

XYLAZINE ET AL

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[Administration](#) [Priorities](#) [T](#)

APRIL 12, 2023

Biden-Harris Administration Designates Fentanyl Combined with Xylazine as an Emerging Threat to the United States



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XYLAZINE



Created by Bayer in 1962

- Antihypertensive
- Not approved for human use – *trials stopped due to hypotension and sedation*

Large animal sedative–analgesic

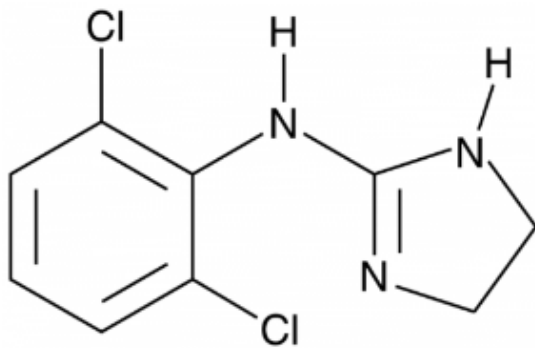
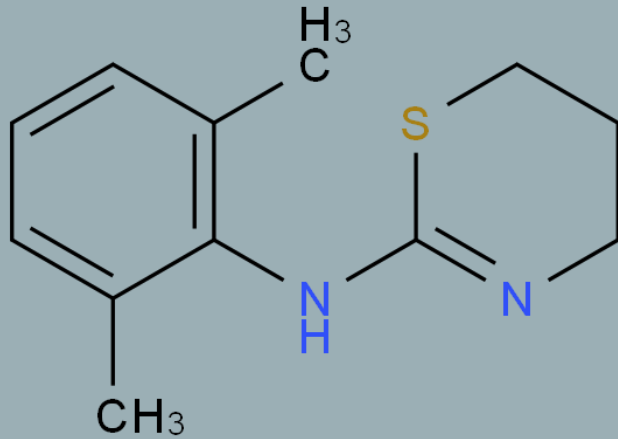
- *Anestica de caballo*
- “Tranq”

Comes in 20, 100, 300 mg/ml soln

Often used with ketamine or barbiturates

Photo via Dechra

XYLAZINE



Clonidine

Alpha adrenergic receptor agonist

Mixed mechanism of action*

- Central alpha-2 agonist
- ↓ NE release
- ↓ ACh release
- Agonizes multiple receptors
- May have opioid receptor activity at mu and kappa****

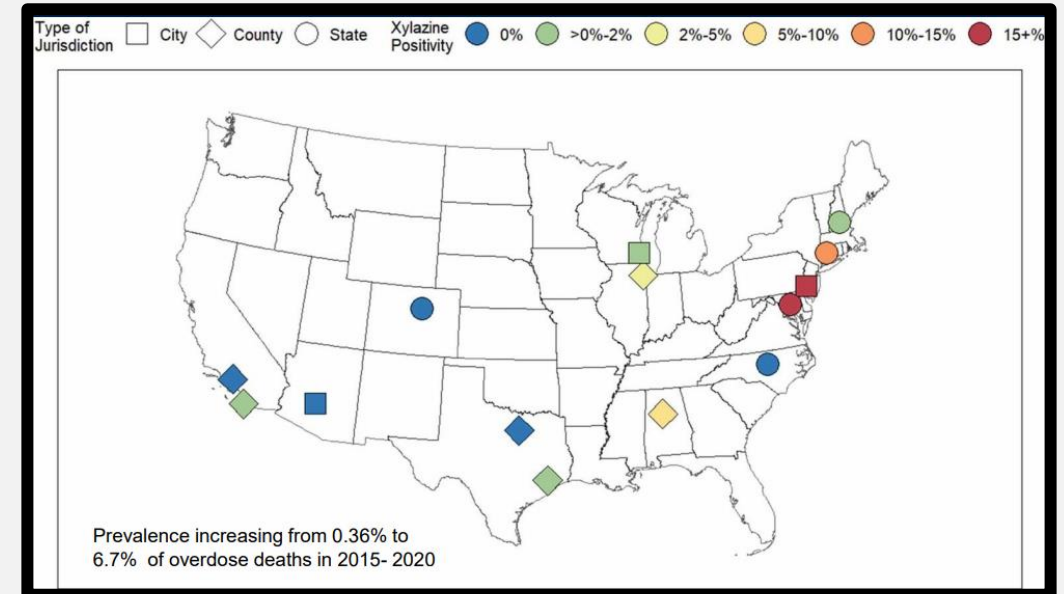
Hypertension followed by hypotension

Respiratory depression

- Potentially lethal dose 40–2400 mg in humans

*

Xylazine Prevalence



Drug Alcohol Depend. 2022 April 01; 233: 109380. doi:10.1016/j.drugalcdep.2022.109380.

Xylazine spreads across the US: A growing component of the increasingly synthetic and polysubstance overdose crisis

Joseph Friedman^{a,b,*}, Fernando Montero^c, Phillippe Bourgois^a, Rafik Wahbi^d, Daniel Dye^e, David Goodman-Meza^f, Chelsea Shover^g

Philadelphia → > 90% of fentanyl samples +xylazine

XYLAZINE GROWTH BY REGION

(U) Figure 1. DEA Forensic Laboratory Identifications of Xylazine by Region

Region	2020	2021	Percent Increase
Northeast	346	556	61%
South	198	580	193%
Midwest	110	118	7%
West	77	163	112%

Source: DEA

(U) Figure 2. Number of Xylazine-Positive Overdose Deaths by Region

Region	2020	2021	Percent Increase
Northeast	631	1,281	103%
South	116	1,423	1,127%
Midwest	57	351	516%
West	4	34	750%

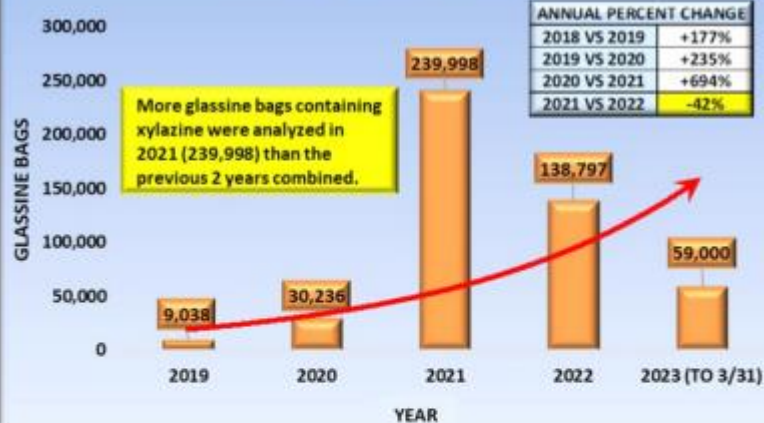
Source: DEA



The Growing Threat of Xylazine and its Mixture with Illicit Drugs

DEA Joint Intelligence Report
OCTOBER 2022

XYLAZINE-RELATED GLASSINE BAGS



YEAR	XYLAZINE-RELATED		ALL SUSPECTED HEROIN	
	SUBMISSIONS	GLASSINE BAGS	SUBMISSIONS	GLASSINE BAGS
2019	368	9,038	13,010	680,807
2020	855	30,236	7,814	500,715
2021	3,052	239,998	10,341	821,171
2022	2,610	138,797	7,365	475,753
2023 (TO 3/31)	848	59,000	1,898	141,225

Office of Drug Monitoring & Analysis
Quarterly Report



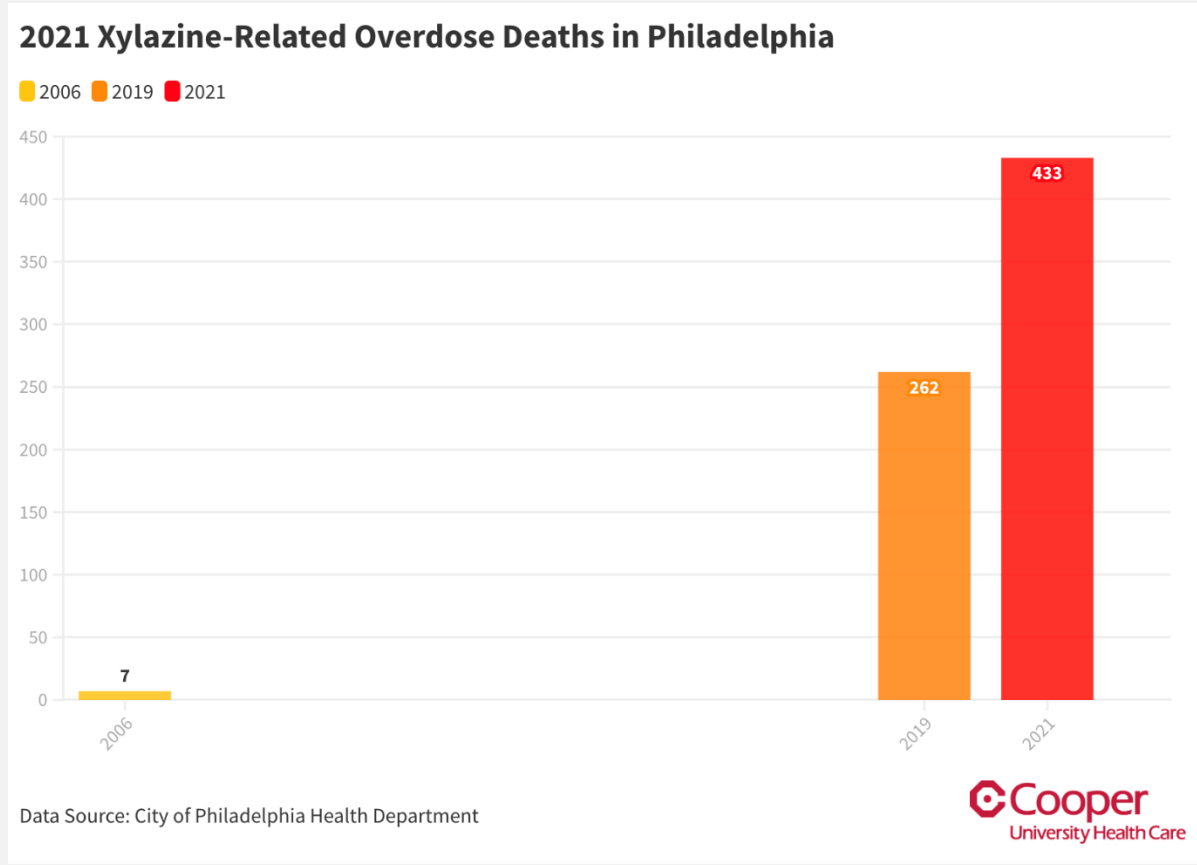
January 1, 2023 ~ March 31, 2023

COUNTY	XYLAZINE-RELATED SUBMISSIONS											
	2019	2020	2021	2022	2023 (TO 3/31)	TOTAL	2019	2020	2021	2022	2023 (TO 3/31)	TOTAL
ATLANTIC	10	94	400	262	70	836	3%	11%	13%	10%	8%	11%
BERGEN	15	28	73	83	26	225	4%	3%	2%	3%	3%	3%
BURLINGTON	73	101	325	250	30	779	20%	12%	11%	10%	4%	10%
CAMDEN	17	90	639	431	107	1,284	5%	11%	21%	17%	13%	17%
CAPE MAY	20	89	128	113	24	374	5%	10%	4%	4%	3%	5%
CUMBERLAND	4	10	28	39	30	111	1%	1%	1%	1%	4%	1%
ESSEX	49	73	202	130	42	496	13%	9%	7%	5%	5%	6%
GLOUCESTER	6	30	141	69	20	266	2%	4%	5%	3%	2%	3%
HUDSON	2	2	8	42	26	80	1%	0.2%	0.3%	2%	3%	1%
HUNTERDON	0	11	17	28	21	77	0%	1%	1%	1%	2%	1%
MERCER	6	78	386	373	193	1,036	2%	9%	13%	14%	23%	13%
MIDDLESEX	48	39	102	134	33	356	13%	5%	3%	5%	4%	5%
MONMOUTH	66	84	195	200	71	616	18%	10%	6%	8%	8%	8%
MORRIS	22	18	60	41	19	160	6%	2%	2%	2%	2%	2%
OCEAN	0	3	12	11	6	32	0%	0.4%	0.4%	0.4%	1%	0.4%
PASSAIC	25	65	242	325	95	752	7%	8%	8%	12%	11%	10%
SALEM	0	7	21	31	8	67	0%	1%	1%	1%	1%	1%
SOMERSET	0	7	24	13	6	50	0%	1%	0.5%	1%	1%	1%
SUSSEX	2	14	13	16	6	51	1%	0.4%	0.4%	1%	1%	1%
UNION	0	4	5	1	4	14	0%	0.5%	0.2%	0.04%	0.5%	0.2%
WARREN	3	8	31	18	11	71	1%	1%	1%	1%	1%	1%
TOTAL	368	855	3,052	2,610	848	7,733	5%	11%	39%	34%	11%	

COUNTY	XYLAZINE-RELATED GLASSINE BAGS											
	2019	2020	2021	2022	2023 (TO 3/31)	TOTAL	2019	2020	2021	2022	2023 (TO 3/31)	TOTAL
ATLANTIC	190	7,656	31,133	15,444	17,548	71,971	2%	25%	13%	11%	30%	15%
BERGEN	116	347	16,809	3,676	599	21,547	1%	1%	7%	3%	1%	5%
BURLINGTON	1046	2,003	5,647	6,088	543	15,327	12%	7%	2%	4%	1%	3%
CAMDEN	111	2,537	27,830	9,967	2,027	42,472	1%	8%	12%	7%	3%	9%
CAPE MAY	521	1,094	7,554	9,141	5,588	23,898	6%	4%	3%	7%	9%	5%
CUMBERLAND	30	84	417	450	331	1,312	0.3%	0.3%	0.2%	0.3%	1%	0.3%
ESSEX	989	2,416	20,809	15,503	2,136	41,853	11%	8%	9%	11%	4%	9%
GLOUCESTER	20	386	2,252	418	264	3,340	0.2%	1%	1%	0.3%	0.4%	1%
HUDSON	3	3	78	987	1,331	2,402	0.03%	0.01%	0.03%	1%	2%	0.5%
HUNTERDON	0	130	234	318	879	1,561	0%	0.4%	0.1%	0.2%	1%	0.3%
MERCER	186	3,722	40,223	30,575	10,139	84,845	2%	12%	17%	22%	17%	18%
MIDDLESEX	1,394	2,733	3,627	4,983	744	13,481	15%	9%	2%	4%	1%	3%
MONMOUTH	3,071	2,031	7,782	4,622	1,665	19,171	34%	7%	3%	3%	3%	4%
MORRIS	394	421	2,618	1,118	450	5,001	4%	1%	1%	1%	1%	1%
OCEAN	0	92	214	372	333	1,011	0%	0.3%	0.1%	0.3%	1%	0.2%
PASSAIC	897	3,530	58,258	25,361	13,128	101,174	10%	12%	24%	18%	22%	21%
SALEM	0	24	130	451	182	787	0%	0.1%	0.05%	0.3%	0.3%	0.2%
SOMERSET	0	139	1,443	180	109	1,871	0%	0.5%	1%	0.1%	0.2%	0.4%
SUSSEX	29	269	812	1,335	230	2,675	0.3%	1%	0.3%	1%	0.4%	1%
UNION	0	478	11,163	68	242	11,951	0%	2%	5%	0.05%	0.4%	3%
WARREN	41	141	965	7,740	532	9,419	0.5%	0.5%	0.4%	6%	1%	2%
TOTAL	9,038	30,236	239,998	138,797	59,000	477,069	2%	6%	50%	29%	12%	

Health Department Releases Data on 2021 Overdose Deaths in Philadelphia

For immediate release: October 26, 2022 | Published by: [Board of Health](#), [Department of Public Health](#) | Contact: James Garrow phpublichealth@phila.gov



Pharmacokinetics

Animal based data

Onset with IV use – minutes

Duration up to 4 hours

Rapid elimination $\frac{1}{2}$ life (25-50 m)

Many metabolites (>20)



Window of detection limited:

- serum – short
- urine – longer but less clinical relevance

TESTING

National Institute of Standards and Technology (NIST) → 35 sites/5 states (6/23) -
40% prevalence in fentanyl
- 77 unique compounds (highlights need for increased surveillance)

Initial reports reflected exposure related harm

Testing and surveillance is limited – not a standard analyte in immunoassays, not included in post mortem and drug seizure testing routinely

Parent compound (not metabolites) → analyte

Confirmatory available with LC-MS, LC-MS/MS, GC-MS, LC-QTOF-MS

Immunoassay based xylazine test strips

forensic/drug checking

interest from PWUD (but market xylazine saturated)

false positives

increased brands/distributers → comparability/consistency

Summary and Key Findings:

- ▶ 219 samples were tested between May and September 2022
- ▶ Fentanyl-xylazine (tranq-dope) proportions varied greatly
- ▶ The average fentanyl purity was 11.7% (range: 0.3-34.8%)
- ▶ The average xylazine purity was 33.8% (range: 0-64.8%)
- ▶ Most dope samples (91%) contained fentanyl and xylazine
- ▶ Synthetic cannabinoids remain dynamic and unpredictable
- ▶ Counterfeit Xanax tablets tested positive for clonazepam
- ▶ Cocaine purity varied greatly (average: 37.8%, range: 0.2-81.8%)

Date	Suspected	Drugs Identified
9/13/2022	Dope	Fentanyl (18.4%), Xylazine (26.9%), 4-ANPP (10.6%) [OPI=1.84]
9/21/2022	Dope	Fentanyl (6.6%), Xylazine (40.5%), 4-ANPP (1.0%), Procaine, Caffeine [OPI=0.69]
9/21/2022	Dope	Fentanyl (7.7%), Xylazine (32.4%), para-Fluorofentanyl (0.3%), 4-ANPP (0.7%) [OPI=0.78]
9/21/2022	Dope	Fentanyl (7.8%), Xylazine (26.6%), 4-ANPP (1.5%) [OPI=0.78]
9/21/2022	Dope	Fentanyl (8.2%), Xylazine (58.4%), 4-ANPP (0.6%) [OPI=0.82]
9/21/2022	Dope	Fentanyl (8.3%), Xylazine (26.3%), 4-ANPP (1.6%) [OPI=0.83] ①
9/21/2022	Dope	Fentanyl (8.8%), Xylazine (30.1%), 4-ANPP (1.7%) [OPI=0.88]
9/21/2022	Dope	Fentanyl (10.0%), Xylazine (36.8%), 4-ANPP (1.7%) [OPI=1.00] ②

Fentanyl Purity, Potency, & Synthesis (CONT.)

DRUG PURITY VS. POTENCY INDEX

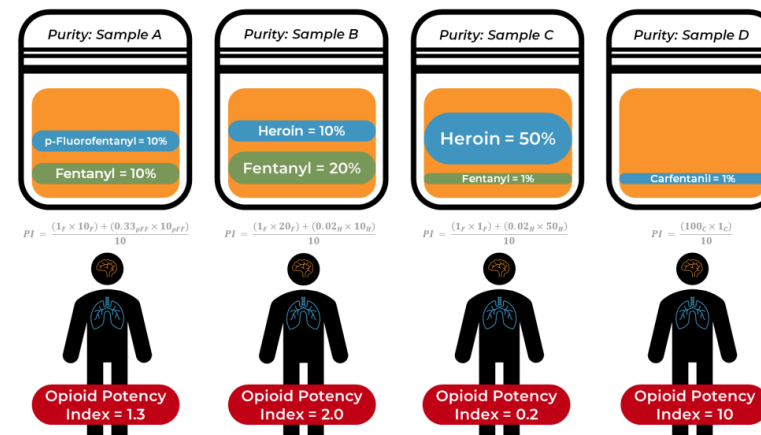


Figure 3: Illustration of drug purity (top) vs. potency index (bottom) with example calculations for opioids commonly encountered in the recreational drug supply.

$$Potency\ Index = \frac{(PF \times Purity) + (PF \times Purity) \dots}{10} \quad (Eq. 1)$$

How Much Opioid is in a Bag of Philadelphia Heroin/Fentanyl?

Net Weight (g)	Purity (%)	Number of Bags	Weight per bag (mg)	Fentanyl per Bag (mg)
22	6.9	767	28.68	1.98
26	1.4	731	35.57	0.50
29	8	684	42.40	3.39
20.1	7	450	44.67	3.13
18	9	449	40.09	3.61
13	5	400	32.50	1.63
14.9	6	390	38.21	2.30
15.8	5	224	70.54	3.53
7.4	10	195	37.95	3.79
7.57	3.5	192	39.43	1.38
10.3	3.2	182	56.60	1.81
5.1	7.4	172	29.65	2.19
4.93	6.5	166	29.70	1.93
9.95	3.3	165	60.30	1.99
4.32	10	159	27.17	2.72
3.98	12	140	28.43	3.41
5.5	6	140	39.29	2.36

Avg fentanyl mg per bag:	2.45
Low	0.50
High	3.80

Source: DEA

Xylazine/Fentanyl overdose

- ◆ Multicenter prospective cohort of patients following an opioid overdose from 9 EDs across the US
 - ◆ Included 321 patients testing positive for an illicit opioid or xylazine
 - ◆ 83% of patients received naloxone (median initial dose 2 mg)
 - ◆ Xylazine-negative patients were more likely to develop a coma within 4 hours of ED arrival and suffer a cardiac arrest
 - ◆ Most patients were discharged from the ED (59 [65.5%] xylazine-positive, vs. 147 [63.6%] xylazine-negative patients)

Love JS: et al. Opioid overdoses involving xylazine in emergency department patients: a multicenter study. Clin Toxicol (Phila). 2023 Mar;61:173-180.

Illicitly Manufactured Fentanyl–Involved Overdose Deaths with Detected Xylazine — United States, January 2019–June 2022

Weekly / June 30, 2023 / 72(26);721–727

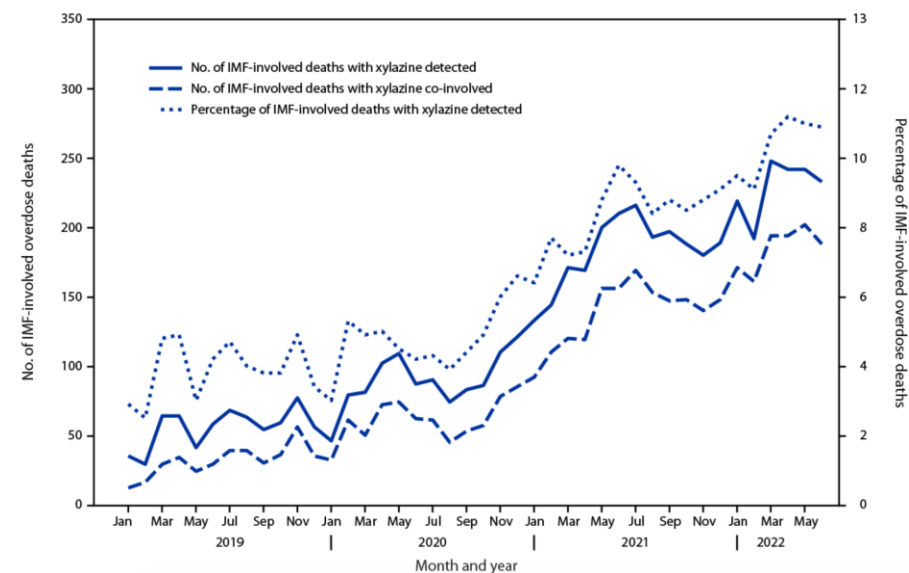
[Print](#)

Mbabazi Kariisa, PhD¹; Julie O'Donnell, PhD¹; Sagar Kumar, MPH¹; Christine L. Mattson, PhD¹; Bruce A. Goldberger, PhD² ([VIEW AUTHOR AFFILIATIONS](#))

Xylazine detection was **NOT** associated with:

- higher proportions of naloxone administration
- decedents having no pulse when first responders arrived.

FIGURE 1. Number and percentage of drug overdose deaths involving* illicitly manufactured fentanyls,[†] by month and xylazine detection or co-involvement — State Unintentional Drug Overdose Reporting System, 21 jurisdictions,[‡] January 2019–June 2022



XYLAZINE WITHDRAWAL???

Clonidine withdrawal*

Hypertensive
emergencies???

Compassionate care

*Geyskes GG, Boer P, Dorhout Mees EJ. Clonidine withdrawal. Mechanism and frequency of rebound hypertension. *Br J Clin Pharmacol.* 1979 Jan;7(1):55-62. doi: 10.1111/j.1365-2125.1979.tb00897.x. PMID: 760743; PMCID: PMC1429594.

Ehrman-Dupre, R., Kaigh, C., Salzman, M., Haroz, R., Peterson, L. K., & Schmidt, R. (2010). Management of xylazine withdrawal in a hospitalized patient: A case report. *Journal of Addiction Medicine, 16*(5), 595-598.



XYLAZINE WITHDRAWAL MANAGEMENT

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Hydromorphone	Patient-controlled anesthesia (PCA) pump; settings: no basal rate, bolus 1 mg q 10 minutes	PCA pump; settings: basal rate 1 mg/hour, bolus 1 mg q 12 minutes	PCA pump; settings: basal rate 1.5 mg/hour, bolus 1 mg q 12 minutes	PCA pump; settings: basal rate 1.5 mg/hour, bolus 1 mg q 12 minutes	PCA pump; settings: basal rate 1.5 mg/hour, bolus 1.2 mg q 12 minutes	PCA pump; settings: basal rate 1.5 mg/hour, bolus 1.2 mg q 12 minutes
Phenobarbital	Load (per institution's intensive care unit alcohol withdrawal protocol)	Taper (per institution's intensive care unit alcohol withdrawal protocol)	Taper (per institution's intensive care unit alcohol withdrawal protocol)	Taper (per institution's intensive care unit alcohol withdrawal protocol)	<i>Discontinued (taper completed)</i>	
Dexmedetomidine	Infusion	Infusion	Infusion	Infusion	<i>Discontinued</i>	
Tizanidine	4 mg q 6 hours PO	<i>Discontinued</i>				
Clonidine		0.3 mg q 8 hours PO	0.3 mg q 8 hours PO	0.3 mg q 8 hours PO	0.3 mg q 8 hours PO	0.3 mg q 8 hours PO
Buprenorphine				300 mcg once buccal	300 mcg BID buccal	450 mcg BID buccal
Gabapentin				300 mg q 8 hours PO	300 mg q 8 hours PO	300 mg q 8 hours PO
Ketamine				Infusion during dressing changes	Infusion during dressing changes	Infusion during dressing changes

Ehrman-Dupre, R., Kaigh, C., Salzman, M., Haroz, R., Peterson, L. K., & Schmidt, R. (2010). Management of xylazine withdrawal in a hospitalized patient: A case report. *Journal of Addiction Medicine, 16*(5), 595-598.

XYLAZINE WITHDRAWAL MANAGEMENT???

	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Hydromorphone	PCA pump; settings: basal rate 1.5 mg/ hour, bolus 1.2 mg q 12 minutes	PCA pump; settings: basal rate 1 mg/ hour, bolus 1.3 mg q 12 minutes	PCA pump; settings: no basal rate, bolus 1.3 mg q 12 minutes	PCA pump; settings: no basal rate, bolus 1.3 mg q 12 minutes	PCA pump; settings: no basal rate, bolus 1.3 mg q 12 minutes	PCA pump; settings: no basal rate, bolus 1.3 mg q 12 minutes
Clonidine	0.3 mg q 8 hours PO	0.3 mg q 8 hours PO	0.3 mg q 8 hours PO	0.3 mg q 8 hours PO	0.3 mg q 8 hours PO	0.3 mg q 8 hours PO
Buprenorphine	2 mg twice daily sublingual	2 mg three times daily sublingual	4 mg q 4 hours sublingual	2 mg four times daily sublingual	4 mg four times daily sublingual	4 mg four times daily sublingual
Gabapentin	300 mg q 8 hours PO	300 mg q 8 hours PO	300 mg q 8 hours PO	300 mg q 8 hours PO	300 mg q 8 hours PO	300 mg q 8 hours PO
Ketamine	Infusion during dressing changes	Infusion during dressing changes	Infusion during dressing changes	Infusion during dressing changes	Infusion during dressing changes	<i>Discontinued</i>

RESULTS: XYLAZINE WITHDRAWAL SYNDROME



Major Phenotypes from Expert Chart Review

1. 52 of 73 patients (71.3%) with no signs of a new withdrawal syndrome
 - Mixed opioid and/or benzodiazepine withdrawal, course as expected
 - Aggressive withdrawal & pain management, improved with opioids
2. 19 patients (26.4%) with a possible withdrawal syndrome
 - Agitated delirium/toxidrome with other substances, +/- ICU admission
 - Naloxone or buprenorphine precipitated withdrawal
 - Insufficiently treated opioid withdrawal, low doses methadone/oxycodone
3. 2 patients (2.7%) with otherwise unexplained symptoms
 - Unexplained hypertension (~180/100s) and/or tachycardia (<100)

XYLAZINE WITHDRAWAL TREATMENT

Standard

- ◆ Clonidine
- ◆ Benzodiazepines
- ◆ Antipsychotics
- ◆ Phenobarbital
- ◆ Gabapentin

ICU

- ◆ Dexmedetomidine
- ◆ Ketamine

Others

- ◆ Ropinirole
- ◆ Tizanidine

XYLAZINE WITHDRAWAL- OVERLAPPING SYMPTOMS

Xylazine	Opioid	Benzodiazepine
<p>Anxiety Dysphoria Restlessness</p>	<p>Tachycardia Diaphoresis Restlessness Mydriasis Body aches Rhinorrhea GI symptoms Tremor Yawning Piloerection Anxiety Dysphoria</p>	<p>Tachycardia Hypertension Diaphoresis Anxiety Tremor Altered mental status Seizures Dysphoria</p>

XYLAZINE ASSOCIATED WOUNDS

Early Stage



Late Stage



44 year-old male



Left upper extremity



Left upper extremity

31 year old Female



Photos from Cooper University Hospital

41 year old male

Photos from Cooper University Hospital



Right forearm



Left forearm



Photo from Cooper University Hospital

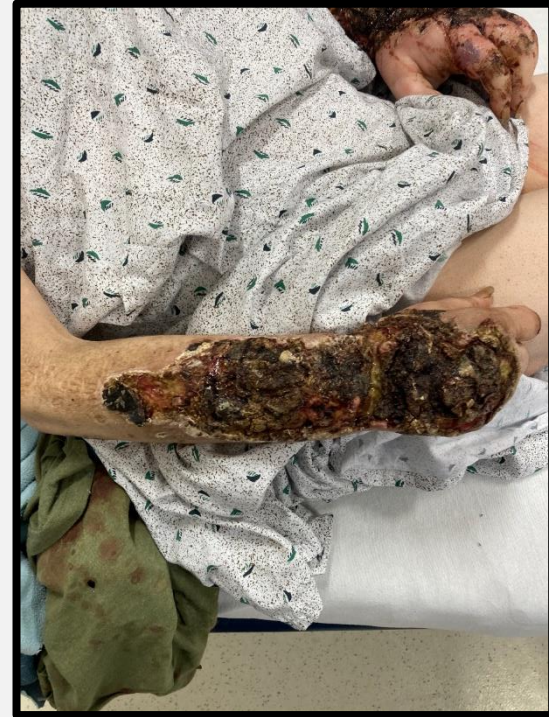


Photo courtesy of Michael Coletta, MD

XYLAZINE WOUND PATHOLOGY

- IVDA has been associated with wounds
- Potential Causes:
 - Skin picking behavior leading to excoriation and ulceration
 - Increased frequency of injection
 - Infection
 - Compression
 - Decreased skin oxygenation
 - Poor wound healing (?malnutrition & elevated blood sugar)
 - Cytotoxic effect of drug or contaminant
 - Obliterative vasculitis from repeated injection “shooters patch”

Wound Treatments

Cessation of injection

Clean with soap/water, chlorhexidine, Dakin's Half Strength Solution, or 1% acetic acid

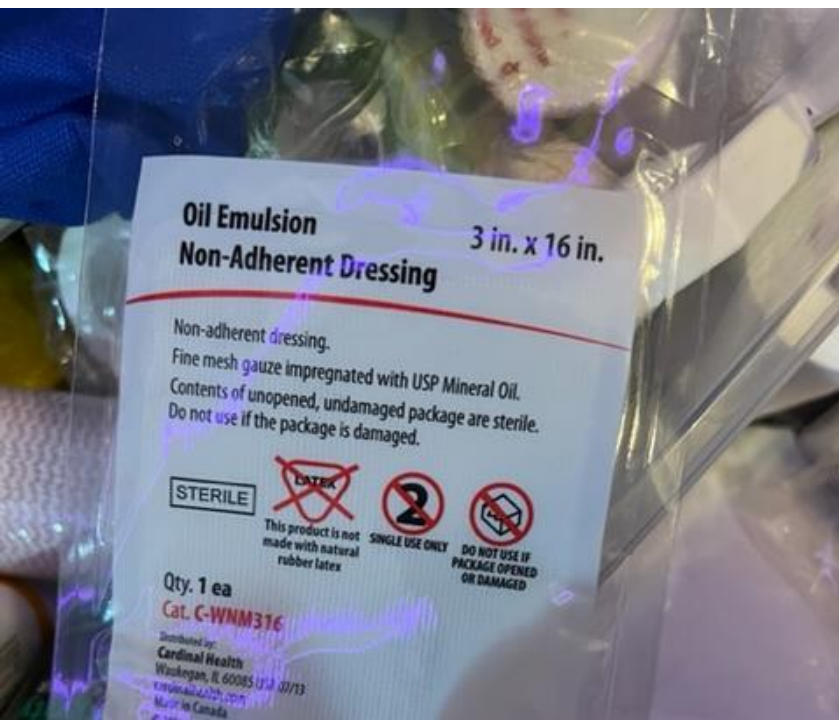
Debridement (enzymatic > surgical)

Antimicrobial coverage (Silver sulfadiazine cream, bacitracin ointment)

Non-adherent (petroleum gauze or other additive to promote moist wound environment) and absorptive dressing

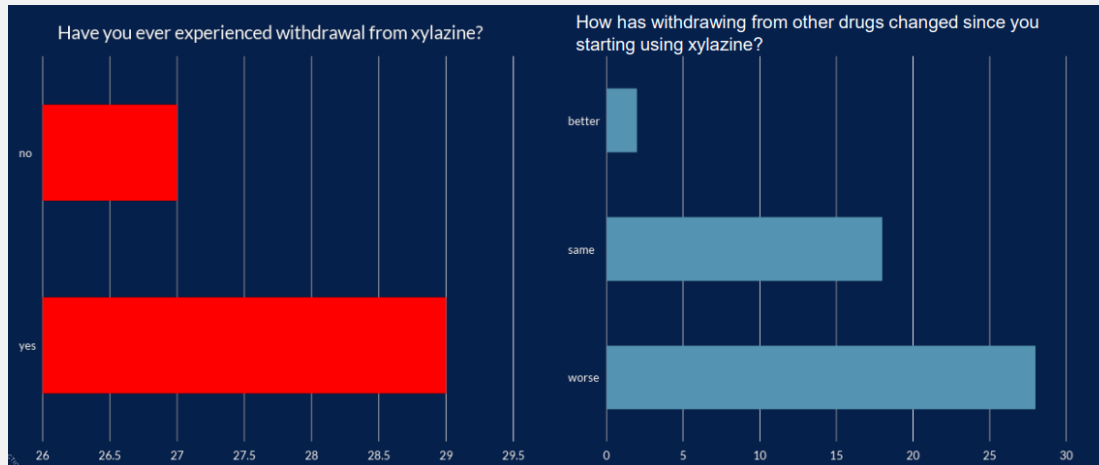
Biodegradable Temporizing Matrix (BTM), skin grafting, epithelialization/complete closure





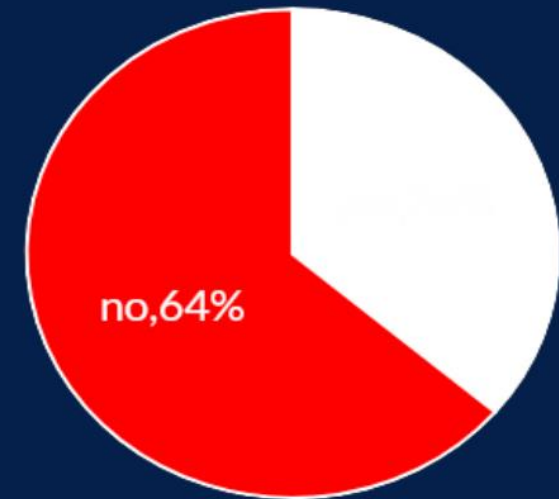
TOXICOSURVEILLANCE OF SOCIAL MEDIA: REDDIT

- Who is describing Xylazine Use?
- How does xylazine impact withdrawal symptoms?
- What complications are people reporting?



Spadaro etal Amersa 2022

Do you seek out xylazine intentionally?



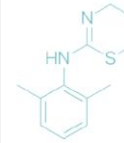
CONCLUSIONS

- Xylazine prevalence has significantly increased across the country
- Appears to be linked to overdose deaths although some of the data is conflicting
- Xylazine dependence is difficult to treat
 - Gabapentin
 - Clonidine (high dose)
 - Dexmedetomidine
- Xylazine associated wounds are difficult to treat
 - May need hospital referral
 - Treat like burns
 - Increased caloric requirement

RESOURCES

- DEA: [The Growing Threat of Xylazine and Its Mixture with Illicit Drugs \(Intelligent Report\)](#)
- NIDA: [Research Topics—Xylazine](#)
- NHRC: [Xylazine FAQ, Education, Webinars](#)
- NEXT Distro: [Xylazine Quick Guide for People Who Use Drugs](#)
- Upenn: [CAMP-Xylazine-Best-Practices- I.pdf](#)

Xylazine



What is Xylazine?

Xylazine is a veterinary anesthetic that's often used as a cut in street drugs. It's sometimes called tranq, tranq dope or sleep cut and people usually use xylazine unknowingly when their drugs are cut with it.

Uses

For humans there isn't a prescribed use because it's intended for use in animals.

Effects

Sedation, analgesia (pain killing like ibuprofen or advil but not opioids) and muscle relaxation. Strong sedative effects and excessive sleepiness without euphoria have been anecdotally reported to happen anywhere from 5 to 200mg.

Side Effects

Xylazine isn't intended for human use and long term use can cause skin lesions or ulcers. In high doses, respiratory depression, passing out or falling unconscious while still standing is common. Deaths are rare but have occurred in humans using anywhere from 40 to 2400mg of xylazine.

Dose

There isn't an established human dose for xylazine use. For harm reduction purposes, use as little as possible if you think your drug contains xylazine. It's recommended to start as low as possible and go slow if using xylazine.

Routes of Administration

Not much is known about the human use of xylazine but there have been reports of people eating, snorting, IVing, IMing, and using xylazine subcutaneously (injection in the skin or skin-popping).

Withdrawal

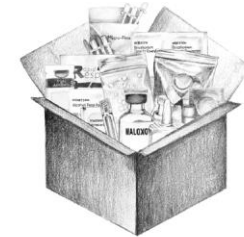
Withdrawal symptoms have been reported to be mild but because of the lack of human information about xylazine your results may vary.

Withdrawal Management

Research suggests that if withdrawal symptoms are present, low dose clonidine can be used to manage withdrawal symptoms.

Overdose Prevention

Treat xylazine like you would any other drug that can cause respiratory depression such as opioids, benzos or alcohol. If combining with other drugs, keep the doses low especially if they are other depressant drugs. There isn't an overdose reversal drug for xylazine so it's recommended to not to use alone and practice harm reduction if you decide to use xylazine.



For more drug-specific information & resources, visit:

www.nextdistro.org/drugspecific

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SMS/Signal 646-389-0752

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This resource is a living document that we will continue to update and refine. If you have input about how the information contained here could be improved or if you have new content to add, please email us at content@nextdistro.org.

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