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# Selected Topics: Toxicology

# SYNTHETIC CANNABINOIDS AND THEIR EFFECTS ON THE CARDIOVASCULAR SYSTEM

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☐ **Abstract—Background: In the past couple of years, there has been an outbreak of synthetic cannabinoid (SC) use in major cities in the United States. Patients can present with various symptoms affecting the central nervous and cardiovascular systems. The effects of endocannabinoid on contractility and $Ca^{2+}$ signaling have been shown through both cannabinoid receptors and a direct effect on ion channels. These effects result in abnormalities in ionotropy, chronotropy, and conduction. Case Report: Here we report on two cases of SC abuse and abnormalities in the cardiovascular system. These cases raise concerns about the adverse effects of SCs and the possibility of QTc prolongation and subsequent complications when using antipsychotic medication in the presence of SC abuse. Why Should an Emergency Physician be Aware of This?: Given the rise in SC use and the potential effect on the cardiovascular system, physicians need to be mindful of potential cardiac complications, such as QTc prolongation and torsade de pointe, especially when administering medications that have the potential to cause QTc prolongation.** © 2016 Elsevier Inc.

☐ **Keywords—synthetic cannabinoids; cardiovascular system; toxicology**

## INTRODUCTION

In the past couple of years, there has been an outbreak of synthetic cannabinoid (SC) use in most US cities, including New York (1). The Centers for Disease Control and Prevention reported a 229% increase in calls to poison control centers related to SC use in a period from January to May 2015 compared with the same time period in 2014. Patients can present with various symptoms of central nervous system (CNS) and cardiovascular system dysfunction, ranging from bradycardia, tachycardia, hypotension, rhabdomyolysis, hyperthermia, and seizure, in addition to various psychiatric symptoms (2–7). One reported death occurred after using the SC brand "You Only Live Once." Given the variety of products commonly referred to by patients as "K2," physicians need to look for new symptoms of exposure to these agents, as the products might not contain the same compounds. We have seen different products, with names like Green Giant, Caution, AK-47, Scooby Snax, Smacked, Bomb Marley, that are referred to as K2 by patients (3). It is not known if all of these products contain the same substance and plant base. The effect of endocannabinoid on contractility and $Ca^{2+}$ signaling has been shown via cannabinoid (CB) receptors and through direct effect on ion channels. These effects result in abnormalities in ionotropy, chronotropy, and conduction (8–10). Cardiac toxicity from SCs has been reported recently (11). These cases will highlight some of the various effects of SCs on

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the cardiovascular system that can lead to potentially life-threatening complications.

## CASES

*Case 1*

A 29-year-old male with a medical history of depression was brought to the adult psychiatric emergency department (ED) with disruptive behavior. He reported that he had been smoking K2 and had been noncompliant with psychiatric medications. He was agitated and combative and required sedation with haloperidol and lorazepam. An electrocardiogram (ECG) performed 5–10 min after medication showed prolonged QTc of 560 ms (Figure 1A). This finding was new compared with a QTc of 412 ms from 8 months earlier (Figure 1B). The patient was transferred to the adult ED. He was slightly lethargic from the sedation, but responded to simple questions. His blood pressure was 117/64 mm Hg with a heart rate of 80 beats/min.

The patient stated that he was prescribed sertraline 100 mg daily and quetiapine 50 mg at bedtime, but he had been noncompliant with medications. The patient was started on the medications 1 year earlier. Laboratory examination revealed normal magnesium and potassium levels, but elevated creatine kinase (CK) of 1,129 (U/L). Urine toxicology was negative for barbiturates, benzodiazepines, cocaine, opiates, methadone, tetrahydrocannabinol, and phencyclidine.

*Case 2*

A 45-year-old male patient with no significant medical history presented to the ED intoxicated after smoking K2. On initial evaluation, he was found to have a blood pressure of 100/70 mm Hg, a heart rate of 32 beats/min, and oxygen saturation of 96% on room air. His ECG showed second-degree atrioventricular block type I (Figure 2). He was given atropine and his heart rate improved to 69 beats/min. Laboratory work-up was significant for CK of 1,230 (U/L). Urine toxicology was positive for cocaine. The patient was evaluated by a cardiologist and admitted to the hospital. He subsequently signed out against medical advice. He returned to the ED the next day with similar symptoms and again left against medical advice after the initial management.

## DISCUSSION

The use of SCs has been associated with numerous adverse effects on the CNS and cardiovascular system, including symptoms of bradycardia, tachycardia, hypotension, seizure, and QTc prolongation (2,11). Small studies have suggested that certain types of SC administration on rats displayed bradycardia and prolonged QTc mediated through cardiac CB receptors (12,13). The effect of endogenous CBs ranges from myocardial depression and conduction abnormalities via CB receptors (14,15). It has been shown that their effect involves blockade of $Na^+$ channel and inhibition of $Na^+/Ca^{2+}$ exchanger (8–10). These cases exhibit patients with stated exposure of SCs and negative urine toxicology. Patient 1 had a normal ECG with QTc of 412 (Figure 2) <8 months before this incident. One explanation for the cardiac abnormalities could be the potency of the SC and its prolonged or stronger effect on the cardiac conduction system and myocytes, leading to decreased stroke volume and conduction abnormalities in comparison with endocannabinoids.

The patient in case 1 was given haloperidol 5 mg intramuscular (i.m.) to control his agitation before the ECG was performed in the ED. Haloperidol can lead to QTc prolongation, but, given haloperidol's i.m. absorption rate of 60% to 70% with $T_{max}$ of 20 min, it is unlikely that the QTc prolongation is from the haloperidol (16). The patient stated he suffers from depression and had been prescribed sertraline 100 mg daily and quetiapine 50 mg at bedtime. Quetiapine can cause QTc prolongation. The patient had been on the medications for 1 year, but he was not taking it regularly, and an ECG performed 8 months earlier showed normal QTc at 412 ms. With no change in medication dose and infrequent use, quetiapine is less likely to have been the cause of the patient's prolonged QTc. In addition, the patient's urine drug toxicology was negative for agents that might have caused his prolonged QTc, including methadone. Electrolyte abnormalities that can cause QTc prolongation were not apparent from his laboratory results.

The direct cause of the patient's prolonged QTc is difficult to assess, as there are many factors, including co-ingested substances, that can lead to prolonged QTc. With the most common possibilities discussed, SCs need to be included in the list of potential causes of cardiac conduction abnormalities and QTc prolongation that can cause life-threatening dysrhythmia, such as torsade de point. Case 1 raises concerns with regard to the use of antipsychotic medication that would prolong QTc in the presence of K2 abuse (17).

## WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Exposure to SCs can cause a multitude of symptoms, one of which is prolonged QTc or heart block. Although less common than other symptoms, physicians need to be mindful of this possible complication, especially when administering medications that have the potential for