Clinical Update: September 2020

Emerging Data on Novel Psychoactive Substances and Clinical Effects

Aegis launched an extensive and industry-leading testing menu of Novel Psychoactive Substances (NPS) in mid-2020, which includes designer benzodiazepines, designer opioids, synthetic cannabinoids, and synthetic stimulants. These test offerings have been previously discussed in additional clinical updates recently published by Aegis. These articles are available at the following links: Designer Opioids and Benzodiazepines and Synthetic Cannabinoids and Stimulants. With such extensive accessibility to these drugs through clandestine sources, there has been much anticipation regarding which substances would be detected first and most often as results of this testing became available.

The substances selected for testing by Aegis in this new NPS offering were carefully chosen based on information from the CDC and DEA regarding use trends, overdose statistics, and drug crime-related seizures. The primary means by which many of the designer opioids and benzodiazepines have reached the street have been related to failed or abandoned attempts to bring a new drug to market, and then further modification of the drug to circumvent regulatory efforts. The drugs included in Aegis' NPS testing were, in most cases, designed with the intent of avoiding detection on drug screens and providing a desirable effect for users. This does not, however, avoid the risks associated with the use of these drugs, alone or in combination with prescription drugs or other illicit drugs.

To review, the following drugs are included in the four classes of NPS testing offered by Aegis. Each class is ordered individually, and, when ordered, the specimen is tested for all the drugs within the class.

Designer Benzodiazepines	**Designer Opioids**	**Synthetic Cannabinoids**	**Synthetic Stimulants**
Bromazolam	2-Furanyl Fentanyl	4-CN-CUMYL-BUTINACA	4-CEC
Clonazolam	2-Furanylbenzyl Fentanyl	5F-AMB	4Cl-Alpha-PVP
Diclazepam	3-Methyl Fentanyl	5F-EDMB-PINACA	Alpha-PiHP
Etizolam	4-Fluoroisobutyryl Fentanyl	5F-MDMB-PICA	Alpha-PVP
Flualprazolam	Acryl Fentanyl	5F-MDMB-PINACA	Benzylone
Flubromazepam	Benzoyl Fentanyl	5F-PB-22	Butylone
Flubromazolam	Benzyl Fentanyl	AB-CHMINACA	Dibutylone
Nitrazolam	Butyryl Fentanyl	AB-FUBINACA	Ethylone
Phenazepam	Cyclopropyl Fentanyl	Adamantyl-CHMINACA	Eutylone
	Despropionyl p-Fluorofentanyl	ADB-FUBINACA	Methoxetamine
	Fluoro Fentanyl	ADB-PINACA	Methylone
	Isotonitazene	APP-BINACA	N-butyl Pentylone
	Norcarfentanil	FUB-144	N-ethyl Hexedrone
	U-47700	FUB-AKB48	N-ethyl Pentylone
	U-48800	FUB-AMB	TFMPP
	Valeryl Fentanyl	FUB-PB-22	
		JWH-018	
		JWH-073	
		JWH-250	
		MAB-CHMINACA	
		MDMB-4en-PINACA	
		MDMB-FUBICA	
		MDMB-FUBINACA	

There has been considerable interest in testing for these drug classes across many of the patient populations Aegis serves. Such interest may be driven by a need for more complete understanding and awareness of a patient's drug use that may be missed by traditional drug testing. There may also be a desire to mitigate risk of drug interactions and adverse effects caused by concomitant use of NPS. This testing also provides a new window into assessing patient risk, as the results can uncover evidence of higher-risk behaviors by the patient that were previously unknown to the clinician. Taking unknown quantities and combinations of substances with largely unpredictable effects can be life-threatening. As a result of the testing ordered thus far, Aegis has observed positive results for the following analytes:

- Clonazolam
- Etizolam
- Flualprazolam
- Flubromazolam
- Valeryl Fentanyl
- 5F-MDMB-PICA
- 5F-MDMB-PINACA
- 5F-PB-22
- MDMB-4en-PINACA
- Eutylone

One of the first questions a clinician may have is, "What other drugs were these patients taking?" Here are some examples of additional co-positive results from actual sample data:

Example #1: Clonazolam + Etizolam + Flualprazolam + Cocaine + Marijuana + Buprenorphine + Naloxone

Drug and/or Metabolites	Result Interpretation	Result	Comment
Buprenorphine	PRESENT	1,970 ng/mL	A prescription drug, not indicated as prescribed on the requisition form, was detected.
Naloxone	PRESENT	182 ng/mL	A prescription drug, not indicated as prescribed on the requisition form, was detected.
Cocaine	PRESENT	2,070 ng/mL	Test result indicates patient has used a non-prescribed drug within 5 days of the date of the urine collection.
Marijuana/Marinol	PRESENT	717 ng/mL	Test result may be due to ingestion of dronabinol, marijuana, or, in rare cases, use of a CBD- or hemp-containing product.
Designer Benzodiazepines	PRESENT	POSITIVE	Test results indicate use of a non-prescribed drug. Based on limited scientific information, the detection period for designer benzodiazepines in urine by LC/MS/MS should be no more than 10 days from last use.

Designer Benzodiazepines	
Clonazolam	POSITIVE
Etizolam	POSITIVE
Flualprazolam	POSITIVE

Possible Scenarios: The patient could have acquired some or all of the designer benzodiazepines intentionally for separate ingestions (some could have been combined). The designer benzodiazepines could have been incorporated into counterfeit benzodiazepine tablets manufactured to mimic prescription benzodiazepines. The designer benzodiazepines may also have been laced into the other illicit drugs used by the patient. There are multiple possibilities for exposure, some of which could be unknown to the patient or unintentional. This further highlights the importance of patient education and counseling based on these results and reinforces the fact that risks associated with illicit drug use can never be fully calculated by the user.

Example #2: Valeryl Fentanyl + Clonazepam + Fentanyl + Gabapentin + Morphine + Phenobarbital + Methamphetamine + Alcohol + Buprenorphine

Drug and/or Metabolites	Result Interpretation	Result	Comment
Buprenorphine	Consistent	587 ng/mL	Test result is consistent and expected with prescribed drug.
Clonazepam	PRESENT	695 ng/mL	A prescription drug, not indicated as prescribed on the requisition form, was detected.
Fentanyl	PRESENT	245 ng/mL	A prescription drug, not indicated as prescribed on the requisition form, was detected.
Gabapentin	PRESENT	400 mcg/mL	A prescription drug, not indicated as prescribed on the requisition form, was detected.
Morphine	PRESENT	1,580 ng/mL	Test result may be due to the use of pharmaceutical morphine or codeine, or from eating poppy seed food products (bagels, muffins, salad dressing, etc.)
Phenobarbital	PRESENT	932 ng/mL	A prescription drug, not indicated as prescribed on the requisition form, was detected.
Designer Opioids	PRESENT	POSITIVE	Test results indicate use of a non-prescribed drug. Based on limited scientific information, the detection period for designer opioids in urine by LC/MS/MS should be no more than 5 days from last use.
Methamphetamine	PRESENT	276 ng/mL	Test result indicates ingestion within 5 days of the urine collection.
d-Methamphetamine	PRESENT	100 %	Stimulant form of methamphetamine present.
EtG/EtS (alcohol metabolites)	PRESENT	>175000 ng/mL	Test result is consistent with alcohol exposure within 72 hours of specimen collection.

Designer Opioids

Valeryl Fentanyl	**POSITIVE**

Drug Drug-Interaction Testing also showed the following results:

Drug-Drug Interactions

4-Hydroxy Omeprazole Sulfide	**POSITIVE**
Phenobarbital	**POSITIVE**
Promethazine Sulfoxide	**POSITIVE**
Quinine	**POSITIVE**
Norsertraline	**POSITIVE**

Possible Scenario: The patient may have been exposed to valeryl fentanyl by heroin use. The sample was not positive for parent heroin or 6-monoacetylmorphine, however the period of detection for these analytes is short (<24 hours). Unexpected co-positive fentanyl and morphine may be indicative of heroin use, but that cannot be conclusively stated based on these results alone. The presence of quinine in the drug-drug interaction testing could also be associated with heroin use, as quinine is a common adulterant in heroin.[1]

Case reports of patient exposure to some of these substances have been described in literature. Interestingly, a liquid chromatography / tandem mass spectrometry (LC/MS/MS) analysis of wastewater samples in Southern Australia – collected over the Christmas-New Year period when recreational drug use tends to be high – revealed the presence of multiple NPS, including butylone, butyryl fentanyl, furanyl fentanyl, methoxetamine, N-ethylpentylone, pentylone, and valeryl fentanyl.[2] Another case report describes a patient who was treated in the emergency department after administering what he stated was a "fentanyl research chemical" that he purchased in the form of a nasal spray from a local drug trafficker.[3] He required CPR and naloxone to restore breathing, and upon admission to the hospital, he required oxygen by nasal cannula and monitoring in the intensive care unit. His urine was analyzed, and cyclopropylfentanyl was detected.

Even children are at risk for use of NPS as reported in a 2016-2017 national survey in the United Kingdom, which showed that 585 patients <18 years old were referred for treatment for NPS misuse.[4] There was also an incidence of flualprazolam use under the street name of "Hulk" among adolescents in Oregon in June 2019.[5] Over the course of a week, six adolescents were transported to local emergency departments from a single high school after receiving "Hulk" as a free sample from another student. They believed they were taking prescription Xanax®. Slurred speech and lethargy were the most common symptoms. One patient suffered respiratory depression (respiratory rate of 10 breaths per minute). Fortunately, all of the patients recovered and were discharged from the emergency department. Analysis of a tablet fragment obtained from one of the patients showed that the tablet contained approximately 2.75 to 3 mg of flualprazolam. Counterfeit tablet makers have a wide range of capabilities, and while the appearance of such tablets may be of high quality, the contents and potency can vary, and users assume a great risk in ingesting these products.

In a 2015 study of recreational drug users presenting to the emergency department, 18 of 179 patients were positive for synthetic cannabinoids.[6] Patients >18 years of age who presented over a six-month period with acute recreational drug toxicity and had a serum sample taken as part of routine care were included in the study. Seven patient samples contained one synthetic cannabinoid, eight samples contained two synthetic cannabinoids, and three samples contained three synthetic cannabinoids. Only half of the patients self-reported synthetic cannabinoid use. A patient who tested positive for AB-CHMINACA presented with tachycardia (heart rate = 123 bpm) and agitation and also suffered a seizure. Another patient presented in a coma and was found to have two synthetic cannabinoids and fentanyl present in their sample. Additional information about the patients' drug use may have been learned if urine samples were analyzed since urine provides a longer period of detection for most drugs than blood.

As illustrated in the cases mentioned above, there is a possibility of desired and adverse effects with use of NPS. Those have been summarized by Tubman, et al. and are listed below:[4]

NPS Class	Desired Effects	Adverse Effects
Designer Benzodiazepines	• Removal of anxiety • Feelings of calmness and relaxation	• Confusion • Lethargy • Overdose states: respiratory depression and death • Withdrawal: severe anxiety, insomnia, and seizures
Designer Opioids	• Euphoria • Relaxation • Analgesia	• Sedation • Nausea and vomiting • Overdose states: respiratory depression and death • Highly physically addictive • Adverse psychiatric effects: typically, confusion and delirium
Synthetic Cannabinoids	• Feeling pleasantly relaxed	• Acute psychiatric effects: agitation, aggression, confusion and psychosis. • Cardiovascular: tachycardia, tachyarrhythmia, and QTc prolongation • Hypertension • Nausea and vomiting • Chest pain and dyspnea • 'Hangover' state (not seen with traditional cannabis)

NPS Class	Desired Effects	Adverse Effects
Synthetic Stimulants	• Euphoria • Increased concentration • Talkativeness • Urge to move • Empathy/emotional openness	• Acute psychiatric effects: agitation, anxiety, psychotic symptoms and delirium • Cardiovascular: tachycardia, arrhythmias, and hypertension • Hyperthermia • Chest pain • Headache • Bruxism • Seizures • Physical addiction (especially the more dopaminergic compounds) • Risk of life-threatening serotonin syndrome (especially when more than one serotonergic agent is involved)

Combinations of effects can also be fatal as was the outcome of a combination of etizolam and caffeine use in a case report published in June 2020.[7] A 49-year-old man was found dead in his home near a bag of pills with the imprint XANAX on them and a glass containing a dried, white, crystalline substance. Later analysis and autopsy determined lethal concentrations of etizolam and caffeine were present. This fatal combination of an "upper" and a "downer" could also occur with concomitant use of various combinations of NPS and prescription drugs. Such dangers further highlight the importance of vigilant monitoring for substance misuse along with prescribed drugs. Not all possibilities have been described in literature, but one can presume that there are dangerous – if not fatal – effects from combined use of prescription amphetamines and designer benzodiazepines, or prescription opiates and synthetic stimulants, just to name some examples of "upper" and "downer" combinations.

NPS are continuing to evolve as recreational chemists continue to develop compounds that will accomplish the desired effects for users while avoiding regulation and detection. As more information is discovered about use prevalence, clinical guidelines may evolve to include more specific testing recommendations. Current knowledge clearly shows that these drugs pose great risks, with many potential unexpected and unintended consequences for the user.

Please call our client services team at 1-800-533-7052 if you require additional information.

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.

References:

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