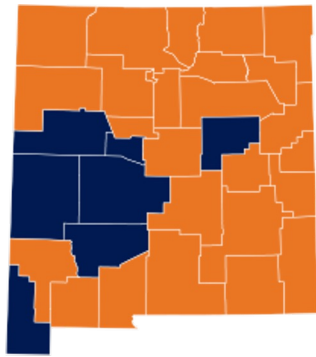
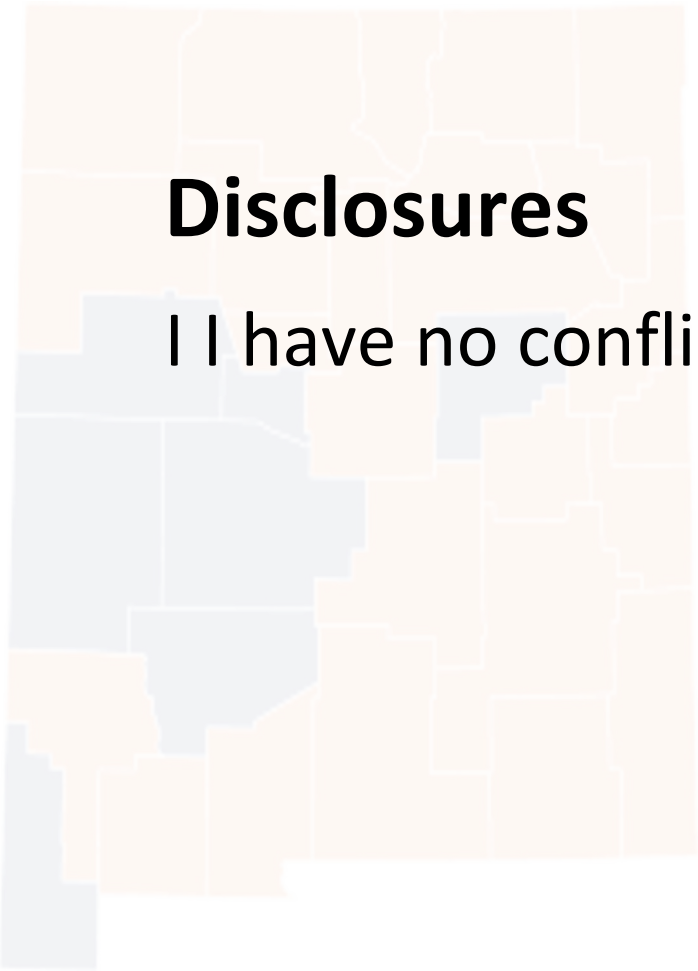


Opioid Remediation Collaborative (ORC) of New Mexico

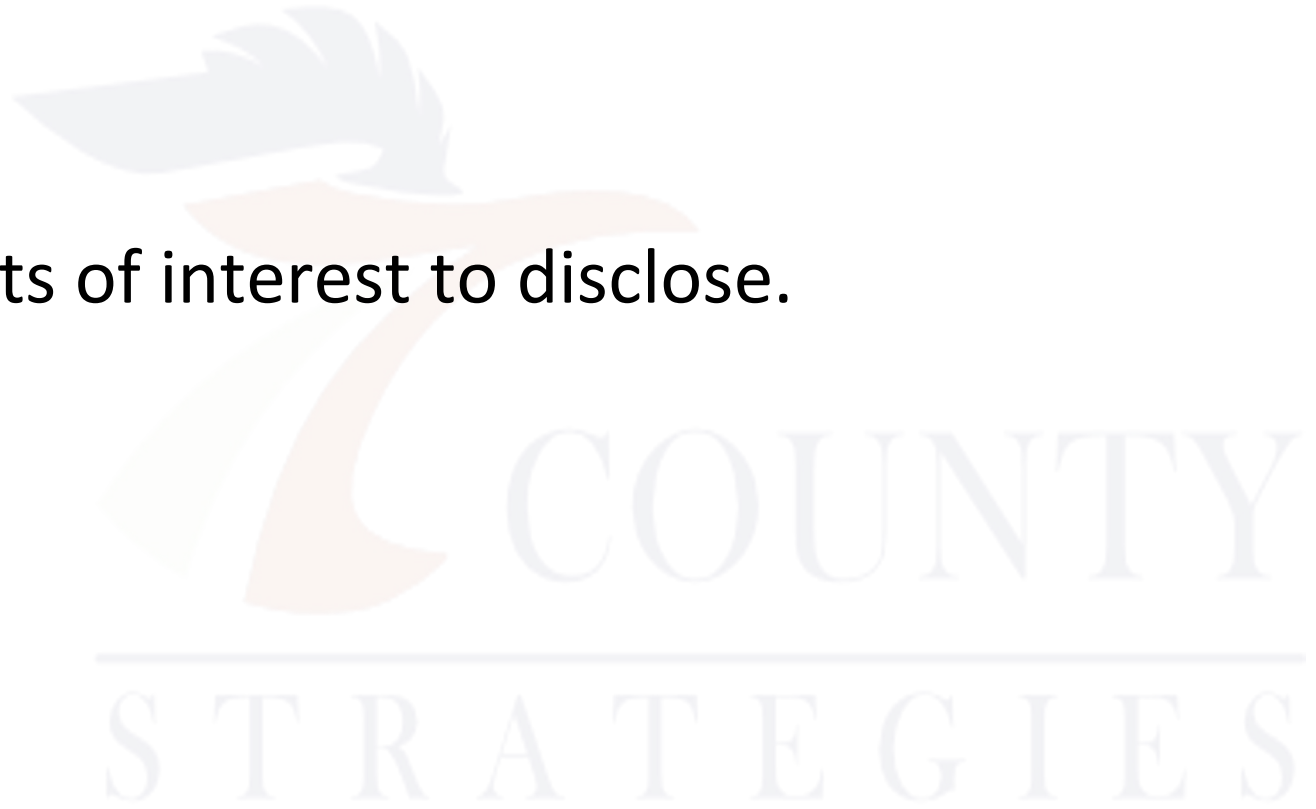


Heroin and Fentanyl Updates and
Pharmacology



Disclosures

I I have no conflicts of interest to disclose.

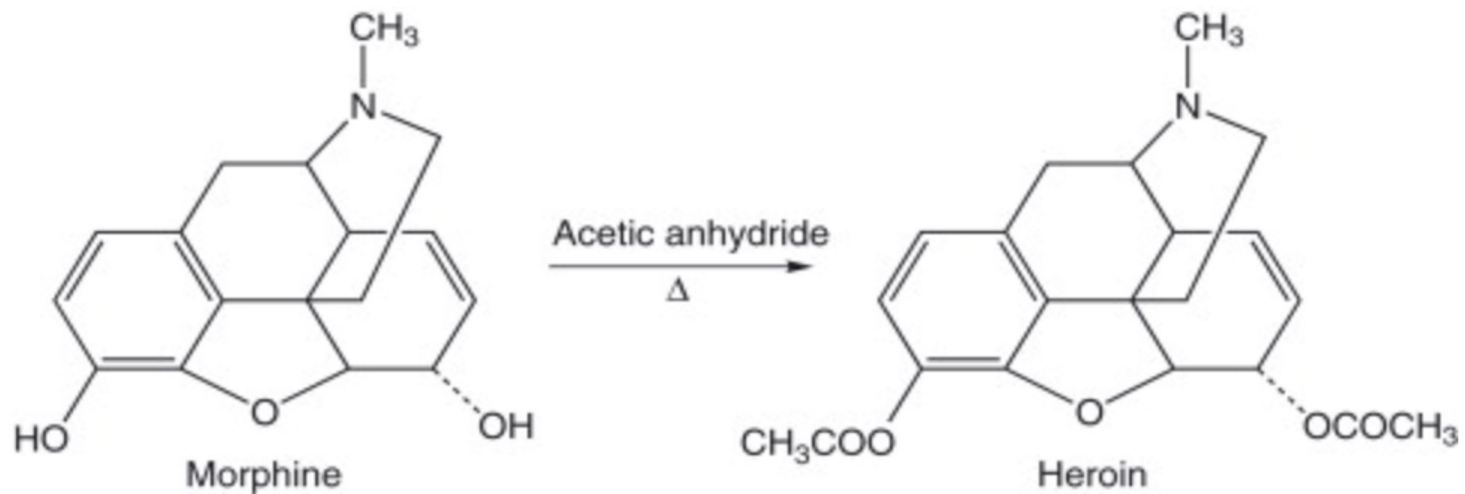


Objectives

1. Describe the pharmacological properties and clinical effects of heroin.
2. Describe how fentanyl became the current dominant opioid supplied to the US.
3. Describe the multiple fentanyl formulations and their potency as well as the unique pharmacokinetic properties of fentanyl that make its treatment challenging.
4. Review the effects of the additive xylazine to fentanyl products and its effect.

Heroin - Diacetylmorphine

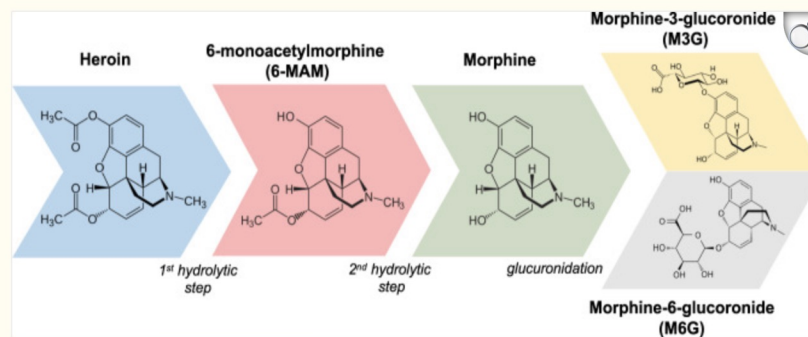
Heroin is derived from the acetylation of morphine:



Heroin – one of the oldest most abused opioids but least studied pharmacologically

Breaks down rapidly

Fig. 1. Molecular structure of heroin and its metabolites.



[Open in a new tab](#)

Schematic representation of the metabolic pathway of heroin with the sequential breakdown into the main metabolites. The involved enzymatic processes are listed in italics.

Milella MS, D'Ottavio G, De Pirro S, Barra M, Caprioli D, Badiani A. Heroin and its metabolites: relevance to heroin use disorder. *Transl Psychiatry*. 2023 Apr 8;13(1):120. doi: 10.1038/s41398-023-02406-5. PMID: 37031205; PMCID: PMC10082801.

Heroin and Fentanyl Updates and Pharmacology

Heroin Properties

- Heroin often considered a “prodrug” – although some say this is not clear.
- It is lipophilic – meaning that it can rapidly pass the blood-brain barrier.
- It is very short acting lasting 3 minutes after IV injection before converted to 6-MAM which is an active metabolite.
- 6-MAM last only about 30 minutes in the blood and is converted to morphine.
- Most IV users will describe a “rush” lasting a minute, to a state of calm and detachment that persist for several hours.
- The rapid onset and short duration of effect result in the user dosing multiple times daily.

Milella MS, D'Ottavio G, De Pirro S, Barra M, Caprioli D, Badiani A. Heroin and its metabolites: relevance to heroin use disorder. *Transl Psychiatry*. 2023 Apr 8;13(1):120. doi: 10.1038/s41398-023-02406-5. PMID: 37031205; PMCID: PMC10082801.

Routes of Use

- Depends on the purity of heroin.
- Pure heroin: White powder can be smoked or snorted.
- Black Tar: sticky tar-like substance which is dissolved and injected. IV, intramuscular, SQ.
- Generally not used orally – if so active ingredients broken down quickly and essentially getting low dose morphine



NIDA. 2021, April 13. What is heroin and how is it used?. Retrieved from <https://nida.nih.gov/publications/research-reports/heroin/what-heroin> on 2025, January 9

Clinical effects of Heroin

Acute/Short Term

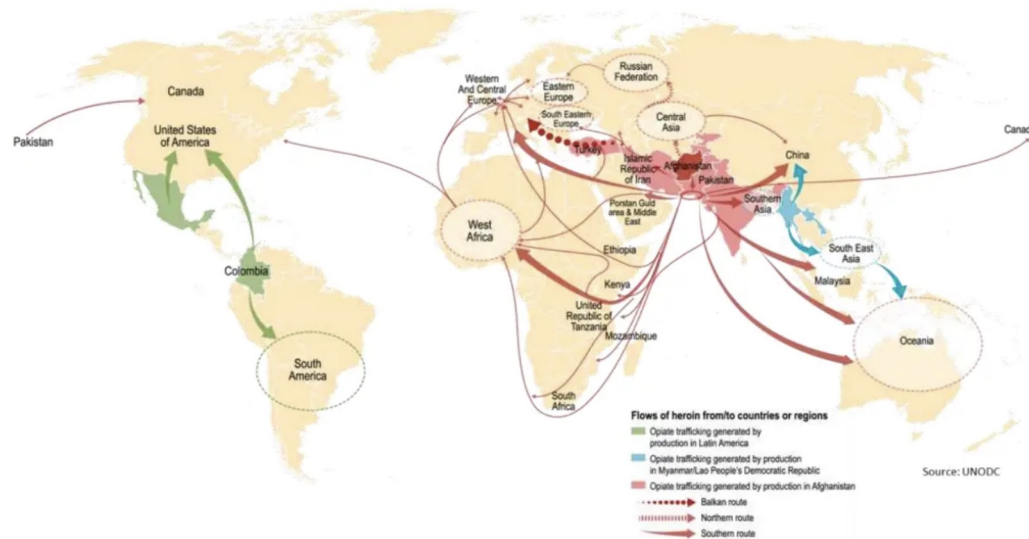
- Rush, followed by flushed skin
- Dry mouth
- Often nausea and vomiting
- Itching
- Drowsiness for several hours
- Cognitive impairment
- PR decrease; BP decrease; RR decrease
- May cause pulmonary edema

Long Term

- Tolerance/ Physical dependence, withdrawal after 8-12 hrs, peaking 24-48 and lasting up to 7 days
- Deterioration of brain's white matter
- Medical complications from IV drug use: endocarditis, blood borne pathogens, osteomyelitis, skin abscesses, venous thrombosis, septic emboli, nephropathy, as well as those adverse effects mentioned in the prior lecture.

Where is Heroin made?

Exhibit 42: The War on Drugs



- The flow of illegal opiates around the world also has geopolitical consequences.
- The production and trade of illegal drugs has links with failed states, black economies and regional instability.
- Afghanistan remains the center of illicit opiate production.

Heroin and Fentanyl Updates and Pharmacology

Poppy Plant Growing is Not Easy

- Requires long daylight hours
- Temperate Climate
- Low Humidity
- Proper soil acidity
- Mostly grown in mountain slopes
- 3-5 months growth time
- Processed to morphine, then heroin.
- 13 Kg of opium produce 1 Kg of heroin



Opium Poppy Cultivation and Heroin Processing,
US Department of Justice, DEA, Sept 1992

Heroin in the early 2010s – Pre-Fentanyl

- Pure heroin (white powder) predominantly from Columbia and South America and dominated the US Markets East of the Mississippi. Use was mostly snorting or smoking
- Black Tar Heroin produced in Mexico and sold predominantly west of the Mississippi. Use dissolved and diluted and injected into veins, muscles or SQ.

NIDA. 2021, April 13. What is heroin and how is it used?. Retrieved from <https://nida.nih.gov/publications/research-reports/heroin/what-heroin> on 2025, January 9

But!!! Here's the problem for the Cartels

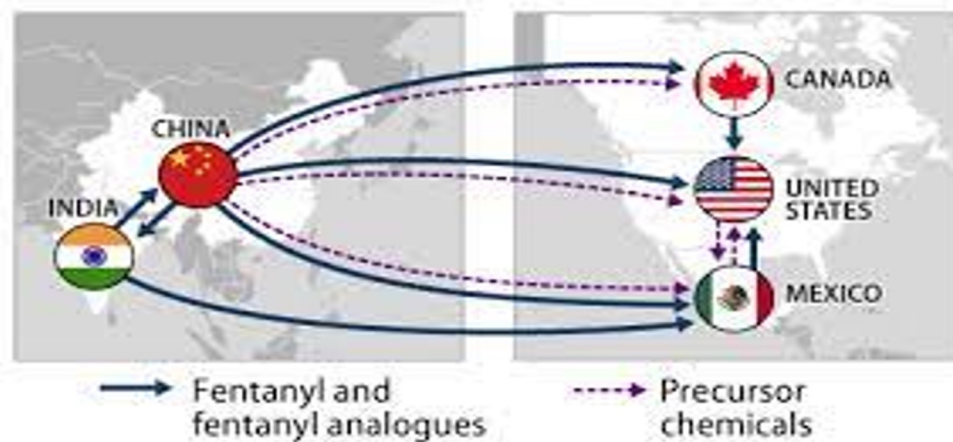
- Crop-based drugs are time-consuming and expensive to produce.
- Traffickers lose product to weather, poor harvest and logistics to getting from the harvest to clandestine labs.
- Risk of government eradication efforts.
- Requires more land and labor for production.

enter...

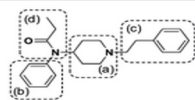
FENTANYL

History

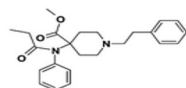
- Fentanyl first synthesized in 1959 and used medically for pain relief
- Regulated by the DEA by CSA 1970
- Recent years manufacturing illicitly of fentanyl, analogs and precursors.
- 144 fentanyl related substances available with no legitimate use.
- Once known precursors become known, producers shift to others not recognized.



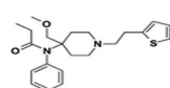
Fentanyl Analogs



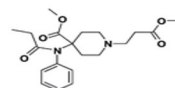
Fentanyl



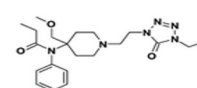
Carfentanyl



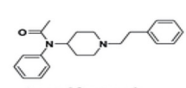
Sufentanil



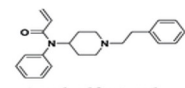
Remifentanyl



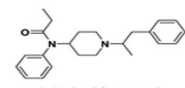
Alfentanil



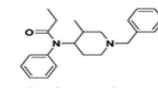
Acetylfentanyl



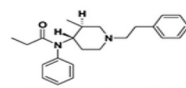
Acryloylfentanyl



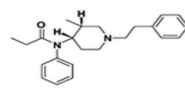
α -Methylfentanyl



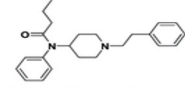
Isofentanyl



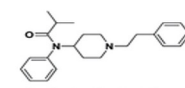
(+)-*Trans*-3-methylfentanyl
(3*S*,4*S*-configuration)*



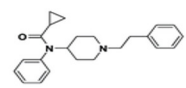
(+)-*Cis*-3-methylfentanyl
(3*R*,4*S*-configuration)*



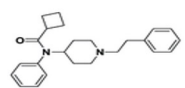
Butyrfentanyl



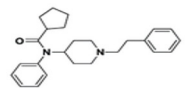
Isobutyrfentanyl



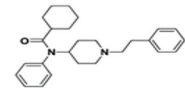
Cyclopropylfentanyl



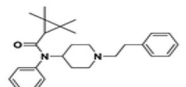
Cyclobutylfentanyl



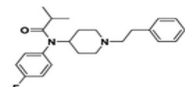
Cyclopentylfentanyl



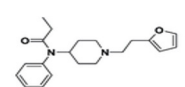
Cyclohexylfentanyl



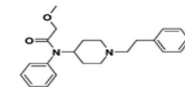
2,2,3,3-Tetramethyl-
cyclopropylfentanyl



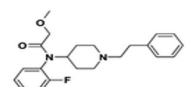
4-Fluoroisobutyrfen-
tanyl



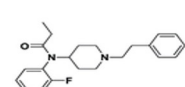
Furanylfentanyl



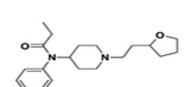
Methoxyacetylfentanyl



Ocfentanyl



Ortho-fluorofentanyl



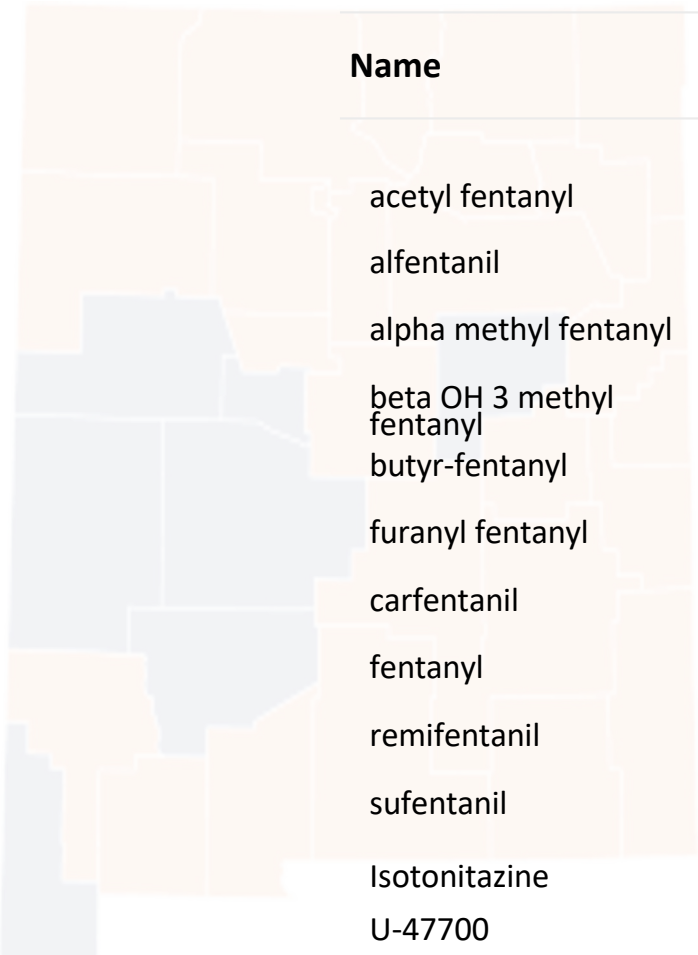
Tetrahydrofuran-
fentanyl

Heroin and Fentanyl Updates and Pharmacology

Some Illicit Fentanyl Products



Heroin and Fentanyl Updates and Pharmacology



Name	Potency ratio to morphine	Potency ratio to fentanyl	Legal status (US)
acetyl fentanyl	15.7	0.29	1
alfentanil	Unknown	0.06	1
alpha methyl fentanyl	56	1.1	1
beta OH 3 methyl fentanyl	6300	28	1
butyr-fentanyl	7	0.13	1
furanyl fentanyl			
carfentanil	10000	100	2
fentanyl	100		2
remifentanil		10	2
sufentanil	1000	10	2
Isotonitazine	500		1
U-47700	7.5	0.1	1

Heroin and Fentanyl Updates and Pharmacology

Suzaki, J A review: Fentanyl and non-pharmaceutical fentanyls, Drug and Alcohol Dependence, Feb 2017, pp107-116. Last 2 items are non-fentanyl opioids – are benzimidazole and benzamide derivatives

What makes fentanyl so potent?

- From our medical use, we know that fentanyl is very fast acting with a high therapeutic index.
- It has similar binding affinity as morphine
- But unlike morphine, fentanyl is very lipophilic. This means:
 - Very rapid entry to CNS across BBB
 - Fentanyl, when used acutely, has a short duration and a rapid exit.
 - But this also means over time with repeat exposure fentanyl stays in fat cells.

Villiger JW, Characteristics of [3H] fentanyl binding to the opioid receptor. *Neuropharmacology* 1983; 22: 447-452. Moss and Carlo Higher doses of naloxone are needed in synthetic opioid era. *Substance Abuse Treatment, Prevention and Policy*. (2019) 14:6. Hug et al. Tissue redistribution of fentanyl and termination of its effects in rats. *Anesthesiology*. 1981; 55: 369-375.

Fentanyl Metabolism

- Fentanyl is metabolized by the Cytochrome P450 system primarily to Norfentanyl which has minimal to no intrinsic activity.
- As yet, with the number of fentanyl analogs most of which follow the same pathway, it is still not known whether active metabolites exist.
- Because of the CYP 3A4 system involvement, coadministration of inhibitors such as macrolides or protease inhibitors may prolong fentanyl activity.
- Caution: Fentanyl and Norfentanyl are excreted in the urine. In chronic use there are reports of positive results > 230 days after last use.

Miranda K. Kiefer, Jamie Cowen, Katherine A. Hinely, Kara M. Rood,

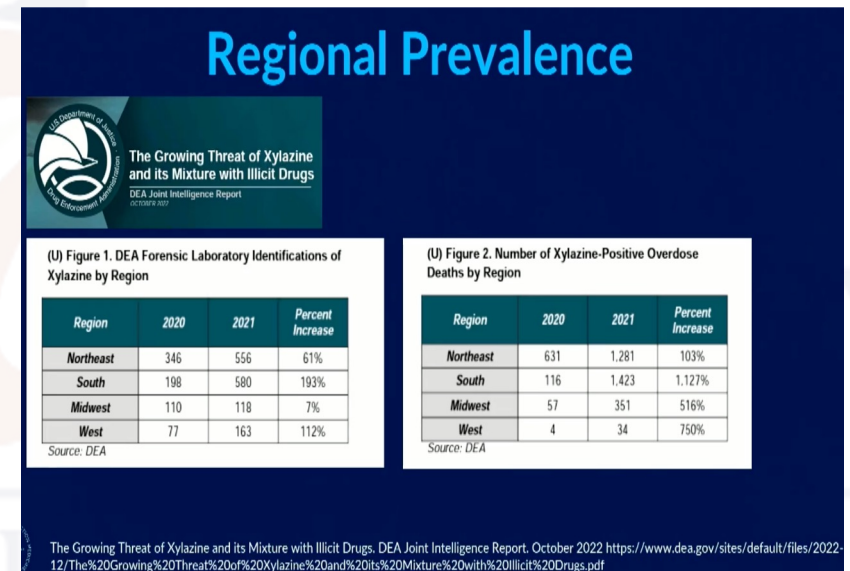
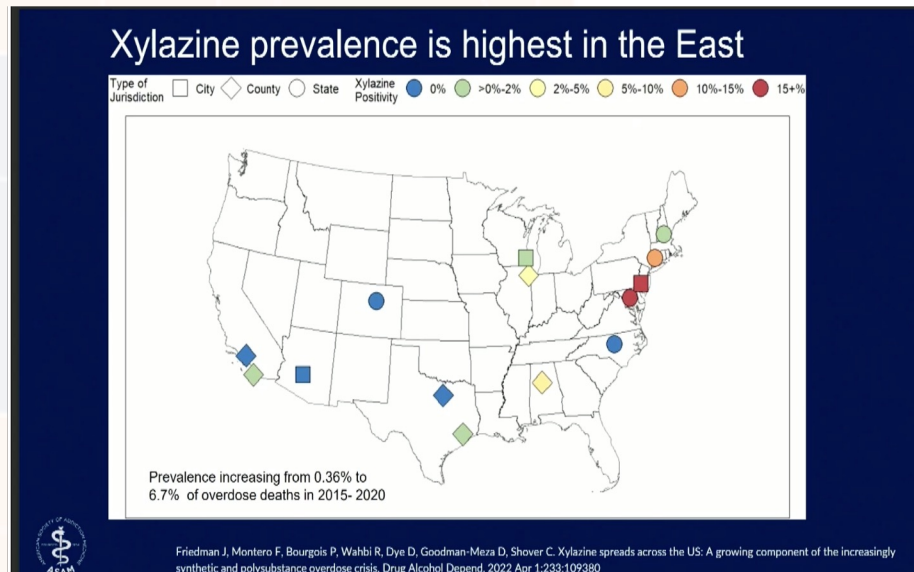
Prolonged detection of urine norfentanyl in individuals enrolled in a medication for opioid use disorder in pregnancy and postpartum program: a case series, AJOG Global Reports, Volume 4, Issue 2, 2024,

What does this mean?

- Challenges to monitoring
- Challenges to overdose management
- Challenges to buprenorphine induction
- Challenges to methadone treatment

We will address these challenges in future presentations!

Additives – Xylazine (Tranq)



Heroin and Fentanyl Updates and Pharmacology

Tranq – What is it?

Xylazine Background

- ◆ Developed in 1962 by Bayer pharmaceuticals as an antihypertensive
 - ◆ Trials in humans stopped due to hypotension and CNS depression
- ◆ FDA approved for veterinary use as a sedative, analgesic, and muscle relaxant
 - ◆ Available in liquid solutions at 20, 100, and 300 mg/mL
 - ◆ Used alone or in combo (e.g. with ketamine, barbiturates)

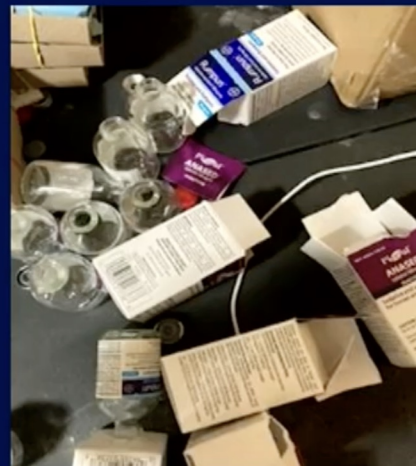


Greene SA, Thurmon JC. Xylazine--a review of its pharmacology and use in veterinary medicine. J Vet Pharmacol Ther. 1988 Dec;11(4):295-313. doi: 10.1111/j.1365-2885.1988.tb00189.x. PMID: 3062194.

Heroin and Fentanyl Updates and Pharmacology

Xylazine Adulteration

- ◆ Found in combo with xylazine in bags of heroin/fentanyl
- ◆ Pharmaceutical grade adulteration of heroin/fentanyl supply
 - ◆ Added locally
 - ◆ Salting of liquid
- ◆ Powder xylazine from China supply



Source: Drug Enforcement Administration Philadelphia Division



USA Xylazine

WhatsApp: 800018145728414

100% Pass Customs

USA Market, 99% Pure White Crystal
Xylazine/Xylazina/Xylazin/ Zylazine/ Zylazina/ Xilazine/ Xil...
US\$ 540-720 / kg (FOB Price)
1 kg (MOQ)
CAS No.: 23076-35-0 Formula: C12h17cin2s
EINECS: 245-417-0 Type: Pharmaceutical Inter... [More ▾](#)

Guangzhou Teng yue Chemical Co., Ltd. [♥](#) [🌐](#) [📱](#)

[Contact Now](#) [🔍](#) [🔄](#)



Xylazine

99% pure
MOQ 1kg

USA market

100% no customs issues

2c22, 3, 4

USA Market USP Bp 99% Purity **Xylazine/Zylazine HCl**
Powder Security Clearance
US\$ 630-750 / kg (FOB Price)
1 kg (MOQ)
CAS No.: 23076-35-9 Formula: C12h17cin2s
EINECS: 245-417-0 Type: Pharmaceutical Inter... [More ▾](#)

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Heroin and Fentanyl Updates and Pharmacology

Why use Xylazine with Fentanyl?

The “high” from fentanyl lasts for a very short time compared to the effects of heroin and other opioids. Xylazine may be added, at least in part, to extend the effects of fentanyl.

Patterns of Xylazine Use

Intentionally Seek Out to Buy Drugs That Contain Xylazine (n = 61)		Drug Use on a Typical Day (n = 60)		Method of Xylazine Exposure (n = 61)		Frequency of Xylazine Use (n = 61)	
Yes	26%	Any opioids	93%	Inhalational (smoking)	20%	Daily	39%
No	74%	Fentanyl	80%	Intranasal (snorting)	57%	1–6 times per week	19%
		Cannabis	45%	Injection	43%	1–4 times per month	15%
		Stimulants	41%	Oral	3%	A few times per year/rarely	27%
		Benzodiazepines	21%				
		Hallucinogens	10%				
Experiences With Xylazine Adverse Effects From Xylazine Use (n = 48)		Have You Experienced Withdrawal From Xylazine? (n = 59)		What Xylazine Withdrawal Symptoms Have You Experienced? (n = 35)		How Has Withdrawing From Other Drugs Changed Since You Started Using Xylazine? (n = 51)	
Increased overdoses/passing out	81%	Yes	53%	Body aches	63%	Worse	57%
Skin wounds or infections	43%	No	47%	Cravings	49%	The same	39%
Increased emergency room visits	17%			Anxiety	91%	Better	4%
				Depressed Mood	74%		

Spadaro, Anthony MD, MPH; O'Connor, Karen MS; Lakamana, Sahithi MS; Sarker, Abeed PhD; Wightman, Rachel MD; Love, Jennifer S. MD; Perrone, Jeanmarie MD. Self-reported Xylazine Experiences: A Mixed-methods Study of Reddit Subscribers. Journal of Addiction Medicine 17(6):p 691-694, 11/12 2023.

Heroin and Fentanyl Updates and Pharmacology

Xylazine Wounds

Early Stage



Xylazine wounds

Xylazine Associated Wounds

Late Stage



Heroin and Fentanyl Updates and Pharmacology