New and Emerging Illicit Psychoactive Substances

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KEYWORDS

• Psychotropic drugs • Novel psychoactive substances • Designer drugs
• Cathinones • Cannabinoids

KEY POINTS

- Globalization and advances in neurochemistry have facilitated the development of novel substances which are often designed to circumvent regulations limiting access to psychoactive drugs.
- Most are in one of 4 broad categories: stimulant, cannabinoid, opioid, or benzodiazepine.
- Some novel stimulants and cannabinoids are potent and users may present with psychosis or seizures.
- Identification of use is hampered by lack of standardized rapid tests to identify these substances and clinicians must rely on history and clinical presentation.
- Treatment of toxicity is generally supportive; naloxone can be used for opioids and flumazenil for benzodiazepine toxicity.

INTRODUCTION

A 28-year-old man is evaluated by emergency medical technicians after a bystander calls 911 for concern about altered mental status. On arrival, the man is slow to respond to questions and has a blank stare. He is brought to the emergency department (ED) where he is lethargic but responds to tactile stimuli. His vital signs and oxygen saturation are within normal limits. On examination, the man has periods of zombielike groaning and moves his arms and legs slowly. Examination is otherwise notable for diffuse diaphoresis, without any focal neurologic deficits. Comprehensive laboratory analysis, including a standard urine immunoassay toxicology test and serum alcohol, is within normal limits without any toxins detected. Seven other patients with similar presentations evaluated in the same hospital on that day also had unremarkable laboratory tests. The patient is placed on an observation unit and his behavior normalizes after approximately 9 hours. On further history obtained later,

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he reports inhalation of a new substance he purchased recently before the episode. Further analysis identifies a novel synthetic cannabinoid, methyl 2-(1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamido)-3-methylbutanoate, in the serum of all 8 patients with similar symptoms.[1]

This case and others illustrate a new and growing phenomenon of individuals presenting with toxicity from psychoactive drugs that have not been seen before. Globalization and advances in neurochemistry have created conditions for the development and dissemination of novel psychoactive substances. Historically, psychoactive drugs have been obtained directly from natural sources (eg, cocaine from coca leaf) or derived from natural sources (eg, heroin derived from morphine in poppy bulbs), but the past few decades have seen the proliferation of drugs that are synthesized de novo without need to access regulated sources or precursors and that, for this reason, are sometimes referred to as designer drugs. Any review of this topic will be limited in that these drugs are new and rapidly evolving. The information on the clinical effects tends to focus on severe presentations and there is limited information on users' typical experience.

Although some of these drugs are brought to North America through traditional smuggling routes from Central and South America, many are marketed through the so-called dark Web (or cryptomarkets) and arrive through the mail.[2] Some arrive through legal channels and are labeled and marketed as not for human consumption or research chemicals to circumvent regulations.

This article provides a brief overview of these drugs, dividing them into 4 broad categories:

1. Stimulants
2. Cannabinoids
3. Opioids
4. Sedatives

Table 1 provides an overview of these substances and **Table 2** provides a summary of the clinical effects, detection, and treatment of exposure.

Stimulants

There are several novel stimulants that have been emerging in the past decades. These can be divided into 4 categories: synthetic cathinones, tryptamines, piperazines, and 2C (2 carbon) phenethylamines.

Synthetic cathinones

Pharmacology Synthetic cathinones are designed to mimic the primary psychoactive substance found in the leaves of the *Catha edulis* plant, colloquially referred to as khat.[3] They are derivatives of phenethylamine and are similar to amphetamines and 3,4-methylenedioxy-N-methylamphetamine (MDMA, or Ecstasy).[4] Cathinones have varying agonist activity on the dopamine, serotonin, and norepinephrine pathways through neurotransmitter reuptake inhibition and stimulation of neurotransmitter release.[5] Contrasting patterns of pathway activation contribute to the clinical effects observed with different compounds: dopamine agonism is associated with psychoactive effects and the addictive potential of cathinones, norepinephrine agonism with sympathomimetic effects, and serotonin agonism with paranoia and hallucinations.[6] The duration of effect is approximately 2 to 4 hours for many synthetic cathinones; 4-methylmethcathinone (mephedrone), the best-studied compound in the class, has a half-life of approximately 2 hours.[3,7]