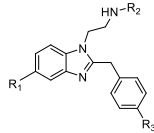
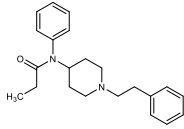


## What are “He-Man” and “Frankenstein” doing in Ohio?



Jon E. Sprague, RPh, PhD  
Director of Science & Research for the Ohio Attorney General  
BCI Eminent Scholar  
Bowling Green State University

## Objectives

- Describe current supply chain information
- Discuss current drug trends in Ohio
- Describe the chemical modifications made to IMFs and nitazenes
- Discuss dangerous counterfeit prescription tablets

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## U.S. Drug Overdose Deaths

- CDC estimates 107,543 drug overdose deaths in 2023
- 74,702 from Illicitly Manufactured Fentanyls (IMFs)
- Estimated annual economic cost to the U.S. is \$1 trillion

Sources: US Commission on Combating Synthetic Opioid Trafficking Report, 2022  
Centers for Disease Control and Prevention

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## Current supply chain information

- The Mexican cartels is the principal source of illicit fentanyl
- Precursor chemicals are sourced largely from the People's Republic of China (PRC)
- traffickers conceal hard-to-detect quantities in packages, in vehicles, and on persons and smuggle the drug across the U.S.–Mexico border



Credit: Peniley Ramirez / Univision

Sources: US Commission on Combating Synthetic Opioid Trafficking Report, 2022

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## The Four Waves of the Opioid Epidemic

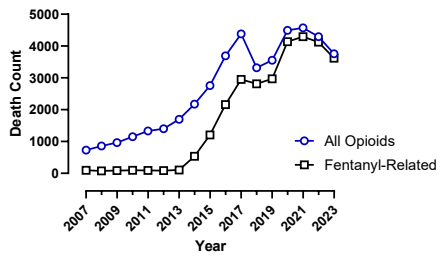
Drug	Time Period of Increasing Presence in Drug Poisoning Deaths in Ohio	Key Points
<b>Wave 1:</b> Prescription Opioids	2000–2014	Opioid prescriptions to treat pain become more common in the late 1990s leading to an increase in pharmaceutical opioid abuse and opioid-related drug poisoning deaths in the early 2000s.
<b>Wave 2:</b> Heroin	2009–2016	Access to prescription opioids is restricted. Those with opioid dependencies increasingly turn to heroin as a substitute.
<b>Wave 3:</b> Fentanyl	2014–2021	Drug trafficking organizations produce synthetic opioids (mainly fentanyl) as a more profitable and potent alternative to heroin.
<b>Wave 4:</b> Other Synthetic Drugs & Polydrug Mixtures Involving Fentanyl	2015–2022	Drug traffickers at all levels of the illicit drug supply chain combine plant-based drugs like cocaine or heroin with synthetic drugs like fentanyl and methamphetamine to create potent polydrug mixtures.

## Ohio Opioid Overdose Death Data

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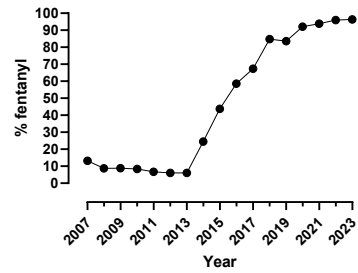
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Ohio Opioid Deaths: All Opioids vs Fentanyl-Related Compounds



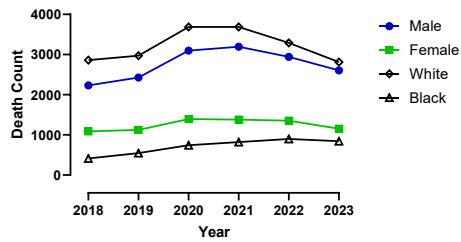
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Ohio Opioid Deaths: % Fentanyl-Related Compounds



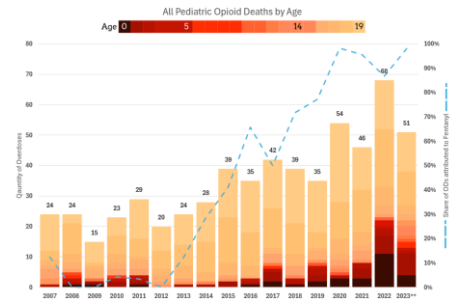
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Ohio Opioid Deaths: Demographic Data



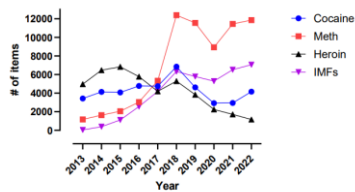
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Ohio pediatric opioid overdose numbers 2007–2023



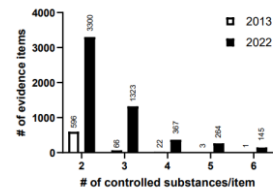
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Drug seizure trends



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Polydrug trends



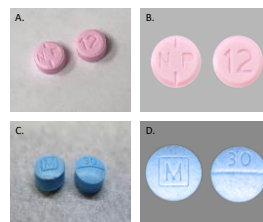
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### Polydrug components 2013 compared to 2022

Drug	2013 # of items (% of total)	2022 # of items (% of total)	Fold Change
Cocaine	275 (39.9%) <sup>a</sup>	1167 (20.7%)	4.24
Heroin	274 (39.8%)	1186 (21.1%)	4.33
Methamphetamine	122 (17.7%)	1151 (20.4%)	9.43
Steroids	77 (11.2%)	11 (0.2%)	0.14
Other stimulants	59 (8.6%)	11 (0.2%)	0.19
Synthetic cannabinoids	49 (7.1%)	29 (0.5%)	0.59
IMFs	15 (2.2%)	5029 (89.3%)	335.27
Benzodiazepines	30 (4.4%)	511 (9.1%)	17.03
Total Submissions	688	5,633	8.19

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### Dangerous Counterfeit Prescription Tablets



Pictures of authentic oxycodone tablets were pulled from Drugs.com <sup>14</sup>

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### Fentanyl pharmacology

- Main pharmacological effects through binding to  $\mu$ -opioid receptor (MOR)
- MOR- G protein coupled receptor (Gi coupled)-uses a secondary messenger system
- Fentanyl acts as an agonist-binds to a receptor and causes a response

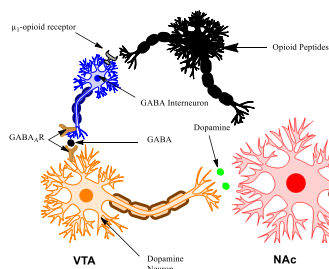
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### Fentanyl effects

- Analgesia
- Anesthesia
- Drowsiness
- Respiratory Depression
- Euphoria
- Nausea, vomiting, constipation
- Hypothermia

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### Fentanyl: Pharmacology



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### The Pharmacophore Rule

The Pharmacophore Rule was written so chemists would be able to identify the basic structural elements required for a compound to bind to their drug targets.

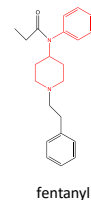
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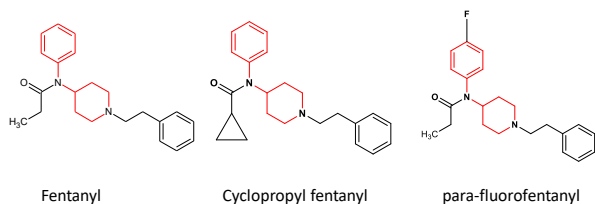
## What is a pharmacophore?

- the portion of drug molecule required for pharmacological activity



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## Example Fentanyl Pharmacophores

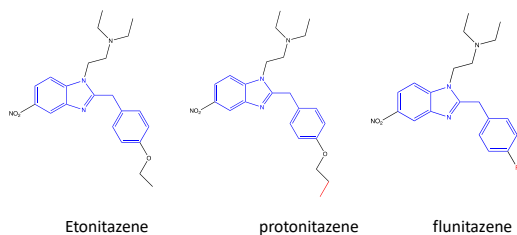


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	Fentanyl	Parafluoro fentanyl	Acetyl fentanyl	Valeryl fentanyl	Butyryl fentanyl	Formyl fentanyl	Parafluoroisobutyl fentanyl	Cis-3-methyl fentanyl
LogP	3.79	3.96	3.62	4.86	4.35	4.55	5.38	4.27
RotB	6	6	5	8	7	6	6	6
Ki	1.6	4.2	64	N/A	3.5	1.3	82	0.32
PNA	23.55	23.55	23.55	23.55	23.55	36.69	23.55	23.55
MW	336.48	354.47	322.45	364.53	350.51	374.48	384.95	350.51

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## The “Frankenstein Opioids”



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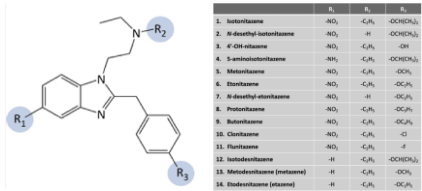
## Nitazene

- First synthesized in the 1950's and 1960's by the Swiss pharmaceutical company CIBA
- Antinociceptive potency 1000-fold greater than that of morphine
- Potency of the nitazenes ranges from 20 to 50 times more potent than fentanyl
- 2000 Americans are estimated to have died from nitazenes.
- Nitazenes have been identified in at least 4300 law enforcement drug seizures in the USA since 2019

Vandeputte et al., 2021  
Samarasekera, 2024

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The “Nitazenes”



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Toxicology: The Narcotic Triad

- Coma
- Respiratory depression
- Miosis (pin-point pupils)

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Tolerance

Tolerance seen to:  
analgesia  
euphoria  
respiratory depressant effects

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Tolerance

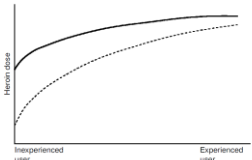


Figure 2. Hypothetical model of tolerance to intoxicating and lethal effects of opioids following repeated administrations. The doses required to produce the respective effects increase with experience, but at different rates. Adapted from Smith et al. (1950)

Addiction 1999; 94(7):961-972.

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Dopesick

Symptoms of administering opioids and of withdrawing opioids	
Administering	Withdrawing
Lowered body temperature	Elevated body temperature
Decreased blood pressure	Increased blood pressure
Skin flushed and warm	Piloerection (gooseflesh)
Pupillary constriction	Tearing, runny nose
Constipation	Diarrhea
Respiratory depression	Yawning, panting, sneezing
Decreased sex drive	Spontaneous ejaculations and orgasms
Muscular relaxation	Restlessness, involuntary twitching and kicking movements
Nodding, stupor	Insomnia
Analgesia	Pain and irritability
Euphoria and calm	Depression and anxiety

\*Probably the source of the expression, "Kicking the habit."  
SOURCE: Adapted from Grilly, David M. (1989). Drugs and human behavior. Boston: Allyn and Bacon, p. 207.

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## Assessment of Opioid Withdrawal

### Clinical Opioid Withdrawal Scale (COWS)

- Can be used inpatient or outpatient

- Scoring

- Mild: 5-12
- Moderate: 13-24
- Moderately severe: 25-36
- Severe: 36+

**Note:** Opioid withdrawal itself is not fatal. However, in rare cases, it is possible for a patient to die from medical complications related to opioid withdrawal

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## COWS Criteria

Resting heart rate: <i>beats per minute</i>	0-4
Sweating: <i>Over past ½ hour not accounted for by room temperature or patient activity</i>	0-4
Restlessness observation during assessment	0-5
Pupil Size	0-5
Bone or joint aches: <i>if patient was having pain previously, only the additional component attributed to opiate withdrawal is scored</i>	0-4
Runny nose or tearing: <i>not accounted for by cold symptoms or allergies</i>	0-4
GI Upset: <i>over last ½ hour</i>	0-5
Tremor observation of outstretched hands	0-4
Yawning observation during assessment	0-4
Anxiety or irritability	0-4
Gooseflesh skin	0-5

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