Abstract:
Emerging drugs of abuse include psychostimulants marketed as household products but containing novel psychoactive substances. These products are easily purchased and frequently change composition in response to regulatory pressure. The synthetic cannabinoids, 2C phenylethylamines, and synthetic cathinones are 3 novel psychoactive substance classes that have recently experienced significant growth and market penetration. Synthetic cannabinoids are potent activators of cannabinoid receptors, often sold as "incense"; have evolved from early compounds to the ultrapotent indazole class; and have been associated with many negative health outcomes and deaths. The 2C drugs are highly serotonergic, hallucinogenic phenylethylamines frequently marketed as "LSD". The "NBOMe" class of 2C drugs has been associated with several case clusters and deaths. The synthetic cathinones possess stimulant and hallucinogenic properties and include the "bath salts" as well as the recent emergence of "flakka," containing α-pyrrolidinovalerophenone. The cathinones can cause severe agitation and aggression. Although specific assays for these agents exist, they are usually not immediately available to clinicians. Fortunately, toxicity from all of the drugs discussed in this article can be treated by controlling agitation and monitoring for and aggressively treating hyperthermia and end-organ damage.

Keywords:
emerging; novel; cannabinoid; hallucinogen; phenylethylamine; sympathomimetic; cathinone

Emerging Drugs of Abuse: Synthetic Cannabinoids, Phenylethylamines (2C Drugs), and Synthetic Cathinones

Matthew Valento, MD*†, Jacob Lebin, MD*

Novel psychoactive substances (NPSs) are frequently introduced to the market and can produce clusters of poisonings. These agents are typically shielded from regulation via clever marketing, being sold as household products (incense, bath salts, plant food) and often labeled "not meant for human consumption." Enterprising producers demonstrate prompt adaptability to changes in legal status, routinely creating new derivatives once a psychoactive agent is listed as a Schedule 1 drug by the Drug Enforcement Agency (DEA) and banned from sale.

Adolescents are a prime target for NPS use given their legal availability and ease of purchase. Although these drugs are often found in head shops or convenience stores, a thriving online market exists as well, including so-called gray marketplaces or darknet (Silk Road, Silk Road 2.0, Pandora) which operates on both the surface and deep Web.[1,2]

Clinicians need to develop and maintain familiarity with major classes of NPSs. Fortunately, despite the rapid evolution of these agents, most can be treated with supportive care and control of

*University of Washington Division of Emergency Medicine; †Washington Poison Center.
Reprint requests and correspondence: Matthew Valento, MD, 1811 38th Ave E, Seattle, WA 98112.
valento@uw.edu

1522-8401

agitation. Although abuse and intoxication with more familiar drugs (eg, heroin, cocaine, methamphetamine) will continue to be a primary concern, the incidence of patients presenting to medical attention intoxicated by novel agents is likely to increase. A recent analysis by the European Drug Emergencies Network, which monitors emergency admissions in 10 European Union countries, found that 9% of all drug-related emergencies involved NPSs.[3] Of newly reported agents, the classes with the largest recent increase are the synthetic cannabinoids (SCs), the phenylethylamines, and the synthetic cathinones.

SYNTHETIC CANNABINOIDS

Introduction

The SCs are a group of more than 50 individual compounds with activity at the cannabinoid receptors. Initially created in the 1980s as ligands for studying human endocannabinoid systems, these agents became popular psychoactive agents in Europe before their introduction to the United States.[4] The SCs are dissolved in a solvent and applied to a base material, typically an inert dried plant, and sold as "herbal incense."[5] The uniformity of SCs marketed under a particular name ("K2," "Spice") can vary, and there can be several SCs present within a single packet.[6]

The first SC-containing product was intercepted in the United States in 2008. The US National Forensic Laboratory Information System (NFLIS) reported 23 cases in 2009. This number rapidly grew to more than 41 000 cases by 2012. The US Drug Abuse Warning Network noted a similar escalation with 11 000 reported cases in 2010 and more than 28 000 in 2011.[7] The number of different SCs reported to the NFLIS has increased every year, from 2 agents in 2009 to 84 in 2015.[8] The annual percentage of SC cases has consistently increased in all 4 US Census regions, and more than 20 clusters of poisoning cases have been reported by the DEA. Users tend to be predominantly male (>80% male in several reported clusters) in their teens and early 20s.[2,9,10] As it frequently takes months for confirmatory testing to be available for individual agents, it is likely that cases of SC intoxication are severely underreported. Nevertheless, a 330% increase in SC-related calls to US poison centers was reported during the first 4 months of 2015.[11]

Several "generations" of SCs have been described as drug manufacturers respond to changing legal status and regulation. The predominant early SC classes detected in the United States in 2009 were the JWH series of aminoalkylindoles, so called for their development at Clemson University by John W. Huffman in the 1990s, and the CP series of cyclohexylphenols developed and patented by Pfizer.[6] Herbal mixtures known as the brands "Spice" and "K2" were found to contain JWH-018 and CP 47497-C8, respectively.[12] JWH-018 was the most widely reported of the early SCs and the most potent activator of cannabinoid receptors.[13] Five agents from these classes were listed as Schedule 1 by the DEA in 2011. The subsequent ban of sale diminished the market presence of the JWH drugs, providing an opportunity for emergence of multiple new SCs. Of particular interest is the recently described "ultrapotent" indazole class and their ester analogues (eg, AMB-FUMINACA, 5F-AMB, MDMB-CHMICA), capable of producing severe agitation and psychosis at very small doses.[14] Limited pharmacologic and pharmacokinetic data are available on newer agents given their rapid production and introduction to the market. As such, clinical effects can be difficult to predict and idiosyncratic.

Pharmacology

The SCs share no structural relationship to delta-9-tetrahydrocannabinol (δ-9-THC), the principal psychoactive component of cannabis (Figure 1). However, they are active at cannabinoid receptors. Indeed, they are often far more potent. δ-9-THC is a partial agonist at cannabinoid receptor 1 (CB1). SCs are frequently full agonists at CB1 and CB2, with much higher binding affinity. This potency is markedly demonstrated by the indazole class, with potencies up to 85 times that of δ-9-THC.[2,9]

CB1 receptors are heavily expressed in brain regions involved with reward, addiction, and cognitive function, such as the amygdala, cingulate cortex, prefrontal cortex, and nucleus accumbens. They are also found in limbic regions that provide excitatory and inhibitory neurotransmission, which influences and modulates reward processing. In addition, many SCs are metabolized to several cannabimimetic compounds capable of activating CB1 receptors.[1]

Noncannabinoid receptor binding by SCs has also been described, including potassium channel inhibition, dopamine agonist activity, and affinity for