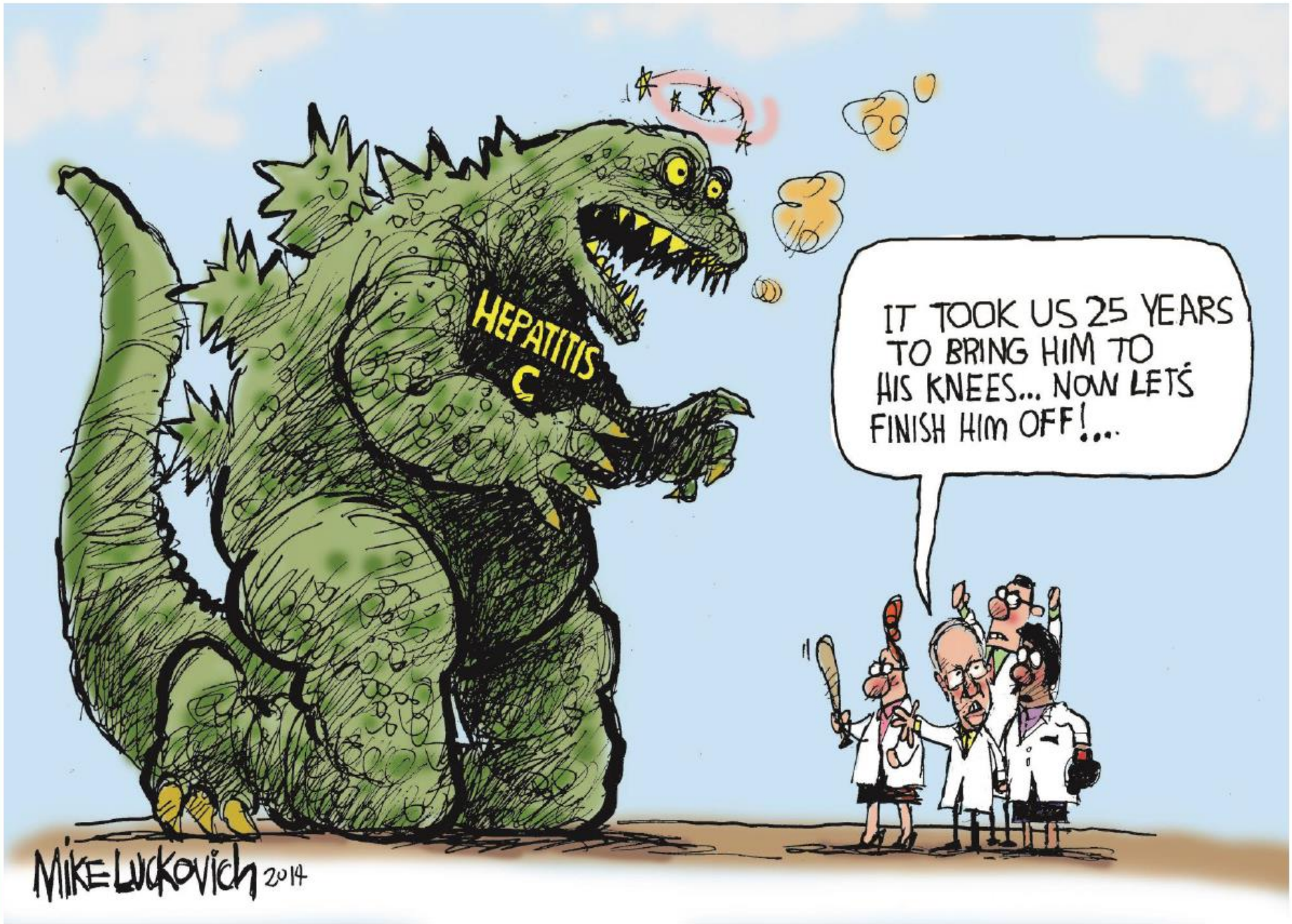
High Country Community Health: A Federally-Qualified Health Center (FQHC)

Photo: Zibbell

Olive Branch Ministry, a faith-based SSP in North Carolina

Kentucky SSPs: The Potential for a Statewide Network of Care for PWID




HEPATITIS C
IT TOOK US 25 YEARS TO BRING HIM TO HIS KNEES... NOW LETS FINISH HIM OFF!...
MIKE LUCKOVICH 2014