



Novel Psychoactive Substances

-Kelly L. Olson, PhD

Objectives

- Describe landscape of ongoing development of novel psychoactive substances (NPS)
- Identify pharmacology and known physiologic effects
- Discuss urine drug testing implications

Background:

Novel Psychoactive Substances (NPS)

- Some originated from pharmaceutical research; rapidly evolving compounds^{1,2}
- Some synthesized due to shortages of other illegal drugs²
- Over a thousand individual compounds identified by the United Nations³
- Most imported from China⁴
- Available via internet, social media, specialty shops, and on the street⁴

1. Spaderna M, Addy PH, D'Souza DC. Spicing things up: synthetic cannabinoids. *Psychopharmacology*. 2013;228(4):525-40

2. Capriola M. Synthetic cathinone abuse. *Clin pharmacol*. 2013;5:109-115

3. United Nations Office on Drugs and Crime. UNODC Early Warning Advisory on New Psychoactive Substances. <https://www.unodc.org/LSS/Page/NPS>. Accessed July 2022.

4. US Drug Enforcement Agency. 2020 National Drug Threat Assessment. https://www.dea.gov/sites/default/files/2021-02/DIR-008-21%202020%20National%20Drug%20Threat%20Assessment_WEB.pdf. Accessed July 2022.

Categories of NPS

Benzodiazepines

Opioids

Synthetic
Cannabinoids

Synthetic
Cathinones

Plant-based
substances

Others

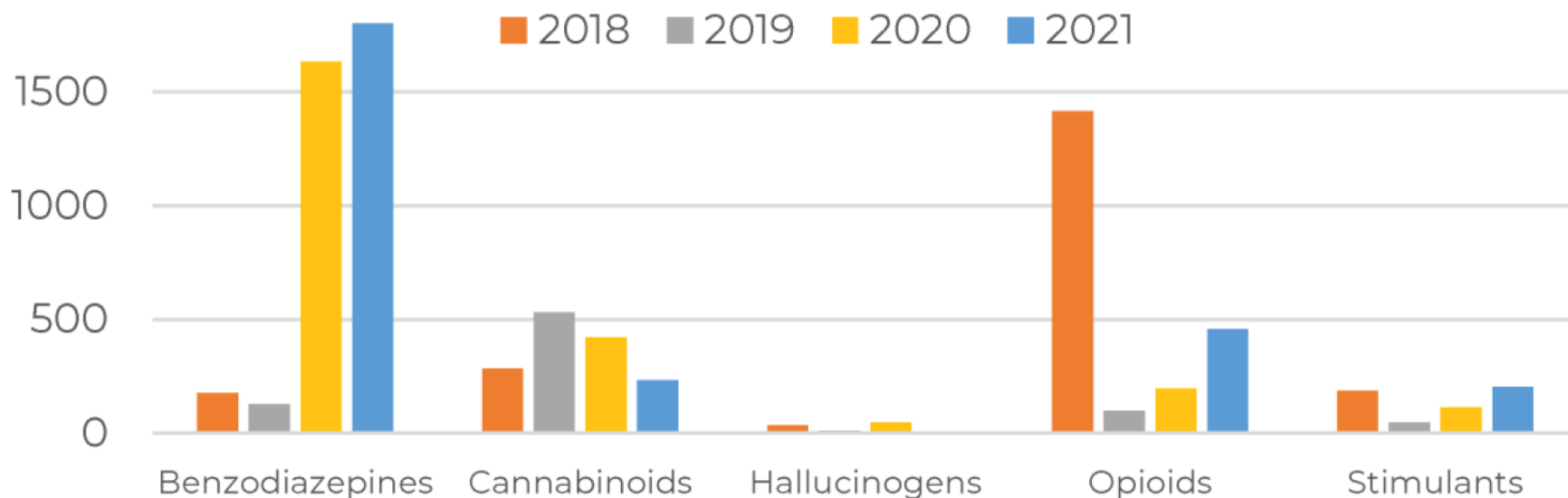
Many cause significant or life-threatening effects

Rosenbaum CD, Carreiro SP. Here Today, Gone tomorrow...and Back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), kratom, Salvia divinorum, methoxetamine, and piperazines. *J Med Toxicol.* 2012;8:15-32.

Center for Forensic Science Research and Education (CSFRE): 2021 Year in Review



NPS detections: All samples analyzed since 2018



As of 2022, “designer” illicit benzodiazepines are the most commonly identified NPS

Background (cont.)

Users may be:

- Experimenting
- Seeking options that are easily available
- Seeking options that are less expensive
- Looking to evade detection
- Believe safer/natural

1. Simon LH, Simon HLT. Clinical toxicology of newer recreational drugs. *Clin Toxicology*. 2011;49:705-719.
2. Center for Forensic Science and Research (CFSRE). NPS Benzodiazepines in the United States. Trend Report: Q2 2022. Available https://www.npsdiscovery.org/wp-content/uploads/2022/07/2022-Q2_CFSRE-NPS-Discovery-Trend-Reports.pdf. Accessed July 2022
3. Center for Forensic Science and Research (CFSRE). Year in Review 2021. https://www.npsdiscovery.org/wp-content/uploads/2022/01/2021_Year-In-Review_NPS-Discovery_123121.pdf. Accessed July 2022.

NPS Benzodiazepines



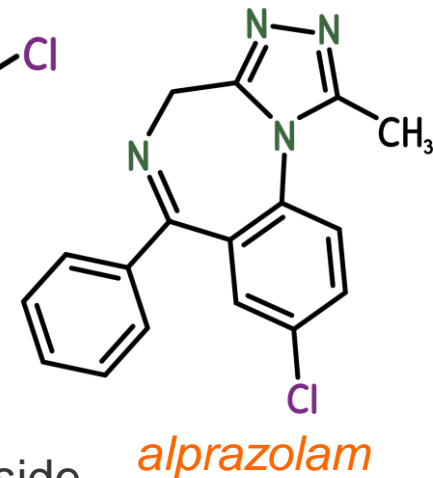
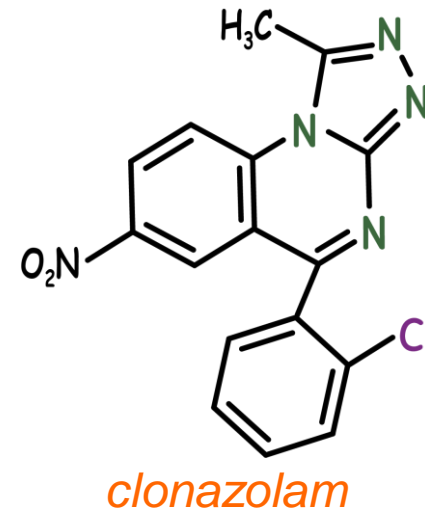
Illicit “Designer” Benzodiazepines

- The most commonly identified NPS in 2022
- Some (e.g., etizolam) have been approved for use in other countries
- Not approved for use in the United States
- Involved in fatal and non-fatal overdoses
 - In combination with opioids and other benzodiazepines
- Sold online or in retail shops, labeled “research chemicals”
- In powder, tablet, and liquid form
 - Can be sold as counterfeit prescription benzodiazepines

1. Center for Forensic Science and Research (CFSRE). NPS Opioids in the United States. Trend Report: Q2 2022. Available at: https://www.npsdiscovery.org/wp-content/uploads/2022/07/2022-Q2_CFSRE-NPS-Discovery-Trend-Reports.pdf. Accessed June 2022.
2. Manchester KR, Lomas EC, Waters L, et al. The emergence of new psychoactive substance (NPS) benzodiazepines: A review. *Drug Test Anal.* 2018;10(2):392-393.
3. US Drug Enforcement Administration. Etizolam Fact Sheet. Published March 2020. Available at: https://www.deadiversion.usdoj.gov/drug_chem_info/etizolam.pdf.
4. US Drug Enforcement Administration. Flubromazolam Fact Sheet. Published August 2019. Available at: https://www.deadiversion.usdoj.gov/drug_chem_info/flubromazolam.pdf. US Drug Enforcement Administration. Flualprazolam Fact Sheet. Published June 2020. Available at: https://www.deadiversion.usdoj.gov/drug_chem_info/flualp.pdf.
5. World Health Organization. Critical review report: Clonazolam. Expert Committee on Drug Dependence. Forty-third meeting. October 2020. Available at: https://www.who.int/docs/default-source/controlled-substances/43rd-ecdd/final-clonazolam-a.pdf?sfvrsn=b8b10967_4. Accessed May 2022.
6. Brunetti P, Giorgetti R, Tagliabracci A, et al. Designer Benzodiazepines: A Review of Toxicology and Public Health Risks. *Pharmaceuticals (Basel)*. 2021;14(6):560.

Mechanism of Action & Effects

- *In vitro*, GABA_A agonists
- Same MOA as prescription benzodiazepines
- Effects:
 - Anxiolytic
 - Central nervous system depression
 - Potential for euphoria, physical dependence and addiction
 - Synergistic CNS depression with opioids
 - Vary in chemical structure, half-life, duration of action
 - Some (e.g., flubromazolam) reported to have unexpected side effects including prolonged, severe intoxication associated with coma and rhabdomyolysis



1. Manchester KR, Lomas EC, Waters L, et al. The emergence of new psychoactive substance (NPS) benzodiazepines: A review. *Drug Test Anal.* 2018;10(2):392-393.
2. Brunetti P, Giorgetti R, Tagliabracci A, et al. Designer Benzodiazepines: A Review of Toxicology and Public Health Risks. *Pharmaceuticals (Basel).* 2021;14(6):560.
3. US Drug Enforcement Administration. Flubromazolam Fact Sheet. Published August 2019. Available at: https://www.deadiversion.usdoj.gov/drug_chem_info/flubromazolam.pdf. Accessed May 2022.

Illicit Benzodiazepines: Drug Test Implications

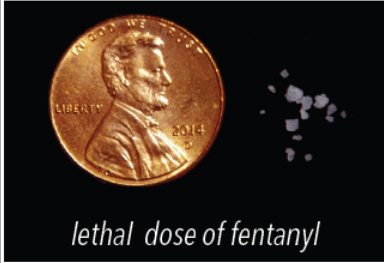
- Numerous compounds; use of specific drugs is constantly evolving
- Immunoassays may have cross-reactivity with certain drugs
 - Not well-characterized in the literature
- Definitive testing necessary to effectively identify use
- Laboratories must continually reassess compounds being used and detected

1. Manchester KR, Lomas EC, Waters L, et al. The emergence of new psychoactive substance (NPS) benzodiazepines: A review. *Drug Test Anal.* 2018;10(2):392-393.
2. World Health Organization. Critical review report: Clonazolam. Expert Committee on Drug Dependence. Forty-third meeting. October 2020. Available at: https://www.who.int/docs/default-source/controlled-substances/43rd-ecdd/final-clonazolam-a.pdf?sfvrsn=b8b10967_4. Accessed August 2022.

Novel Psychoactive Substances (NPS) LC-MS/MS Test Offerings

Novel psychoactive substances (NPS) are illicit drugs designed to mimic effects of other illicit drugs, often with the purpose of evading law enforcement. They are not typically detected by presumptive, immunoassay point-of-care or desktop analyzer drug tests.¹

Millennium Health offers comprehensive detection of the most relevant and emerging novel psychoactive substances based on extensive research and analysis.

Drug Category	Description	Millennium Health Test Offerings
<p>Fentanyl & Analogues²</p> 	<ul style="list-style-type: none"> Over 70% of drug overdose deaths involve a synthetic opioid, with majority involving illicit fentanyl 	<ul style="list-style-type: none"> Fentanyl Norfentanyl 4-ANPP Acetyl fentanyl Acetyl norfentanyl Acrylfentanyl Carfentanil Para-fluorofentanyl
<p>Illicit Novel Benzodiazepines (aka "designer benzodiazepines")³⁻⁸</p>	<ul style="list-style-type: none"> Similar effects on the body as prescription benzodiazepines Not approved for medical use in the United States Involved in cases of fatal and non-fatal overdoses 	<ul style="list-style-type: none"> Clonazolam (tested as 8-aminoclonazolam) Etizolam Alpha-hydroxyetizolam Flualprazolam Flubromazolam
<p>Illicit Novel Opioids (aka "synthetic opioids")⁹⁻¹³</p>	<ul style="list-style-type: none"> Similar effects on the body as other opioids Not approved for medical use in the United States Involved in cases of fatal and non-fatal overdoses 	<ul style="list-style-type: none"> 2-methyl-AP-237 Brorphine Metonitazene

NPS Opioids



Illicit Synthetic Opioids

- Often synthesized using early research
 - Discontinued development due to adverse effects
- Structurally distinct from fentanyl analogues (FAs)
 - Note that FAs are a subcategory of synthetic opioids and sometimes grouped together under DEA and CSFRE reports
- Involved in fatal and non-fatal overdoses
 - Often in combination with other drugs
- Sold online or by dealers under opioid's actual name or as other drugs
- May be in powder form or pressed into tablets and sold as counterfeit prescription opioids

1. Vandeputte MM, Krotulski AJ, Papsun DM, et al. The Rise and Fall of Isotonitazene and Borphine: Two Recent Stars in the Synthetic Opioid Firmament. *J Anal Toxicol.* 2021;bkab082.
2. United Nations Office on Drugs and Crime. The Growing Complexity of the Opioid Crisis. *Global Smart Update.* 2020; 24. Available at: https://www.unodc.org/documents/scientific/Global_SMART-2020-Vol_24_web.pdf. Accessed July 2022.
3. US Drug Enforcement Administration. Benzimidazole-Opioids Fact Sheet. Published June 2021. Available at: https://www.deadiversion.usdoj.gov/drug_chem_info/benzimidazole-opioids.pdf. Accessed April 2022.
4. US Drug Enforcement Administration. 2-Methyl-AP-237 Fact Sheet. Published June 2021. Available at: https://www.deadiversion.usdoj.gov/drug_chem_info/2-Methyl-AP-237.pdf. Accessed April 2022.
5. US Drug Enforcement Administration. Borphine Fact Sheet. Published July 2021. Available at: https://www.deadiversion.usdoj.gov/drug_chem_info/borphine.pdf. Accessed April 2022.

Mechanism of Action & Effects

- In vitro, central nervous system depressants which bind to opioid receptors
- Effects
 - Reduced perception of pain (analgesia)
 - Drowsiness, mental confusion, nausea, constipation, slowed breathing
 - Potential for euphoria, dependence and/or addiction



1. United Nations Office on Drugs and Crime. The Growing Complexity of the Opioid Crisis. Global Smart Update. 2020; 24. Available at: https://www.unodc.org/documents/scientific/Global_SMART-2020-Vol_24_web.pdf. Accessed April 2022.
2. Ujváry I, Christie R, Evans-Brown M, et al. DARK Classics in Chemical Neuroscience: Etonitazene and Related Benzimidazoles. ACS Chem Neurosci. 2021;12(7):1072-1092.

Fentanyl and Fentanyl Analogues



Credit: Bruce A. Taylor, NH State Police Forensic Lab



Photographs used with authors' permission

- Fentanyl: 50-100 times more potent than morphine
 - Street Names: Apache, China White, Dance Fever, Goodfella, Jackpot, Murder 8, TNT, and Tango and CashChina
- Fentanyl Analogues (e.g., carfentanil, acetyl fentanyl, para-fluorofentanyl)
 - Para-fluorofentanyl: 3 times less potent than fentanyl
 - Carfentanil: up to 1,000 times more potent than fentanyl

1. 2017 National Drug Threat Assessment Summary. U.S. Department of Justice Drug Enforcement Administration. https://www.dea.gov/sites/default/files/2018-07/DIR-040-17_2017-NDTA.pdf. Published October 2017. Accessed September 30, 2020.
2. Fentanyl. National Institute on Drug Abuse Website. <https://www.drugabuse.gov/drugs-abuse/fentanyl>. Accessed September 30, 2020.
3. NPS Discovery. Examining the Evidence on Fluorofentanyl Power Point Presentation for SOFT Annual Meeting. Published October 2021. [PowerPoint Presentation \(npsdiscovery.org\) Accessed November 3, 2021.](#)

Illicit Synthetic Opioids: Drug Test Implications

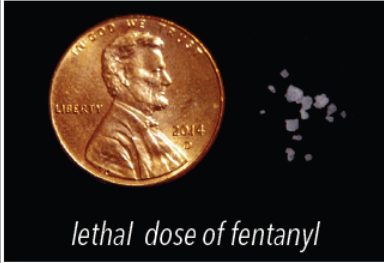
- Numerous compounds; use of specific drugs is constantly evolving
- Typically not detected by immunoassay (POC or lab)
- Fentanyl analogues may have cross-reactivity with laboratory fentanyl immunoassays
 - Not well-characterized in the literature
 - No CLIA-waived fentanyl POC immunoassay strips
- Definitive testing necessary to effectively identify use
- Laboratories must continually reassess compounds being used and detected

1. United Nations Office on Drugs and Crime. The Growing Complexity of the Opioid Crisis. Global Smart Update. 2020; 24. Available at: https://www.unodc.org/documents/scientific/Global_SMART-2020-Vol_24_web.pdf. Accessed April 2022.
2. Armenian P, Vo KT, Barr-Walker J, et al. Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review. *Neuropharmacology*. 2018 May 15;134(Pt A):121-132.

Novel Psychoactive Substances (NPS) LC-MS/MS Test Offerings

Novel psychoactive substances (NPS) are illicit drugs designed to mimic effects of other illicit drugs, often with the purpose of evading law enforcement. They are not typically detected by presumptive, immunoassay point-of-care or desktop analyzer drug tests.¹

Millennium Health offers comprehensive detection of the most relevant and emerging novel psychoactive substances based on extensive research and analysis.

Drug Category	Description	Millennium Health Test Offerings
<p>Fentanyl & Analogues²</p> 	<ul style="list-style-type: none"> Over 70% of drug overdose deaths involve a synthetic opioid, with majority involving illicit fentanyl 	<ul style="list-style-type: none"> Fentanyl Norfentanyl 4-ANPP Acetyl fentanyl Acetyl norfentanyl Acrylfentanyl Carfentanil Para-fluorofentanyl
<p>Illicit Novel Benzodiazepines (aka "designer benzodiazepines")³⁻⁸</p>	<ul style="list-style-type: none"> Similar effects on the body as prescription benzodiazepines Not approved for medical use in the United States Involved in cases of fatal and non-fatal overdoses 	<ul style="list-style-type: none"> Clonazolam (tested as 8-aminoclonazolam) Etizolam Alpha-hydroxyetizolam Flualprazolam Flubromazolam
<p>Illicit Novel Opioids (aka "synthetic opioids")⁹⁻¹³</p>	<ul style="list-style-type: none"> Similar effects on the body as other opioids Not approved for medical use in the United States Involved in cases of fatal and non-fatal overdoses 	<ul style="list-style-type: none"> 2-methyl-AP-237 Brorphine Metonitazene

Medical Necessity

Criteria to establish medical necessity must be based on patient-specific elements identified during the clinical assessment and documented in the patient's medical record by the provider.

Documenting Medical Necessity

- Orders must be individualized
- Tests ordered and reasons for testing must be documented in the patient's medical record
- Risk assessment and stage of treatment should match testing frequency

Documenting How the Test Results Were Used

- Review of results and use in the treatment plan



Other Trends

Gabapentinoids¹

- Gabapentin (Neurontin[®]) and pregabalin (Lyrica[®])
- Euphoric potential, particularly when combined with other drugs

Loperamide (Imodium[®])²

- Over-the-counter anti-diarrheal; mu-opioid agonist
- Alleviates opioid withdrawal and causes euphoria at high doses
 - May cause cardiac dysrhythmias

Bupropion (Wellbutrin[®])^{3,4}

- Aminoketone antidepressant affecting norepinephrine & dopamine
 - Produces stimulant-like effects at high doses

Dextromethorphan⁵

- Over-the-counter anti-tussive
- Produces dissociative state, hallucinogenic effects

1. Throckmorton DC, Gottlieb S, Woodcock J. The FDA and the Next Wave of Drug Abuse— Proactive Pharmacovigilance. *NEJM*. 2018 May 30.
2. Loperamide [package insert]. <https://www.rxlist.com/imodium-drug.htm>. Accessed June 27, 2018.
3. Bupropion [package insert]. <https://www.rxlist.com/wellbutrin-drug.htm>. Accessed June 27, 2018.
4. Evans EA, Sullivan MA. Abuse and misuse of antidepressants. *Subst Abuse Rehabil*. 2014; 5:107-20.
5. National Institute on Drug Abuse. Commonly Abused Drugs Charts. Available at: <https://www.drugabuse.gov/drugs-abuse/commonly-abused-drugs-charts#Dextromethorphan>. Accessed July 2018.