Clinical Update: March 2024

DETECTION OF NPS IN BUPRENORPHINE SAMPLES

Aegis recently conducted a retrospective analysis of patient samples from individuals who were prescribed buprenorphine to ascertain how frequently novel psychoactive substances (NPS) were detected. Novel Psychoactive Substances (NPS) are a diverse group of synthetic substances created to mimic the effects of scheduled or illicit drugs; however, they may vary widely in both toxicity and potency from the drugs they are intended to mimic. Buprenorphine is commonly prescribed to individuals with opioid use disorder to initiate medically supervised opioid withdrawal. It is also prescribed to those with chronic pain in some instances.

In 2023, Aegis detected buprenorphine in 252,835 samples where buprenorphine was indicated as prescribed to the donor for treatment of opioid use disorder or chronic pain. Of these samples, 803 were highly suspicious of being adulterated samples based on the ratio of buprenorphine to its metabolite, norbuprenorphine therefore, these samples were excluded from further analysis. Of the remaining 252,032 samples, 4,818 (1.9%) contained at least one NPS. Aegis offers clinicians the ability to order NPS testing for opioids, benzodiazepines, cannabinoids, stimulants, hallucinogens, dissociatives, and other substances based on their medical judgement. As such, the 252,032 samples were not uniformly tested for all NPS classes. This likely results in an underrepresentation of actual NPS use by the patients in this study.

Bup Prescribed and included in NPS analysis	**252,032**	**%**
Any NPS*	**4,818**	**1.912**
Designer Opioid	**1,604**	**0.636**
Designer Benzodiazepine	**1,599**	**0.634**
Synthetic Stimulant	**284**	**0.113**
Synthetic Cannabinoid	**238**	**0.094**
Hallucinogen/Dissociative	**9**	**0.004**
Misc. NPS		
Xylazine	**1,653**	**0.656**
Phenibut	**302**	**0.120**
Tianeptine	**175**	**0.069**
Medetomidine	**11**	**0.004**

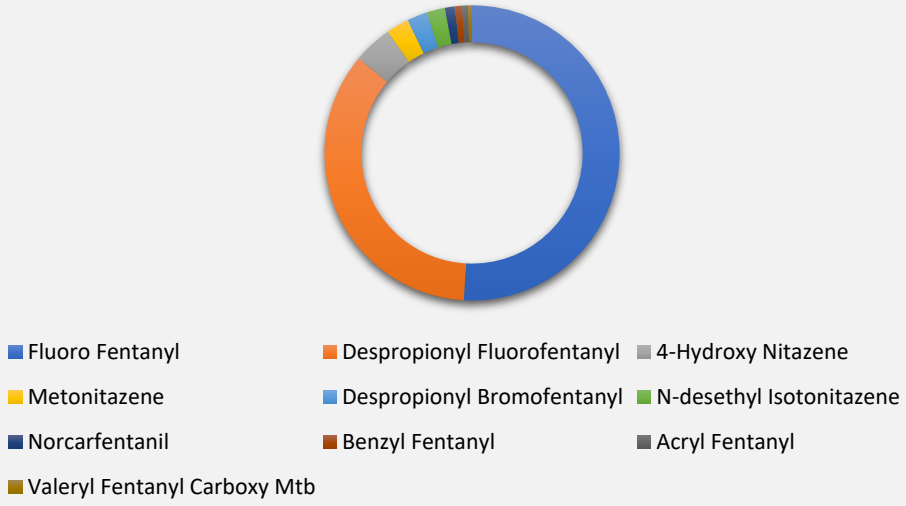
*All samples were not tested for every NPS class. Some samples contained more than one NPS class.

Designer Opioids

Designer opioids are sometimes referred to as fentanyl analogs (fentalogs) however, other non-fentalogs are increasingly detected in Aegis' testing. In this study, a designer opioid was detected in 1,604 samples and 8 of the 20 designer opioid analytes detected were markers of nitazene analogs, highlighting the increasing prevalence of these compounds. Table 2 contains the list of designer opioids analytes detected from most to least prevalent. Figure 1 illustrates the top 10 designer opioid analytes detected as part of this study. It is important to note that plain, illicitly manufactured fentanyl (IMF) is not included in Aegis' NPS testing.

Table 2. Designer Opioids Detected in Expected Buprenorphine-positive Samples, 2023
Fluoro Fentanyl
Despropionyl Fluorofentanyl
4-Hydroxy Nitazene
Metonitazene
Despropionyl Bromofentanyl
N-desethyl Isotonitazene
Norcarfentanil
Benzyl Fentanyl
Acryl Fentanyl
Valeryl Fentanyl Carboxy Mtb
Despropionyl Chlorofentanyl
N-Pyrrolidino 4-OH Nitazene
Protonitazene
N-desethyl Etonitazene
N-pyrrolidino Etonitazene
N-Pyrrolidino Metonitazene
Fluoroisobutyryl Fentanyl
Valeryl Fentanyl
Bromofentanyl
Dipyanone

Figure 1. Top 10 Designer Opioid Analytes Detected in Expected Buprenorphine-positive Samples, 2023



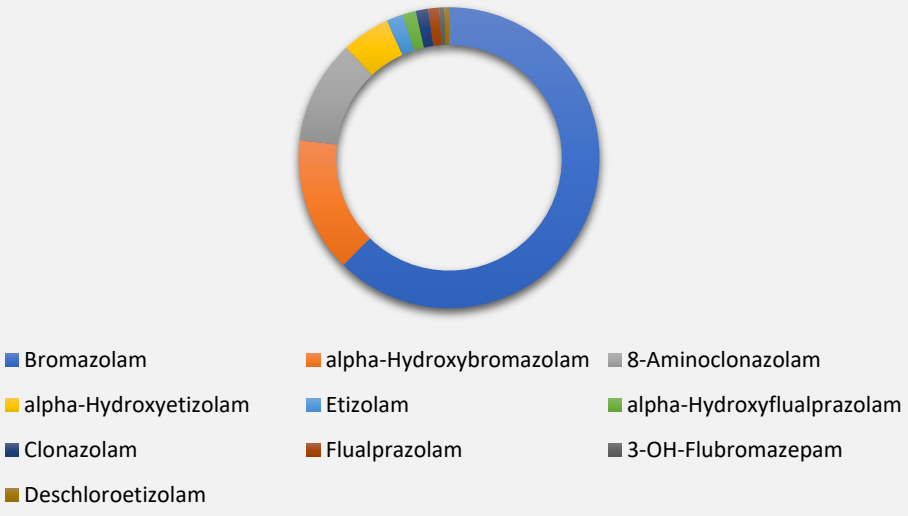
Designer Benzodiazepines

Designer benzodiazepines are often found as counterfeit versions of commonly recognized prescription benzodiazepines, such as alprazolam 2mg "bars" and, in many cases, more than one designer benzodiazepine is present in counterfeit tablets. A designer benzodiazepine was detected in 1,599 samples, with markers of bromazolam, clonazolam, etizolam, flualprazolam and flubromazepam being the top five benzodiazepines detected in this study. Bromazolam has emerged as the most detected designer benzodiazepine over the last 12 months. Table 3 lists the designer benzodiazepines detected in study samples from most to least prevalent, while Figure 2 shows the top 10 analytes.

Table 3. Designer Benzodiazepines Detected in Expected Buprenorphine-positive Samples, 2023
Bromazolam
alpha-Hydroxybromazolam
8-Aminoclonazolam
alpha-Hydroxyetizolam
Etizolam
alpha-Hydroxyflualprazolam

Clonazolam
Flualprazolam
3-OH-Flubromazepam
Deschloroetizolam
Flubromazepam
alpha-Hydroxyflubromazolam
Flubromazolam
Metizolam
Delorazepam
N-desmethyl Adinazolam
4Cl-Deschloroalprazolam
Fluclotizolam

Figure 2. Top 10 Designer Benzodiazepine Analytes Detected in Expected Buprenorphine-positive Samples, 2023

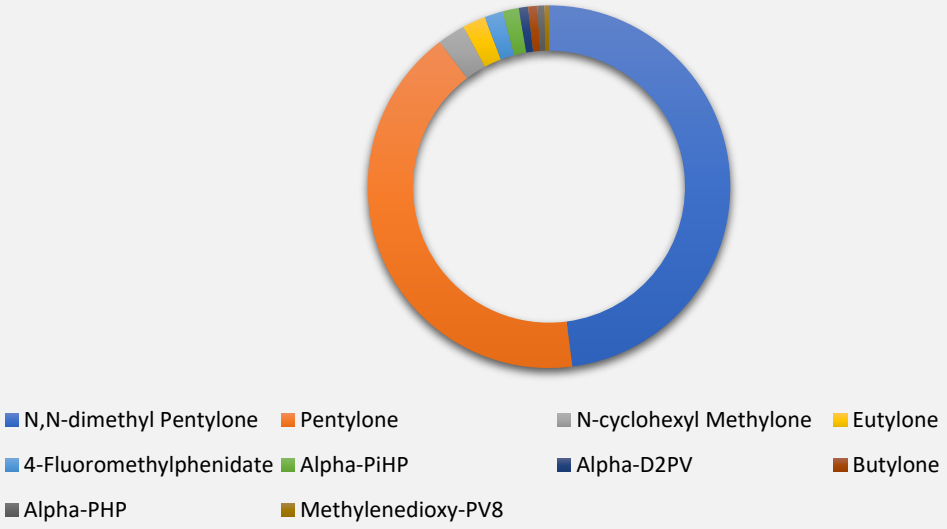


Synthetic Stimulants

A synthetic stimulant was detected in 284 samples. Synthetic stimulants are distributed in a variety of forms, including powders, crystalline formulations, and in pressed tablet forms. They are intended to mimic substances such as methamphetamine, cocaine, or ecstasy. The most widely known substances found in this class are synthetic cathinones, which are sometimes referred to as bath salts. Cathinones represented 12 of 18 stimulant analytes detected in this study, with markers of N,N-dimethyl Pentylone being the dominant analytes. Analogs of methylphenidate, methamphetamine, and piperazine were detected in smaller quantities (Table 4). Figure 3 represents the top 10 stimulant analytes detected.

Table 4. Synthetic Stimulants Detected in Expected Buprenorphine-positive Samples, 2023
N,N-dimethyl Pentylone
Pentylone
N-cyclohexyl Methylone
Eutylone
4-Fluoromethylphenidate
Alpha-PiHP
Alpha-D2PV
Butylone
Alpha-PHP
Methylenedioxy-PV8
N-cyclohexyl Butylone
Alpha-PVP
Chloro-N,N-Dimethylcathinone
MDPHP
TFMPP
2-Fluoromethamphetamine
2-Fluoroamphetamine
3/4-Fluoromethamphetamine

Figure 3. Top 10 Synthetic Stimulant Analytes Detected in Expected Buprenorphine-positive Samples, 2023



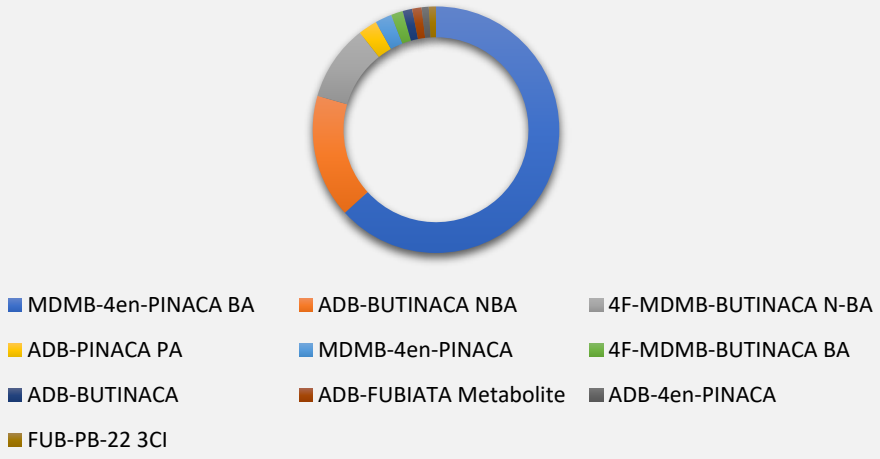
Synthetic Cannabinoids

Synthetic cannabinoids are among the oldest designer drugs in circulation, originally developed during research searching for compounds with medical properties similar to marijuana. Today, they are often used recreationally as alternatives to marijuana. They have been referred to as K2 or spice and are sprayed onto plant material and smoked or used in vaping devices. A synthetic cannabinoid was detected in 238 samples. Table 5 shows the breadth of synthetic cannabinoids detected in this study, with markers of MDMB-4en-PINACA and ADB-BUTINACA accounting for the majority of detections. Figure 4 further illustrates the top 10 analytes detected.

Table 5. Synthetic Cannabinoids Detected in Expected Buprenorphine-positive Samples, 2023
MDMB-4en-PINACA BA
ADB-BUTINACA NBA
4F-MDMB-BUTINACA N-BA
ADB-PINACA PA
MDMB-4en-PINACA
4F-MDMB-BUTINACA BA

ADB-BUTINACA
ADB-FUBIATA Metabolite
ADB-4en-PINACA
FUB-PB-22 3CI
ADB-FUBIATA BA
MDMB-5Br-INACA
5F-MDMB-PICA M7
CH-PIATA
MMB-FUBICA M3
4F-MDMB-BUTICA BA
5F-MDMB-PICA/5F-EMB-PICA

Figure 4. Top 10 Synthetic Cannabinoid Analytes Detected in Expected Buprenorphine-positive Samples, 2023

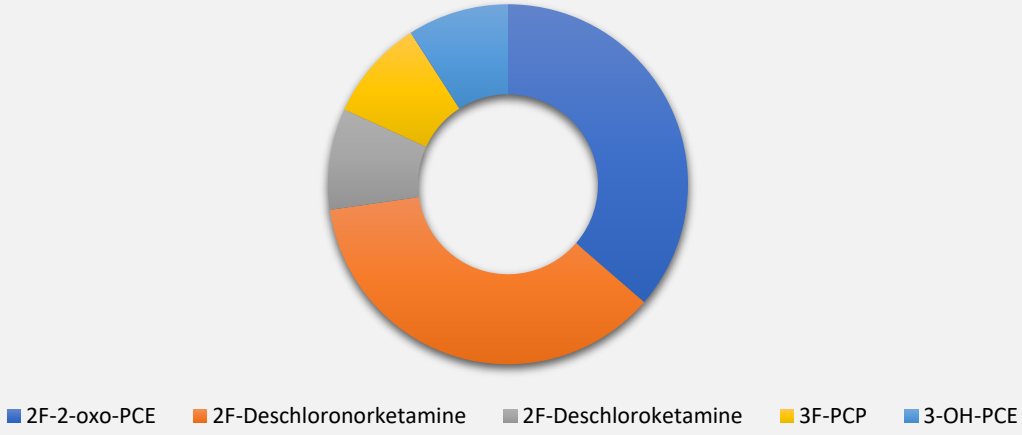


Hallucinogens/Dissociatives

Designer hallucinogens and dissociatives were developed to mimic the effects of PCP, LSD, or ketamine, while remaining legal. While testing orders for these substances is not as frequent as other classes, some of these substances were detected in nine samples. Analogs of PCP and ketamine were detected, as illustrated in Table 6 and Figure 5.

Table 6. Hallucinogens/Dissociatives Detected in Expected Buprenorphine-positive Samples, 2023
2F-2-oxo-PCE
2F-Deschloroketamine
3F-PCP
3-OH-PCE

Figure 5. Hallucinogens/Dissociatives Detected in Expected Buprenorphine-positive Samples, 2023

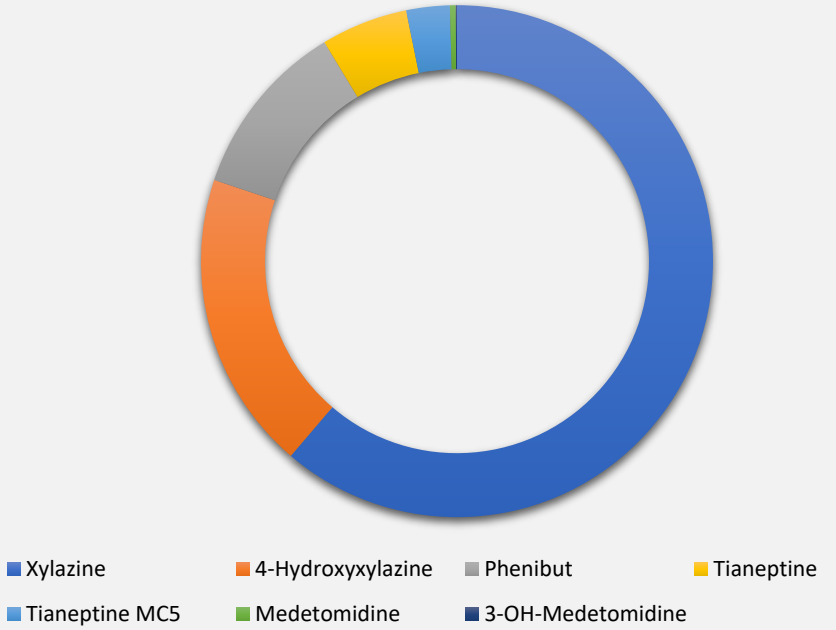


Miscellaneous NPS

Some NPS do not fit neatly into one of the previous classes for various reasons, so they are not included in previously discussed drug classes. These are found in Table 7. Xylazine has been the most notable substance detected in this grouping for the last three years and was detected in 1,653 samples. It is known to cause central nervous system (CNS) depression and many individuals exposed to it also develop skin and soft tissue infections which can result in amputations or systemic infections if left untreated. Tianeptine is sometimes referred to as “gas station heroin” because it is sold over the counter (OTC) in the US. In other countries, it is a prescription drug used as an antidepressant. Management of individuals exposed to tianeptine can be complex because of mixed actions at various receptors, including opioid receptors. In many cases, individuals use tianeptine for this effect at opioid receptors, either to replace an opioid, or to attempt to taper off an opioid. It was detected in 175 samples in this study. Phenibut is sold in many countries as a prescription anti-anxiety agent and was detected in 302 samples. Similarly to tianeptine, it is available as an OTC supplement in the US. Medetomidine has recently been detected in the illicit drug supply. Like xylazine, it contributes to CNS depression without activity at opioid receptors. Testing for medetomidine was introduced for clinicians in October, which is one reason it was only detected in 11 samples; however, it is not as prevalent in the illicit supply as xylazine (Figure 6).

Table 7. Miscellaneous NPS Detected in Expected Buprenorphine-positive Samples, 2023
Xylazine
Phenibut
Tianeptine
Medetomidine

Figure 6. Miscellaneous NPS Detected in Expected Buprenorphine-positive Samples, 2023



Conclusion

This analysis demonstrated the potential for patients undergoing medication-assisted treatment with buprenorphine to continue substance use that could otherwise go undetected without specialized testing for NPS. Having definitive results regarding recent substance use allows for more transparency in clinical decision making that helps improve outcomes. A laboratory's decision to offer NPS testing must be accompanied by a commitment to relevant and up-to-date testing, guided by established research organizations such as the Center for Forensic Science Research & Education, among others. This increases the likelihood of the test providing meaningful results that help with achieving treatment goals.

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.