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## A new side effect of synthetic cannabinoid use by the bucket (waterpipe) method: Acute respiratory distress syndrome (ARDS)

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### ABSTRACT

The use and content of synthetic cannabinoids (SCs) has been rapidly increased in the last decades. The complex content of these substances bring along a wide spectrum of side effects. In addition to the expected neuropsychological side effects of pleasure-inducing substances such as agitation, anxiety, panic attack and hallucinations, rare cases of cerebrovascular diseases, seizures, acute renal injury, myocardial infarction and chronic lung injury have also been previously reported.

Here we report a 19-year-old male who was presented with acute respiratory distress syndrome (ARDS) within hours of inhaled SC use with the rarely preferred bucket method. There is limited information in the literature about pulmonary effects of SCs and we could not detect any other ARDS case that developed within hours after consumption of SC with the bucket method.

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### 1. Introduction

The use of synthetic cannabinoids (SCs) as an alternative to marijuana and similar euphoria-inducing substances has rapidly increased in many countries.<sup>1,2</sup> SCs are illegal in Turkey and, according to the report of the national police department, the number of persons detained in relation to SC use increased by 19-fold between the years 2011 and 2012.<sup>3</sup> In addition to a cigarette-like form, there also exist oral, sublingual, intranasal forms, as well as a less common form known as the “bucket” method, where water-distilled smoke is directly inhaled into lungs using a water pipe-like mechanism (Fig. 1). Known by various names as Bonzai, K<sub>2</sub>, Spice, Armageddon, Black mamba in different countries, SCs are constantly changing formulas by the addition of various new

substances. European Monitoring Center for Drugs and Drug Addiction (EMCDDA) reported 30 new SCs in 2014<sup>4</sup> and, according to the report of EU Early Warning System in 2015, the number of SC varieties reached 137.<sup>5</sup> Such a complex content of these substances brings along a wide spectrum of side effects. In addition to the expected side effects of pleasure-inducing substances including agitation, anxiety, panic attack, hallucinations, euphoria, and mental status changes,<sup>2</sup> rare cases of cerebrovascular diseases (CVD),<sup>6</sup> cardiac dysrhythmia<sup>7</sup> have also been reported.

Herein, we report a 19-year-old young male who presented with ARDS within hours of inhaled SC use with the rarely preferred bucket method.

### 2. Case presentation

A 19-year-old man without an underlying disease was brought by an ambulance to the emergency department (ED) after loss of consciousness following consumption of bonzai with the bucket method. On admission, he was unconscious with Glasgow coma score of 5 (E1V2M2); his pulse rate was 102/minute(min), arterial blood pressure 80/60 mmHg, and body temperature 36.4 C<sup>0</sup>. As he had shallow breaths at a rate of 5–6/min, he was orotracheally intubated and large amount of pink frothy and a little bloody secretion soon flooded the endotracheal tube.

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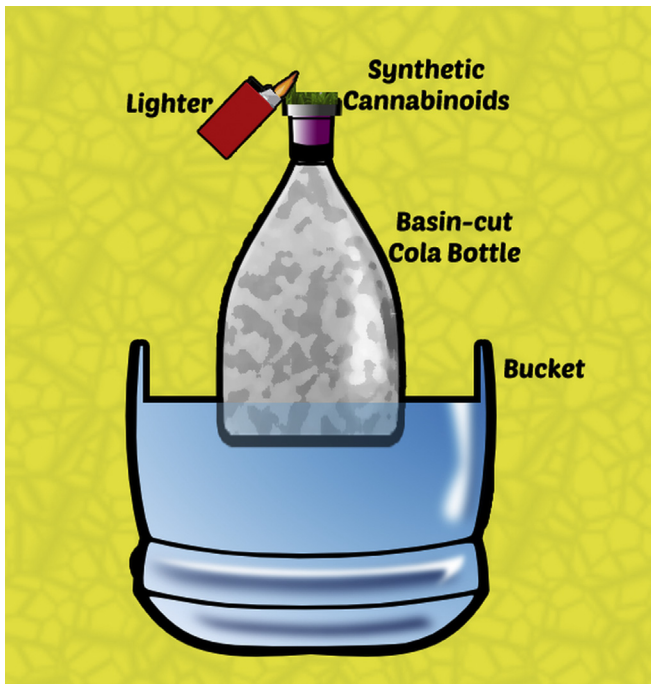


Fig. 1. The "bucket" method has been schematized.

A detailed medical history of the patient revealed SC addiction for the last 3–4 years, with seldom (rarer than once a week) use of the SC like smoking. In addition, there are no other substances habits besides 5 pack/year tobacco consumption. It was learned that he and two of his friends consumed the SC with alcohol (100 cc beer), as usual but this time he took the SC with the bucket method. The patient was usually using a maximum of one dose SC (as much as one cigarette) at one time. But this time he used two doses SC in a shorter time with the bucket method. His friends told that he began to have euphoria and exhibit bizarre behaviors more quickly than usual and he fell asleep within 30 minutes upon continuous use of the bonzai. And his friends also stated that they were together throughout the day and denied taking another substance or drug.

An arterial blood gas analysis (ABGA) prior to intubation revealed respiratory acidosis (PH:7.01, PaCO<sub>2</sub>:100.7 mmHg, PaO<sub>2</sub>:17.7 mmHg, HCO<sub>3</sub>act: 25.2 mmol/L). Despite ventilation by surevent with 100% oxygen at a pressure of 25–30 cm H<sub>2</sub>O after endotracheal intubation, peripheral oxygen saturation could only be increased to 85%. ABGA under 100% oxygen after intubation were: PH: 7.28, PaCO<sub>2</sub>: 47.5 mmHg, PaO<sub>2</sub>: 92.6 mmHg, HCO<sub>3</sub>act: 21.8 mmol/L. Laboratory studies revealed WBC:13.6 10<sup>3</sup> μL, potassium: 2.69 mEq/L, CK:202 U/L, and glucose: 326 mg/dL. Liver function tests, coagulation tests and cardiac troponin I level were all within normal limits. A cranial CT was free of any abnormality, but a thoracic CT showed diffuse areas of consolidation containing patchy air bronchograms of groundglass density in both lungs (Fig. 2a–b). Bedside echocardiography revealed no left ventricular systolic dysfunction.

Approximately 300 ml of bloody and pink frothy secretion were aspirated from the endotracheal tube within first 4 h of follow-up. However, hemoglobin and hematocrit values did not change significantly.

The patient was treated with a mechanical ventilation protocol for ARDS. Enteral feeding started from the first day. Proton pump inhibitor, antibiotics and isotonic fluid were administered intravenously. Specific antitoxic agent was not administered. No acid-

resistant bacteria were detected in the tracheal sputum aspirate, nor any bacterial proliferation occurred in his blood cultures. Anti-LKM, mitochondrial antibody (AMA), antinuclear antibody (FANA) (IFA), smooth muscle antibody (ASMA), anti-GBM antibody were all negative. ELISA tests for active hepatitis viruses and HIV were also negative. The patient was taken to the regular ward on 8th day upon the elimination of the need for mechanical ventilation and intensive care.

### 3. Discussion

In 2012, ARDS diagnostic criteria were reorganized as "Berlin Definition". According to the Berlin Definition, the term "acute" refers to respiratory symptoms that begin or worsen within a period of a week. In our patient, the symptoms developed within hours. As a second criterion, there must be bilateral opacities consistent with pulmonary edema on chest X-Ray or thoracic CT, which cannot be explained by other chronic causes.<sup>8</sup> Our patient had bilateral air-bronchograms containing patchy ground glass density unexplained by a separate condition. The third criterion states that it should be demonstrated that these lung opacities are not secondary to cardiogenic pulmonary edema. Our patient had neither left ventricular systolic dysfunction on bedside echocardiography, nor he had cardiomegaly on thoracic CT (Fig. 2a and b). As a fourth, according to the impairment of oxygenation, moderate ARDS is marked by a ratio of arterial oxygen tension to fraction of inspired oxygen (FiO<sub>2</sub>) of 100–200.<sup>8</sup> Our patient's PaO<sub>2</sub>/FiO<sub>2</sub> was 147.

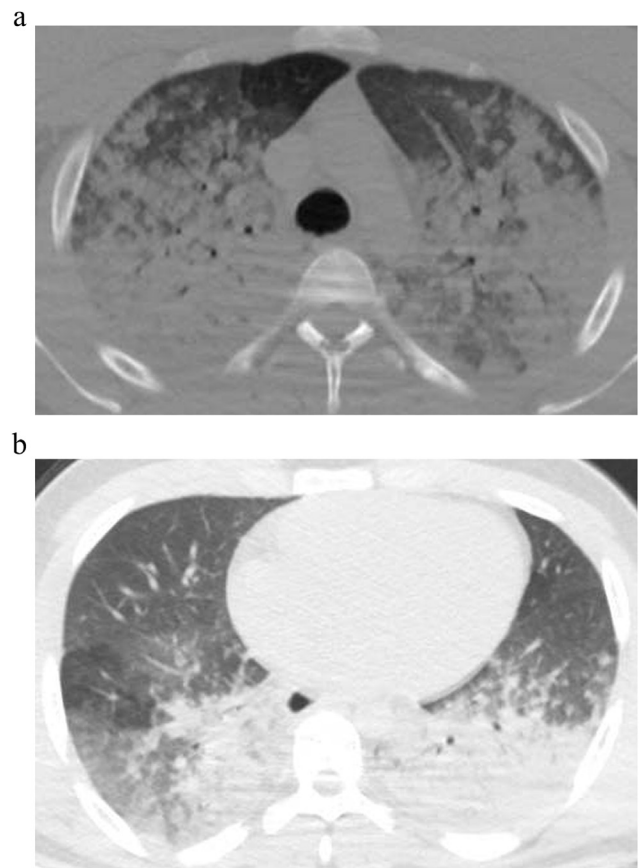


Fig. 2. Thorax CT demonstrated bilateral widespread infiltration in the lung extending to the apices, which is not accompanied by cardiomegaly. a: Thorax CT apical level of lung. b: Thorax CT middle cardiac level.

We could only access two case reports with diffuse lung injury associated with SC use and need of mechanical ventilation. The first of these reports was reported by Alhadi et al. about a 21-year-old man with cough and bloody sputum for two months and bilateral infiltrations on chest X-Ray, which the authors associated this presentation with chronic SC use.<sup>9</sup> Although their patient showed similarity by ours in terms of diffuse lung infiltrations, his chronic symptoms suggest a rather slowly progressive lung injury. The second case presentation was reported by Loscher et al. about a 19-year-old man with a two-month history of regular SC use. The man was found unconscious and with abundant blood around his mouth; his chest X-Ray revealed bilateral alveolar infiltrations, which was thought to be secondary to diffuse alveolar hemorrhage during bronchoscopy.<sup>10</sup> That patient was associated with chronic SC use and diffuse alveolar hemorrhage was reported as the outcome of chronic lung injury. Unlike that patient, our patient had only rarely used SC. Eugene et al. examined pulmonary effects of SCs in four patients, and they reported that SCs cause diffuse miliary-micronodular changes on chest X-ray and diffuse centrilobular nodules and a histopathological pattern of organizing pneumonia on CT.<sup>11</sup> The mechanism by which SCs induce lung injury is unclear. In addition, there are reports of hemorrhagic CVD by an increased bleeding tendency via direct action or by hypertensive effects of SCs.<sup>6</sup> However, unlike other cases, our patient used SCs by direct inhalation of water-distilled smoke by a “bucket” method, which suggests that SCs may cause direct lung injury by direct action. The use of SCs by the “bucket” method can be likened to rapid and direct inhalation of bronchodilator drugs into the lungs. Therefore, when synthetic cannabinoid is used with this method, a high amount of substance is directly instilled into the lungs in a short time. For this reason, it is expected that the possibility of direct damage to the lungs is more likely by this method. Our patient had previously used the same product like cigarette smoking method and was not suffered any health problem. In addition, bloody and pink frothy aspirate supporting acute lung injury was seen in endotracheal tube after intubation. And our patient used SCs in greater amounts than his friends. The absence of any signs of ARDS in his friends who used the same substance albeit at a lower amount suggests that this side effect may be related to the amount of the substance, method of use and personal characteristics.

The other possible effect of SCs on respiratory system is respiratory depression. Shimid et al. demonstrated the respiratory depressant action of SCs on rats.<sup>12</sup> The authors hypothesized that an increased bronchial airway resistance via peripheral chemoreceptors over CB<sub>1</sub> receptor by an unknown mechanism caused respiratory depression, which ultimately led to hypoxia, hypercarbia, and respiratory acidosis.<sup>12</sup> Our patient similarly breathed shallowly, at a rate of 5–6 breaths per minute, and his respiratory drive was depressed and his peripheral oxygen saturation was low; he also featured signs of respiratory depression at blood gas analysis. It is therefore likely that the SCs' side effect of respiratory depression was pivotal for the progress toward ARDS.

#### 4. Limitations

SC metabolites were not studied in blood or urine in this case since SC metabolites are not studied in our center. However, it should be kept in mind that SCs have constantly changing formulas by the addition of various new substances each passing day. For this reason, current laboratory tests may be insufficient to detect all of the synthetic cannabinoid forms.<sup>2,13</sup>

#### 5. Conclusion

Acute intoxication of SC may cause ARDS by causing lung injury in relation to method of use and amount of substance inhaled.

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#### Conflict of interest

The authors declare no conflict of interest.

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