Novel Psychoactive Substances (NPS) are a diverse group of synthetic substances created to mimic the effects of scheduled or illicit drugs; however, they vary in both toxicity and potency. An important point of reference is that a substance only needs to be newly observed to be considered “novel.” Synthetic cannabinoids and synthetic stimulants are traditionally the most common classes of NPS available and abused in the United States; however, other classes of NPS are available and will be discussed in August’s Clinical Update.

Reports of usage in the past five years have slowly declined for both synthetic cannabinoids and synthetic stimulants. This is likely due to legislation that targets specific chemical structures and entire classes of substances. The problem remains that once an NPS has been regulated as a controlled substance, often one or more new, non-regulated NPS make their way into a community. There is a wide array of “replacement” compounds in which slight chemical modifications have been made. This continues to be a battle in which regulatory and enforcement agencies, monitoring institutions, clinical laboratories, and healthcare providers are always playing catch-up with drug. The real usage of synthetic stimulants and synthetic cannabinoids is very difficult to capture. One of the deadliest variables that can obscure the public’s real rates of consumption is drug adulteration. Data show that products labelled with the same name may contain different compounds. There is a high risk for unknowingly or unintentionally using NPS which has been added to illegal drugs or has been mislabeled with legal drug names. Lack of manufacturing regulations and an absence of quality assurance mean that there is also a high likelihood of contamination and adulteration. As a result, it is highly unlikely that NPS users can be sure of what they have ingested. It is difficult to keep pace with what these products contain, what psychoactive effects they have, and how best to manage patients who are taking them.

Synthetic drug classes are derived from a variety of sources. John W. Huffman, a Clemson University organic chemistry professor, synthesized more than 300 brand new chemical compounds in the early 1990’s. His goal was to understand the newly found cannabinoid receptor with hopes of creating helpful, new medicines. Almost 20 years later, one of his compounds (JWH-018) was found in “spice.” It was found that independent chemists had stolen his work and have since created over 500 new synthetic drugs that are being abused. This is a good example how clandestine chemists use formulas from scientific literature, manipulate known molecular entities and change formulas to avoid drug scheduling, drug screens, or to enhance a desired effect.

Cannabinoids:
When synthetic cannabinoids first appeared in the early 2000’s, they were sold as legal replacements for cannabis. Since then, they have gained a reputation for having powerful intoxicating effects. Typically, the synthetic material is sprayed onto herbal plant material and smoked. Some of the physiological effects of synthetic cannabinoids that users desire are euphoria and relaxation, intensification of sensory...
experiences, altered perception, pronounced cognitive effects, altered state of consciousness, and time distortion. Unfortunately, other effects also include agitation, hypertension, palpitations, hypokalemia, short-term memory loss, anxiety, attention deficits, nausea, vomiting, paranoia, confusion, hallucinations, seizures, and death.\textsuperscript{11,12}

The abuse of synthetic cannabinoids has continued due to their euphoric highs, addictive qualities, easy accessibility, lack of detection in typical urine drug screens for THC, and the belief that they are “natural” products and therefore harmless.\textsuperscript{13} The ingredients and strength of products containing synthetic cannabinoids are almost impossible for the user to know.\textsuperscript{14} In the spring of 2018, >470 cases of hypocoagulopathy and bleeding were associated with synthetic cannabinoids that were found to be laced with brodifacoum, a very long-acting anticoagulant commonly used in rat poison. It was thought that the anticoagulant may extend the duration of the drug euphoria or “high.” There were at least eight fatalities.\textsuperscript{15,16} The CDC’s Clinician Outreach and Communication Activity (COCA) Clinical Action issued an Outbreak Alert\textsuperscript{15} and the U.S. Food and Drug Administration (FDA) issued warning statements.\textsuperscript{16}

A case study included a young adult patient, with histories of recurrent synthetic cannabis and recreational cannabis use, who had developed drastic physiological and psychiatric symptoms, including the development of acute-onset psychosis.\textsuperscript{17} There are various reports suggesting that synthetic cannabinoid intoxication is associated with acute psychosis as well as exacerbations of previously stable psychotic disorders. Also, intoxication may have an inclination to trigger a chronic psychotic disorder among individuals that appear vulnerable.\textsuperscript{18} Synthetic cannabis has more injurious physical and psychiatric implications and has no benefit when compared to traditional cannabis.\textsuperscript{19} There is hope that toxicology labs can aid in the development of medical intervention strategies. Aegis’ enhanced cannabinoid testing class includes the following parent drugs:

<table>
<thead>
<tr>
<th>Cannabinoid</th>
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<tbody>
<tr>
<td>4-CN-CUMYL-BUTINACA</td>
<td>Adamantyl-CHMINACA</td>
<td>JWH-018</td>
</tr>
<tr>
<td>5F-AMB</td>
<td>ADB-FUBINACA</td>
<td>JWH-073</td>
</tr>
<tr>
<td>5F-EDMB-PINACA</td>
<td>ADB-PINACA</td>
<td>JWH-250</td>
</tr>
<tr>
<td>5F-MDMB-PICA</td>
<td>APP-BINACA</td>
<td>MAB-CHMINACA</td>
</tr>
<tr>
<td>5F-MDMB-PINACA</td>
<td>FUB-144</td>
<td>MDMB-4en-PINACA</td>
</tr>
<tr>
<td>5F-PB-22</td>
<td>FUB-AKB48</td>
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<tr>
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<tr>
<td>AB-FUBINACA</td>
<td>FUB-PB-22</td>
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</table>

Stimulants:
One example of synthetic stimulants is synthetic cathinones. 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 acting duration of physical and psychological effects similar to stimulants like amphetamine. Synthetic cathinones first
appeared in the early 2000’s and are still erroneously sold as “bath salts” which resemble Epsom salts, incense, and plant food and are labeled “Not for human consumption” to avoid regulation. The top reasons users choose synthetic cathinones include availability, affordability, and avoidance of legal ramifications. They are often sold as replacements when MDMA, cocaine, heroin, amphetamine, or other stimulants are in short supply. However, synthetic stimulants can be much more potent than the drugs they are intended to mimic. Stimulants can cause an elevated mood, increased energy and alertness, and sociability.

Adverse effects can include agitation, combative violent behavior, tachycardia and hypertension, hallucinations, paranoia, confusion, vomiting, hyperthermia, seizures and death. Single-patient case reports have also reported hyperpyrexia, seizures, hyponatremia, rhabdomyolysis, metabolic acidosis, and death. 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. A growing number of studies have demonstrated synthetic stimulant adulteration of illegal drugs, such as ecstasy or MDMA. People may be unaware that they are using a synthetic stimulant in many cases.

As classes of drugs become regulated, new derivatives appear to market to evade the law. 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. Lastly, piperazines have also been found to be combined with legal and illegal substances including synthetic cannabinoids, cathinones, and herbal products. Effective toxicology screening techniques continue to be needed to identify and limit the use of synthetic stimulant drugs. Aegis’ enhanced stimulant testing class includes the following parent drugs:

<table>
<thead>
<tr>
<th>Stimulant</th>
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<tbody>
<tr>
<td>4-CEC</td>
<td>Butylone</td>
<td>Methylone</td>
</tr>
<tr>
<td>4Cl-Alpha-PVP</td>
<td>Dibutylone</td>
<td>N-butyl Pentylone</td>
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<td>Alpha-PiHP</td>
<td>Ethylone</td>
<td>N-ethyl Hexedrone</td>
</tr>
<tr>
<td>Alpha-PVP</td>
<td>Eutylone</td>
<td>N-ethyl Pentylone</td>
</tr>
<tr>
<td>Benzylone</td>
<td>Methoxetamine</td>
<td>TFMPP</td>
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References NPS Clinical Update July 2020