**Synthetic Cannabis: A Case of Complicated Intoxication and Withdrawal**
Adriana de Julio1, MD, MSPH, Jude Registere2, BS, MPH; Merlyn Abraham3, BS
Department of Psychiatry, Advocate Lutheran General Hospital General Medicine, Chicago Medical School, Rosalind Franklin University

**Abstract**
INTRODUCTION: Synthetic cannabis (SC) has become well known as a drug of abuse. It is reported that “12% of U.S. high school students have used synthetic cannabis in the past year.” Although the use of synthetic cannabis is growing, treating SC intoxication and withdrawal continues to be difficult. A recent study of emergency room physicians practicing in urban areas revealed that only 20% felt prepared to take care of patients with a synthetic cannabis intoxication (2). Here we present a case that highlights the medical, neurological, and psychiatric sequelae from acute intoxication as well as the psychiatrist’s role in integrative medical teams treating SC withdrawal.

**CASE DESCRIPTION:** A 28-year-old Middle Eastern man with a prior history of cannabis and nicotine use presented to the Emergency Department after being found by paramedics detained at a train station. Paramedics witnessed the man to have a tonic-clonic seizure. After transport to the emergency room two subsequent seizures were witnessed. Neurology was consulted and performed a battery of exams with no abnormal findings. Soon after admission the patient developed acute kidney failure and required dialysis. As the patient recovered and continued dialysis he began experiencing anxiety.

**INTERVENTION:** Psychiatry was requested to evaluate the patient after he began to have insomnia and panic attacks. A full psychiatric evaluation revealed extensive synthetic cannabis use over a 4-year period. The patient was placed on low-dose benzodiazepine and clonidine to treat synthetic cannabis withdrawal. After the patient’s kidney functions returned to baseline gabapentin was utilized to replace the benzodiazepine. The patient was admitted to an outpatient addiction treatment program at the time of discharge.

**Patient Presentation**
A healthy 28-year-old Middle Eastern man, with a history of alcohol and cannabis use, was found by paramedics unresponsive at a train station. Upon arrival the paramedics noted the patient’s Glasgow Coma Scale as a 9 and bluish coloration was noted on the patient’s mouth and lips as well as abrasions along his right face and torso. Soon after their arrival the patient had a tonic-clonic seizure for approximately 1 minute. Midazolam was administered and the patient was intubated and transported to an emergency department (ED). In the ED he was confused and combative. Telemetry readings revealed sinus tachycardia. The patient subsequently experienced two more tonic-clonic seizures and multiple medications were administered: midazolam, succinylcholine, propofol, and lorazepam.

Laboratory results showed: a WBC of 33,000, elevated creatinine, standard urine drug screen was negative, blood alcohol content was undetectable and toxicology for acetaminophen and salicylate was unremarkable. CT of the head showed no acute injury.

Neurology performed a lumbar puncture and ordered levetiracetam; Infectious Disease ordered vancomycin, ceftazidime and azyclolav. The patient was stabilized and admitted to the intensive care unit.

The patient’s family reported that he was using “K2” a type of SC, but initial differential diagnosis did not include seizure secondary to SC intoxication.

**Initial Hospital Course**
Hospital Day 1: The patient was intubated, placed on oxygen, and was able to participate in a urine drug screen. He stated he had not used in his urine for the past 3-4 weeks, but he had not sought medical attention. He also admitted to using SC sporadically.

Hospital Day 2: CSF examination was reported as normal. Renal function continued to decline. Creatinine increased from 1.47 mg/dl to 6.92 mg/dl. dialysis was initiated and he was dialyzed, started on piperacillin/tazobactam, and a course of steroids.

Hospital Day 4: His respiratory functions improved. He underwent a third dialysis treatment. Kidney biopsy was performed and pathology confirmed acute tubular necrosis (ATN).

Hospital Day 6: The patient began to have complaints of increasing anxiety, chest pain, palpitations, fear of dying, and uncontrollable crying that was accompanied by tachycardia and sweating. These episodes were treated effectively with lorazepam. Underwent initial and final dialysis.

Hospital Day 8: The patient continued to be anxious and was unable to sleep. He was started on lorazepam and clonazepam. Episodes of anxiety were treated with lorazepam with some relief.

**Psychiatric Consultation**
Psychiatry was consulted on hospital day 7 as the patient continued to experience frequent panic attacks. A complete psychiatric history was obtained that revealed the patient had suffered from social anxiety. His social anxiety caused him to sweat and 5 years prior he sought a medical consultation from a plastic surgeon for hyperhidrosis of the axilla. He underwent botulinum toxin injections that improved the hyperhidrosis, but admitted that he was also using cannabis to feel comfortable in social situations.

He reported drinking alcohol twice weekly and never more than four drinks at any one time. He had begun a job 4 years prior that administered regular urine drug screen and at that time he decided use SC to avoid detection. Initially he was using 1 gram a day, but reported that over the past 2 months he was using up to 3 grams a day of SC.

He reported a history of panic attacks associated with withdrawal from SC. Since being admitted the patient had complaints of severe anxiety, restlessness, nightmares, chest pain, headache, profuse sweating, and nausea.

The exam did not reveal any other psychiatric, neurological, or substance abuse history.

**Differential Diagnosis**
Differential Diagnosis of presenting seizures included: encephalitis causing generalized seizure; alcohol withdrawal seizure; and seizure secondary to synthetic cannabis intoxication.

Differential Diagnosis of patient’s anxiety starting on Hospital Day 5 included: synthetic cannabis withdrawal, alcohol withdrawal, and unspecified anxiety.

Research was conducted to obtain more information about synthetic cannabis. Case reports and a literature review were conducted on PubMed.

Diagnostic Criteria from DSM-5 was reviewed for Substance Induced Anxiety Disorder, with onset during withdrawal.

**Synthetic Cannabis**
Beginning in the 1980’s Clemson University began research aimed at making a synthetic cannabinoid compound that would not be detected in endogenous cannabinoid receptors in the human brain. The first such compound that was synthesized was named JWH-018. Many other analogues have since been synthesized (Fig 1).

The first reports of synthetic cannabis being used as a drug of abuse began in the early 2000’s and were marketed under genericized trademarks of K2 and Spice. Synthetic cannabis is a blend of herb and plant material sprayed with one or more synthetic cannabinoids and packaged in single use foil and paper (Fig 2, 3).

In 2008 European countries became concerned about SC products and conducted laboratory tests confirming synthetic cannabinoids and soon after banned them. In 2010, U.S. poison control centers received over 2,500 calls related to synthetic cannabis and with concern growing the DEA, using emergency powers, mandated that synthetic cannabinoids illegal in 2011. In 2012 the Synthetic Drug Abuse Prevention Act was passed that bans synthetic compounds found in synthetic cannabis, stimulating research.

Rates of synthetic cannabis use have continued to be high. In 2012 12% of the student population reported use in the past month (Fig 4). The only way of detecting synthetic cannabis is through gas or liquid mass spectrometry.

**SC Intoxication and Withdrawal**
The pathogenic mechanism of renal failure caused by ATN in patients with SC intoxication is not clear, but it may be that SC substrate metabolism may be nephrotoxic (4). Unlike marijuana (9-THC), that is a partial agonist at cannabinoid receptors, synthetic cannabis is a full agonist as it is a synthetic analog of both cells and receptors.

Additionally, SC binds with higher affinity than 9-THC. This distinct pharmacological activity of SC as compared to 9-THC makes it much more toxic and may be part of the explanation for it’s seizure potential, renal insults, and prolonged anxiogenic effects during withdrawal (6).

This case is one of three cases reports of prolonged withdrawal syndrome from synthetic cannabis (5,6). The probable chemical mechanisms that increase levels of anxiety have been studied in the rodent model. There is a body of evidence that demonstrates that SC withdrawal increases the noradrenergic activity by increasing the firing rate of locus coeruleus neurons causing anxiogenic like responses that last up to 8 days (7,8). Multiple cases have been reported of persons having psychiatric breaks and committing suicide while intoxicated on SC. There is evidence that because SC is a full agonist at both endogenous cannabinoid receptors and augments the left lateral and hippocampus this contributes it’s increased psychotropic effects (11).

**Treatment Plan**
Two diagnoses were made: seizure secondary to acute SC intoxication and SC induced anxiety disorder, with withdrawal onset.

The Psychiatry Team formed a treatment plan based on case reports, DSM-5 criteria, a literature review and worked collaboratively with Addiction Medicine, Internal Medicine, Neurology, and Nephrology.

The patient was started on IV lorazepam initial and then moved to low dose clonazepam and clonidine. As the patient’s renal function improved and at discharge his creatinine was 4.67 mg/dl.

The patient was admitted to a six week outpatient substance abuse partial hospitalization program. He was an active participant and all urine drug screens, ordered to include SC by GC-MS, were negatives.

**Clinical Pearls**
If SC intoxication is suspected the acute effects can be managed supportively. The CDC recommends that patient’s be given IV fluids if seizure is a presenting factor or if there is an increased creatinine to present renal injury. Approximately 25% of patients will become agitated and anxious a benzodiazepine should be used for these patients. Teams must carefully monitor patient’s neurological, psychiatric, and renal status if SC is suspected.

While alcohol, tobacco, and cannabis have higher rates of use amongst youth and young adults, synthetic cannabis (SC) is a large unknown drug that is associated with SC, look-alike and look alike challenge, as standard urine drug screens do not detect SC. The literature review suggests that SC should especially be aware that a negative drug screen might not guarantee that a patient is substance free.

The serious neurological and psychiatric sequelae of SC are often the reason psychiatrists will be consulted to assist in treating these patients. Teams should remain mindful of the effects of SC so as to not misdiagnose symptoms as psychiatric rather than substance related. They also must consider the serious medical sequelae before prescribing medications to assist with intoxication and withdrawal symptoms.

**References**