**Abstract**

**Introduction**

In recent years, synthetic drugs have been used increasingly by young people on a regular basis and in larger quantities in big music festivals. Some of the synthetic drugs that are popular include “molly” and “spice”. These drugs of abuse are on the rise and currently popular among young people and already known for causing health-related complications. The aim of this review was to discuss the drugs of abuse that are on the rise.

**Conclusion**

Physicians should be aware of drug-related symptoms and consider synthetic drug abuse in patients especially those without a history of underlying medical condition, who present with unexplained mental disturbances, seizure, kidney injury, stroke or heart attack and negative urine toxicology.

**Introduction**

In recent years, synthetic drugs have been used increasingly by young people on a regular basis and in larger numbers in big music festivals. According to a new study by the substance abuse and mental health services administration (SAMHSA), approximately 70% of the emergency department (ED) was Ecstasy-related and it involved patients aged 18–29 years. Shockingly, 17.9% involved adolescents aged 12–17 years. Some of the synthetic drugs that are popular include molly, 3,4-methylenedioxy-N-methylamphetamine (MDMA), synthetic Marijuana (K2 or spice), synthetic cathiones (bath salts), phenylcyclidine (PCP) and 3,4-methylenedioxypyrovalerone (MDPV). Our ED that is located in the heart of Manhattan, New York City receives a significant amount of patients who have used these synthetic drugs with different symptoms ranging from agitation, combativeness, altered mental status (AMS), seizure and death. This concise review focuses on some drugs of abuse that are on the rise and currently popular among young people and already known for causing health-related complications particularly molly and K2.

Molly, the powdered and possibly a more potent form of MDMA, has been popular in the past couple of years. Another assumption is that molly might be a mixture of MDMA and other agents to potentiate the effect. Commonly, the MDMA in a pill form is known as “ecstasy”. Historically, MDMA was discovered in 1914 and it was re-synthesised in the USA. It has since been used as an adjuvant psychotherapeutic agent and for recreational purposes, and could be acquired legally. Studies on animal and humans have shown neurotoxic effect of MDMA which led the Food and Drug Administration (FDA) to classify them as schedule 1 drugs.

The pharmacology of MDMA involves action on serotonin, 5-hydroxytryptamine (5-HT) and dopamine (DA) receptors. It is an amphetamine derivative that causes increase in the brain serotonin and DA. The toxicology of MDMA was first examined by the military in the USA. It has been shown in animal models that MDMA releases and depletes 5-HT. Oral doses of MDMA given to monkeys caused a reduction in 5-HT, but the doses given to these animals were much higher than the usual dose consumed for recreational purposes. In people who use MDMA chronically, it causes reduction of serotonin and decreased serotonin reuptake transporter (SERT) binding as well as increased serotonin-2A receptors leading to increased cortical excitability. In addition, there have been studies showing that MDMA-induced DA and norepinephrine release, but to a lesser extent when compared with 5-HT release. The more prominent effect of MDMA use on the brain is the reduction of 5-HT, SERT and metabolites of 5-HT. Other factors that may potentiate the neurotoxicity of 5-HT in MDMA users are the use of other drugs such as amphetamines and the ambient temperature. Long-term use of MDMA leads to loss of monoamine neurons in the central nervous system (CNS). Other consequences of long-term exposure to MDMA are long-term memory and learning impairment and neonatal tremors in animal models and neuropathological effects in humans. This is the concerning aspect of long abuse of the substance. Most abusers are young with a long lifespan and the effect of MDMA on cognition and memory impairment may manifest itself with possibly devastating outcomes.

The other agents that are popular are the synthetic cannabinoids (SCs).
They began to emerge in the early to mid-2000s due to their easy availability, relatively low cost and non-detection by conventional urine drug screens\textsuperscript{7,21}. Sold under many names including K2, Spice, Fake weed, Yucatan Fire, Skunk, Moon Rocks and others, they refer to a variety of herbal mixtures that are intentionally adulterated with SCs compounds in order to produce marijuana-like effects\textsuperscript{7,22}. They are clearly labelled as ‘not for human consumption’ and are easily available on the Internet, gas stations, convenience stores and head shops\textsuperscript{21}.

The main compounds of these substances are THC-like compounds such as JWH-018, HU-210 or CP-47 that were initially developed for research purposes in the mid-90s in order to explore the cannabinoid receptor ligand-binding\textsuperscript{22}. The CB1 receptor is a G-protein-coupled receptor found in the CNS (basal ganglia, cerebellum, hippocampus and cortex) and is the receptor responsible for elevating person’s mood and conversely inducing emotions such as anxiety and panic\textsuperscript{21}. Of clinical relevance, THC is only a partial agonist of the CB1 receptor, while the SCs are full agonists, meaning that they have no ceiling effect on dose-response relationship and greater potential for overdose and severe toxic effects\textsuperscript{24,25}. Some authors suggest that the SC also act on the CB2 receptors located in the peripheral tissues of the immune system, spleen, lymph nodes and tonsils producing immune-modulatory effects\textsuperscript{26}. In 2010, a 18-year-old Iowa male committed suicide after smoking ‘K2’, prompting many legislative efforts that led the Congress to classify SCs as schedule one substances\textsuperscript{27}. Users may mistakenly believe that these new drugs are a safe alternative to marijuana but the long-term effects of these compounds remain unknown\textsuperscript{7}.

Several studies in adults and adolescents have linked the use of SC to psychiatric, cardiovascular and neurological symptoms. These products can initially cause marijuana-like effects such as euphoria, relaxation or altered perception; however, unlike marijuana, they can produce severe agitation, hallucinations, delusion and confusion. A few studies report seizures after smoking SCs and they hypothesise that the more intense inhibition of the gamma-aminobutyric acid (GABA) neurotransmission in the brain by SCs compared with THC may be associated with convulsions and seizures.

**Discussion**

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

A nationwide campaign to inform and educate people about the use and deadly consequences of prescription drugs is on the way, but less is done regarding synthetic drugs. The reason for this maybe multiple: synthetic drugs are legal, cheap and easy to acquire. Manufacturers keep making more substances by altering the structures of the existing compounds and making them legal so that they may be sold as herbal incenses and aromatic products. There is no legislative rule that prohibits the use and distribution of these agents. Chemical constituents of some of the synthetic and recreational drugs are not listed on state and federal controlled substances and can be sold easily.

ED visits related to synthetic drugs in the USA have been rising in the past 3 years and our ED has had a similar experience. Over the past 3 years, during the rave party weekends, nearly 100 patients were seen in our ED. Most of these patients were very young. In 2011 and 2012, on Labour Day weekend alone, we evaluated 60 patients who came from an organised party for drug-related complaints. Their symptoms ranged from agitation, intoxication from co-ingested alcohol, hyperthermia, hallucination and seizure. Some patients required intubation and admission to intensive care unit (ICU) and some had persistent seizures from hyponatraemia requiring treatment with hypertonic saline. In 2013, the festival was stopped after two deaths.

Studies have shown that seizure activity is observed from drug use and abuse. It is a serious complication of recreational and other drug use. Seizure can lead to acidosis, hyperthermia and anoxic brain injury, and carries mortality as high as 2%\textsuperscript{28}. Life-threatening complications associated with seizure, particularly status epilepticus, include anoxic brain damage, aspiration leading to pneumonitis, respiratory failure and recurrent seizures\textsuperscript{29,30}. One of the major concerns with these agents is the long-terms equelae on psychosocial, behavioural, organ and cognition aspects, particularly those who use the agents frequently and in combination with other drugs. Long-term follow-up may reveal delayed sequelae in the psycho-behavioural or psychosocial and organ-related side effects of these agents. Young individuals are at risk for complication from prolonged exposure.

With regard to SC use, during the last 6 months we have seen more than 50 cases of young male adults intoxicated with SCs in our psychiatric ED. Most of these patients were brought by EMS presenting with severe agitation, assaultive behaviour, delusions and hallucinations. Benzodiazepines and antipsychotics were used to control the symptoms, and in some cases, brief psychiatric admission was required for stabilisation.

**Licensee OA Publishing London 2013. Creative Commons Attribution License (CC-BY)**

**Critical Review**

Physicians should be aware of the cardiorespiratory effects of SCs as they are usually mixed with vitamin E contaminated with clenbuterol. They can produce sympathomimetic-like effects such as anxiety, tremors, hypertension, xerostomia, tachycardia and tachydysrhythmia. Myocardial infarction and chest pain are also common adverse effects that caused death in young healthy adults. Nausea, vomiting and appetite changes are also common presentations. Synthetic cannabinoids also produce increased psychomotor activity leading to increase risk of renal failure from rhabdomyolysis.

Since we do not have any specific antidote to reverse the SCs effects, it is very important to recognise the symptoms of the SCs intoxication in order to prevent life-threatening events. Initial management should include telemetry monitoring, intra- venous fluids and ensuring secure airway. Routine laboratory tests such as complete blood count, basic metabolic panel, creatinine phosphokinase (CPK) and urine toxicology should be part of the initial testing. Cardiac enzymes should be considered if the patient complains of chest pain or if the patient has electrocardiogram abnormalities suggesting ischaemia. Psychiatric symptoms can be treated with benzodiazepines (especially lorazepam) and antipsychotics although the latter should be used judiciously because of their propensity to lower the seizure threshold. Educating patients and providing addiction counselling and treatment should be an essential part in their management to avoid poly substance use and the development of tolerance.

Conclusion
Synthetic drugs have become a health concern because of their increased popularity and their severe adverse effects including death. Physicians should be vigilant and consider synthetic drug abuse in patients especially in those without history of underlying medical condition, who present with unexplained mental disturbances, seizure, kidney injury, stroke or heart attack and negative urine toxicology. Management guidelines are evolving and the safety and pharmacology of these new drugs remain unknown. The potential for multiple long-term effects such as impairment of cognition, memory loss, psychiatric and medical complications need to be further studied. In the meantime, the authors encourage physicians to familiarise themselves with the signs and symptoms, and management of the SCs intoxication, as we expect this epidemic to increase.

Acknowledgement
We thank Dr. Shaw for reviewing the manuscript.

References
21. Vardakou I, Pistou C, Spiliopoulou C. Spice drugs as a new trend: mode of