Clinical Update: November 2023

SYNTHETIC STIMULANTS

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. Synthetic stimulants, along with synthetic cannabinoids, are NPS for which traditional toxicology testing is widely available. However, it is important to know what compounds are in circulation in the illicit drug supply when evaluating a test menu, as a single synthetic stimulant's availability typically rises and falls over time in response to regulation and is replaced with new compounds.[1-3]

The most common type of synthetic stimulants in circulation today are cathinones, so they are the focus of this update. They are derivatives of the naturally occurring compound cathinone, which is the primary psychoactive component of khat. They are "euphoric stimulants," meaning they have a short duration of physical and psychological effects like more common stimulants such as amphetamine. Synthetic cathinones first appeared in the early 2000s and were sold as "bath salts" but have also been erroneously labeled as incense, plant food, or jewelry cleaner and are typically labeled "Not for human consumption" to avoid regulation. The top reasons users choose synthetic cathinones include availability, affordability,[4] and avoidance of legal ramifications.[5] They are often sold as MDMA or may be incorporated into other drug products when more common stimulants are in short supply.[6-9] However, synthetic stimulants can be much more potent than the drugs they are intended to mimic. Adverse effects can include agitation, combative violent behavior, tachycardia and hypertension, hallucinations, paranoia, confusion, vomiting, hyperthermia, seizures, and death.[10,11] Single-patient case reports have also reported hyperpyrexia, seizures, hyponatremia, rhabdomyolysis, myocarditis, metabolic acidosis, and death.[12-20] In a case series of three reported deaths from methylone (synthetic cathinone) intoxication, all patients had hyperpyrexia and seizures, with metabolic acidosis, disseminated intravascular coagulation, and acute renal failure.[12,21]

As classes of drugs become regulated, new derivatives appear to market to evade the law.[2,3,22] Piperazines are a class of synthetic stimulants that share the abuse and dependence potential of dextroamphetamine, cocaine, LSD, and MDMA. As expected, they also cause psychoactive and sympathomimetic-like symptoms. In some cases, they have been found to cause severe complications and death.[23] Piperazines have also been found to be combined with legal and illegal substances including synthetic cannabinoids, cathinones, and herbal products.[24] Effective toxicology screening techniques continue to be needed to identify and limit the use of synthetic stimulant drugs.[25]

Testing menus that are not routinely updated may be searching for compounds that are not in circulation. As an illustration, Aegis' testing trends for select synthetic cathinones are shown below. In **Figure 1**, a rise in eutylone samples from 2020 to 2021 is followed by a sharp decline. The peak detection of eutylone in 2021 coincides with the appearance of pentylone, which was later determined to be present as a metabolite of a new cathinone, N,N-dimethylpentylone. Pentylone and N,N-dimethylpentylone are the most common cathinones detected currently, but their detection may have reached a peak in mid-2023, as the number of positive samples decreased in Q3 2023.

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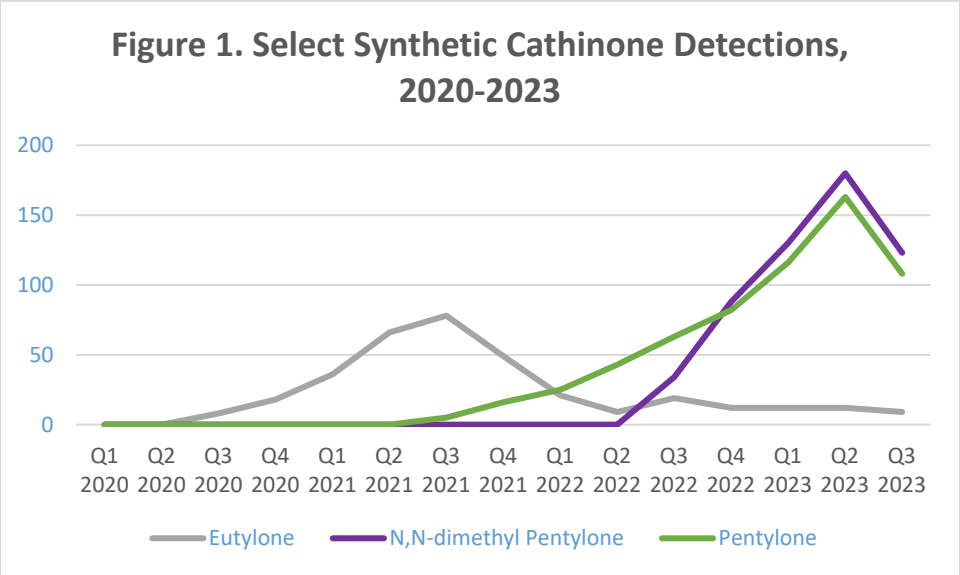
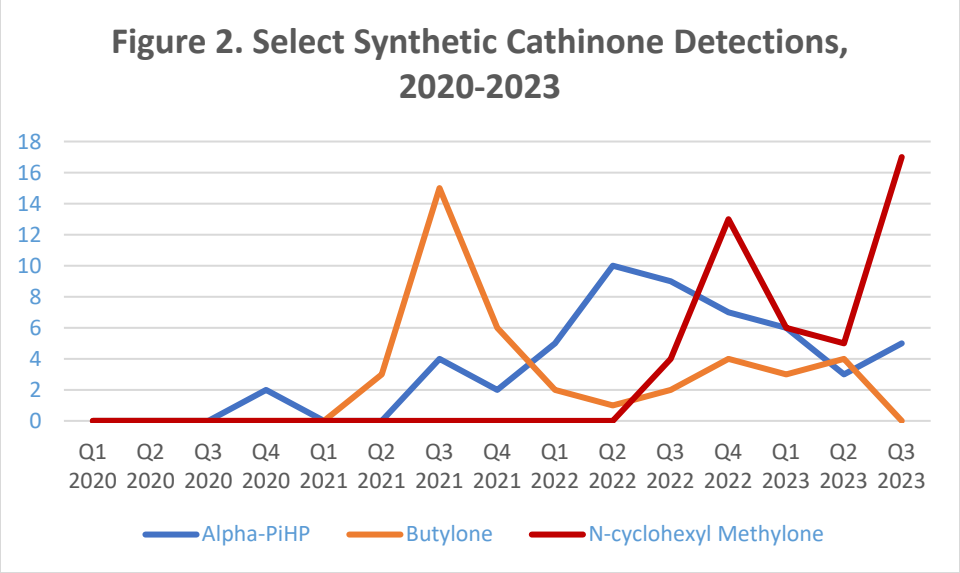


On a different scale, **Figure 2** shows N-cyclohexyl methylone, which is one of the emerging cathinones that may replace the most detected cathinones from Figure 1. It was first detected in Q2 2022 and is on a general upward trend. **Figure 2** also illustrates the rise and decline of butylone from its peak in Q3 2021. As butylone began to decline, a slight increase in alpha-PiHP detections began, although it has declined somewhat since the peak in Q2 2022. The declines in butylone and alpha-PiHP also closely coincide with the sharp increases in pentylone and N,N-dimethylpentylone detection previously illustrated in **Figure 1**.



Laboratories' test menus are developed at a fixed point in time to reflect drug trends at the time of development. As illustrated above, these trends change and regular updates to testing menus are as important, or possibly more important, than having a test offering at all. Updates can greatly reduce the likelihood of false-negative results and undetected drug use. Most importantly, when evaluating test menus, clinicians should have an awareness of what drugs are in circulation in their area to determine if test coverage is adequate.

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Aegis' Synthetic Stimulant Test Menu (as of 11/1/2023)

2-Fluoromethamphetamine**	Butylone*	N-ethyl Heptedrone*
3/4-Fluoromethamphetamine**	Chloro-N,N-DMC*	N-ethyl Hexedrone*
3/4-Methylmethcathinone*	Dimethylone*	N-ethyl Pentedrone*
3,4-DMMA**	Eutylone*	N-propyl Butylone*
4F-3-methyl-alpha-PVP*	MBZP**	NM N-cyclohexyl Methylone*
4-Fluoromethylphenidate**	MDPHP**	N,N-dimethyl Pentylone*
Alpha-D2PV*	Methylenedioxy-PV8*	Pentylone*
Alpha-PiHP*	N-butyl-Hexedrone*	TFMPP**
Alpha-PHP*	N-cyclohexyl Butylone*	
Benzylone*	N-cyclohexyl Methylone*	

*Denotes synthetic cathinone

**Non-cathinone stimulant

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.

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