New 'legal' highs: Kratom and methoxetamine

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The demand for "legal highs"—intoxicating natural or synthetic substances that are not prohibited by law—continues to increase. Young adults may use these substances, which are widely available on the internet, at "head shops," and at gas stations. Such substances frequently cause adverse medical and psychiatric effects, exemplified by recent reports concerning the dangers of using synthetic cannabinoids (eg, "Spice," "K2") and synthetic cathinones ("bath salts"). Although these 2 substances now are illegal in many jurisdictions, other novel substances of misuse remain legal and widely available, including Kratom and methoxetamine.

Because these substances usually are not detectable on standard urine toxicology screens, clinicians need to be aware of them to be able to take an accurate substance use history, consider possible dangerous interactions with prescribed psychotropics, and address medical and psychiatric complications.

Kratom is an herbal product derived from *Mitragyna speciosa*, a plant native to Southeast Asia. Traditionally used as a medicinal herb, it increasingly is being used for recreational purposes and remains legal and widely available in the United States. Kratom's leaves contain multiple alkaloids, including mitragynine and 7-hydroxymitragynine, which are believed to act as agonists at the μ-opioid receptor. Mitragynine also may have agonist activity at post-synaptic α2-adrenergic receptors, as well as antagonist activity at 5-HT2A receptors.[1] Mitragynine is 13 times more potent than morphine, and 7-hydroxymitragynine is 4 times more potent than mitragynine.[2]

Kratom is available as leaves, powdered leaves, or gum. It can be smoked, brewed into tea, or mixed with liquid and ingested. Effects are dose-dependent; lower doses tend to produce a stimulant effect and higher doses produce an opioid effect. A typical dose is 1 to 8 g.[3] Users may take Kratom to experience euphoria or analgesia, or to self-treat opioid withdrawal symptoms.[3] Kratom withdrawal syndrome shares many features of classic opioid withdrawal—diarrhea, rhinorrhea, cravings, anxiety, tremor, myalgia, sweating, and irritability—but has been reported to be less severe and shorter-lasting.[1] Kratom withdrawal, like opioid withdrawal, may respond to supportive care in combination with opioid-replacement therapy. Airway management and naloxone treatment may be needed on an emergent basis if a user develops respiratory depression.[2] There have been case reports of seizures occurring following Kratom use.[2]

Methoxetamine is a ketamine analog originally developed as an alternative to ketamine. It isn't classified as a controlled substance in the United States and is available on the internet.[2] Methoxetamine is a white powder typically snorted or taken sublingually, although it can be injected intramuscularly. Because methoxetamine's structure is similar to ketamine, its mechanism of action is assumed to involve glutamate *N*-methyl-D-aspartate receptor antagonism and dopamine reuptake inhibition.

continued

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Kratom and methoxetamine usually are undetectable on toxicology screens

Doses range from 20 to 100 mg orally and 10 to 50 mg when injected. Effects may not be apparent for 30 to 90 minutes after the drug is snorted, which may cause users to take another dose or ingest a different substance, possibly leading to synergistic adverse effects. Effects may emerge within 5 minutes when injected. The duration of effect generally is 5 to 7 hours—notably longer than ketamine—but as little as 1 hour when injected.

No clinical human or animal studies have been conducted on methoxetamine, which makes it difficult to ascertain the drug's true clinical and toxic effects; instead, these effects must be surmised from user reports and case studies. Desired effects described by users are similar to those of ketamine: dissociation, short-term mood elevation, visual hallucinations, and alteration of sensory experiences. Reported adverse effects include catatonia, confusion, agitation, and depression.[4] In addition, methoxetamine may induce sympathomimetic toxicity as evidenced by tachycardia and hypertension. Researchers have suggested that patients who experience methoxetamine toxicity and require emergency treatment be managed with supportive care and benzodiazepines.[5]

Staying current is key

A paucity of clinical research on these substances means their effects are poorly understood, which creates a dangerous situation for users and physicians. In addition, many users assume these substances are safer than illegal substances. New and potentially dangerous substances are being produced so quickly distributors are able to stay ahead of regulatory efforts. When one substance is declared illegal, another related substance quickly is available to take its place. To provide the best care for our patients, it is essential for psychiatrists to stay up-to-date about these novel substances.

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