

# Gastrointestinal Manifestations of Synthetic Cannabinoids: A retrospective Cohort Study

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## Research article

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# Abstract

**Introduction:** Synthetic cannabinoids (SCs) are chemical substances similar to tetrahydrocannabinol that are used as illicit drugs and often smoked as recreational herbal mixtures. The usage of SCs is rapidly increasing worldwide. The adverse effects of SCs are wide ranging, and span from mild behavioral changes to death. The knowledge regarding gastrointestinal (GI) manifestations of SCs use is sparse.

**Methods:** Medical records of patients with presentations to the hospital due to SCs use between January 2014 and February 2018 were retrieved from Hadassah Mount Scopus Hospital's computerized database. The records were reviewed for clinical outcomes and laboratory tests.

**Results:** Fifty-five patients were identified with hospital presentations due to SCs use. Twenty-one out of 55 patients (38%) reported GI complaints, with the most common being abdominal pain and vomiting. 28% had recurrent emergency department presentations due to abdominal pain and 66% presented with leukocytosis. Serum lactate was elevated in 66% of patients with GI manifestations. One patient had an abnormal computerized tomography (CT) abdominal angiography scan, which was compatible with intestinal ischemia.

**Discussion and conclusions:** The clinical spectrum of GI manifestations in SCs intoxication ranges from mild symptoms including abdominal pain and vomiting to intestinal ischemia. Clinicians should be aware that abdominal pain and other GI complaints can be associated with SCs usage.

## Introduction

Since the early 2000s, synthetic cannabinoid (SCs) compounds, first developed by researchers to study the cannabinoid receptor (CB<sub>1</sub>), have become popular recreational drugs of abuse mostly due to their psychoactive properties and similarity to tetrahydrocannabinol (THC). SCs were first synthesized in the 1960s to explore potential medical uses of compounds designed to target CB<sub>1</sub>. Over time they have been modified and distributed widely for illicit use with most SCs users being male [1]. The life prevalence of SCs usage was demonstrated to be 7.6% in a survey of more than 3,100 college students [2] and was found to be as high as 17% in an anonymous online survey among nearly 15,000 participants in the United Kingdom [3].

SCs usually appear in the illicit drug market as smokable herbal mixtures containing plants, but can also be consumed via vaporized liquid, inhaled in e-cigarettes, or by ingestion. The herbal mixtures that carry the active SCs are sprayed following dissolution of the synthetic substance in acetone or similar solvents [4]. New SCs are constantly being developed, and new compounds are legal to possess until they are eventually formally banned. Due to the ability of laboratories to rapidly change the chemical structure of SCs, it is especially difficult to monitor and restrict their use by law enforcement agencies [5]. SCs products sold on the street and online, are referred to by various names [6]. The active chemicals are not characterized using controlled laboratory testing, and many products are mixed with potentially

dangerous substances such as other illicit drugs, rat poison, or embalming fluids [7]. Thus, the clinical consequences of SCs use are not well-defined [8].

Patients admitted to the hospital due to SCs intoxication mostly present with neurological and psychiatric manifestations, such as agitation, psychosis, or anxiety, and may also present with seizures [9] (reported to lead to rhabdomyolysis and hyperthermia), acute renal failure [10], or myocardial ischemia, even in teenagers [11]. The gastrointestinal (GI) effects of SCs use have not been thoroughly described. GI symptoms in SCs intoxication may be the result of SCs interaction with CB1 and CB2 [12]. Of note, CB1 has been detected in most peripheral tissues, including the GI tract [13]. While reports on the epidemiology and clinical spectrum of GI manifestations of SCs usage are limited, cases have noted that SCs can impact the GI tract, causing varying symptoms such as vomiting and abdominal pain [8], and can lead to a hyperemesis syndrome similar to cannabis hyperemesis syndrome [14]. In this study, using a cohort of patients presenting to the hospital after SCs use, we examine the association between SCs use and the GI tract and try to understand its clinical impact, pathophysiology, and prognosis.

## Results

One hundred and five patients with SCs use were identified. Two of the patients were excluded as they were under the age of eighteen and 16 patients were excluded due to uncertainty of SCs usage in the medical chart. Thirty two patients were excluded because SCs exposure was reported as a part of prior medical history, rather than being part of the current hospitalization. The remaining 55 patients were included in the study (Fig. 1).

Twenty-one out of the 55 patients (38%) were admitted with GI symptoms, and the rest of the common symptoms leading to admission were chest pain, nausea, agitation, and restlessness. Of the patients with GI symptoms, 20 out of 21 were male (95%). Eighty percent of the patients (n = 17) were of Arab origin and the rest were either of Jewish or Christian origin. The average age of the 21 patients with GI symptoms was  $32.9 \pm 10.4$  years, while the average age of patients without GI symptoms was  $35.4 \pm 10.9$  years ( $p = 0.22$ ).

Abdominal pain was the primary reason for presentation in 18 of the 21 patients (85.7%) with GI manifestations and 12 of the patients (57.1%) reported vomiting. Repeated ED admissions due to GI symptoms were noted in 28% (n = 6) of patients, and, of these, two patients had seven prior admissions to the ED due to various complaints related to SCs usage. The average number of ED presentations per patient amongst those with GI manifestations was  $2 \pm 1.9$ , and the average number of ED presentations amongst those without GI manifestations was  $1.6 \pm 1.2$  ( $P = 0.3$ ).

Of those with GI manifestations secondary to SCs use on ED presentation, 24% (n = 5) were hospitalized due to these GI symptoms, while the rest were discharged from the ED for outpatient follow-up. The average length of hospitalization in patients with GI manifestations was  $0.9 \pm 2.1$  days as compared to  $2.3 \pm 4.3$  days ( $p = 0.22$ ) in those without GI symptoms. (Table 1) Two of the hospitalized patients in the GI group were admitted to the intensive care unit, and both had multiple prior presentations to the ED

secondary to SCs use. One of these patients died, likely due to small intestinal perforation leading to severe shock. The second patient presented with severe hypokalemia and a potassium of 1.7 mEq/L (normal range 3.5–5.1 mEq/L).

Table 1  
Socio-demographic characteristics of patients in those with and without GI symptoms.

	<b>With GI symptoms</b>	<b>Without GI symptoms</b>	<b>p value</b>
Age (mean+/- SD)	32.2 +/- 9.2	35.4 +/- 10.9	0.22
Male (%)	95	85	-
Hospital encounters (mean+/- SD)	2 +/- 1.9	1.6 +/- 1.2	0.3
Hospitalizations (mean+/- SD)	0.5 +/- 1.4	0.4 +/- 0.7	0.55
Length of longest hospitalization (mean+/- SD)	0.9 +/- 2.1	2.3 +/- 4.3	0.22

The average potassium levels of those with GI manifestations were 3.76+/- 0.75 mEq/L as compared to 3.82+/- 0.5 in those without GI manifestations (P = 0.5). The creatinine levels were 104.8 +/- 60 mmol/Liter (normal range 60–115 mmol/Liter) in those with GI manifestations and 85.1 +/- 26 in those without GI manifestations (0.24). Ten patients of those with GI manifestations had blood gas testing performed in the ED, two of whom had a metabolic acidosis, one had metabolic alkalosis, and one had a respiratory alkalosis. The remaining six who underwent blood gas testing were found to be within the normal range.

All 21 patients with GI manifestations underwent complete blood count laboratory testing, 16 of whom (76%) had leukocytosis (normal range: 4-10E9/L), with six patients (28%) having leukocyte levels greater than 20 E9/L. Serum lactate (normal range: 0.5–2.4 mmol/L) was measured in eight patients (38%) in those with GI manifestations and was measured in six (17%) patients in those without GI manifestations. Lactate was elevated in six patients (66%) in those with GI manifestations and in two patients (33%) in those without GI manifestations. In two patients with GI manifestations, serum lactate was severely elevated (greater than eightfold higher than the upper limit of normal range). (Table 2)

Table 2

Clinical and Laboratory results of patients with GI and without GI presentation of SCs intoxication

	With GI symptoms	Without GI symptoms	p value
Temperature (mean +/- SD)	36.5 +/- 0.6	36.6 +/- 0.5	0.5
Heart rate (mean +/- SD)	72.9 +/- 20.8	79.3 +/- 17.3	0.26
Systolic BP (mean +/- SD)	131 +/- 18.6	134.2 +/- 18.5	0.84
WBC (mean +/- SD)	17.2 +/- 8.3	14.0 +/- 5.6	0.09
HGB (mean +/- SD)	16.3 +/- 1.3	15.6 +/- 1.7	0.19
ALT (mean +/- SD)	22.2 +/- 14.5	41.0 +/- 68.9	0.3
ALK PHOS (mean +/- SD)	81.9 +/- 24.0	91.8 +/- 36.8	0.37
pH (mean +/- SD)	7.4 +/- 0.1	7.3 +/- 0.2	0.19
Lactate (mean +/- SD)	4.3 +/- 4.9	4.5 +/- 4.4	0.92
Potassium mEq/Liter (mean +/- SD)	3.76 +/- 0.75	3.82 +/- 0.5	0.5
Creatinine mmol/Liter (mean +/- SD)	104.8 +/- 60.3	85.1 +/- 26	0.24

One third of the patients with GI manifestations (n = 7) underwent an abdominal computed tomography (CT) scan, of which six were normal and only one was abnormal, showing thromboses in the splanchnic arteries, mesenteric ischemia, and bowel perforation. Half of the patients with GI manifestations (n = 11) underwent standard urine toxic screen examination. In four (36%) of these patients the test was positive for THC, in four (36%) patients the test was positive for amphetamines, in two (16%) patients the test was positive for benzodiazepines, and in two (16%) patients the test was positive for methadone traces. Four patients (36%) had a negative urine toxicology screen. None of our patients underwent GC-MS testing in the hospital at the time of presentation.

## Methods

Electronic medical records of patients admitted to a single tertiary-care referral medical center between January 2014 and February 2018 were retrospectively reviewed. The electronic medical record database was searched for keywords "synthetic cannabinoids" and "Mr. Nice Guy" (one of the most commonly used SCs product in Israel). The medical records of patients admitted with SCs use were then reviewed and data was collected, including demographics, clinical and laboratory results, reason for hospital admission, length of hospital stay, placement in the hospital, diagnostic tests for SCs levels (i.e., Gas Chromatography-Mass Spectrometry (GC-MS) urine tests for synthetic cannabinoids and other unknown materials), imaging tests (including computed tomography (CT)), and patient outcomes. Records were also reviewed for GI manifestations of SCs use.

Patients were excluded if they were younger than 18 years old, had a confirmed diagnosis of an active psychiatric disorder, or had a known chronic GI disorder. GI manifestations were defined as symptoms of abdominal pain, vomiting, or diarrhea that were present in the emergency department (ED) as documented in the medical records. The study was approved by the hospital ethics committee and was exempt from patient consent given the retrospective nature of the study and that data was stored anonymously.

## Discussion

This is, to our knowledge, the first study describing the GI manifestations of SCs use in the acute setting. Among symptomatic SCs users presenting to the ED, 38% had GI manifestations and abdominal pain was reported by of those with GI symptoms. Still, the clinical presentation, laboratory results, and imaging findings ranged in severity among these patients. Most patients had only mild abdominal pain, while others had severe elevations of serum lactate with one patient having an intestinal perforation. Nevertheless, the vast majority of patients (20/21) had complete resolution of abdominal pain and normalization of serum lactate levels within a few hours of presentation.

When comparing the differences between the patients with GI manifestations and those without GI manifestations, there were no statistically significant differences in their prognoses, clinical severity, or laboratory values. However, the patients with GI manifestations had higher lactate levels likely caused by the intestinal involvement and more patients with severe leukocytosis. Still, due to the relatively low number of patients the statistical difference was not significant. The mechanism causing the varied effects of SCs on the GI tract is unclear, but may be related to a previously reported effect of THC and cannbinoidiol on CBr1 and CBr2, which influence GI function, motility, and sensation [15, 17]. Our study suggests that SCs GI symptoms are unpredictable and can vary from minimal or no symptoms to intestinal perforation and death [16]. This varied GI response to SCs may be due to the varying potency of SCs, especially with the development of new ultra-potent SCs that may impact the GI tract more than regular cannabis [18]. Others have suggested that the variability of SCs on the GI tract may be due to adulterants (such as caffeine, nicotine, and tramadol), which can contribute to clinical effects and toxicity [19].

An additional mechanism of SCs induced GI symptoms may involve vascular spasm. SCs have been shown to rapidly alter neurotransmitter release from nerve terminals, thereby potently activating vascular smooth muscle cells, potentially resulting in vascular spasm. Rose et al. reported two cases of subarachnoid hemorrhage following SCs consumption and used digital subtraction angiography to confirm transient vasospasm [20]. Moreover, Mir et al. reported two patients with ST-elevation MI following SCs use with subsequent normal coronary angiography [21]. SCs impacting the GI tract and GI vasculature was also reported. Buyukbese Sarsu described a young patient who developed duodenal perforation as a complication of peptic ulcer disease following chronic SCs use [22]. Therefore, transient spasm occluding the mesenteric vessels might cause the severe abdominal pain that was present in some of our patients and also may explain the transiently elevated lactate levels. The low proportion of

abnormal imaging in patients with severe abdominal pain, as in our study, supports the vasospasm theory as vasospasm is reversible, and no vascular pathological findings were demonstrated.

Currently, with the increasing prevalence of marijuana use by the public, there is extensive awareness of GI symptoms related to cannabis use, including abdominal pain and vomiting [23]. However, SCs related GI symptoms are less frequently reported. Furthermore, the lack of identifiable SCs in the toxicology screening in routine use make the diagnosis of SCs related GI symptoms difficult. With the increasing usage of SCs, it is important to recognize their potential to cause GI symptoms in the acute setting.

One limitation of our study is a lack of diagnostic serum and urine analytical studies to diagnose objective SCs use, a challenge noted in many SCs cohorts. As in many hospitals, the availability of gas chromatography and mass spectrometry testing in the acute setting is lacking, and similar to other studies in this field, we rely on patient and/or family reported history. A second limitation of our study is that patients presenting with SCs use often have concomitant drug intoxication, such as amphetamines and marijuana, which can also impact GI symptoms in a similar manner although not in the same rates of GI involvement compared to SCs. A third limitation is the lack of autopsy and post mortem imaging aside from one post mortem CT. Notwithstanding these limitations, we present the first cohort of patients presenting with various GI symptoms and SCs use in the acute setting. This can help to raise awareness and potentially guide future studies to evaluate the mechanisms of SCs GI involvement, including the hypothesis that transient arterial vasospasm causes the acute GI symptoms. GI consequences occurring with SCs use are often short-lived and resolve quickly though, in certain instances can be life-threatening (e.g. intestinal perforation; as demonstrated by one case in this cohort). Awareness of the breadth of clinical presentations and GI signs/symptoms common to SCs intoxication is important for providers treating these patients. Better analytic testing and drug confirmation is needed along with prevention of SCs use via counseling in at-risk populations is vital to reduce public health implications and morbidity from SCs use.

## **Conclusions**

Physicians and clinicians in the acute setting should consider SCs use as an etiology for unexplained vomiting and severe abdominal pain in young patients, especially when illicit drug use is suspected.

## **Abbreviations**

Synthetic cannabinoid (SCs), Cannabinoid receptor (CB<sub>1</sub>), tetrahydrocannabinol (THC), gastrointestinal (GI), computed tomography (CT), emergency department (ED),

## **Declarations**

### **Ethics Approval and Consent to Participate**

The study was approved by our hospital's (Hadassah medical center) Helsinki ethics committee. This article does not contain any studies with human participants or animals performed by any of the authors.

### **Competing interests**

The authors declare that they have no conflict of interest and competing interests.

### **Funding**

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### **Availability of data and materials**

The datasets analyzed during the current study available from the corresponding author on reasonable request

### **Contributions**

D.H the concept and design of the study and drafted the manuscript

A.B interpreted the results

T.K interpreted the results

M.W drafted the manuscript

S.I data acquisition

S.S data acquisition

Y.G data acquisition

M.M the concept and design of the study and drafted the manuscript

All authors read and approved the final manuscript

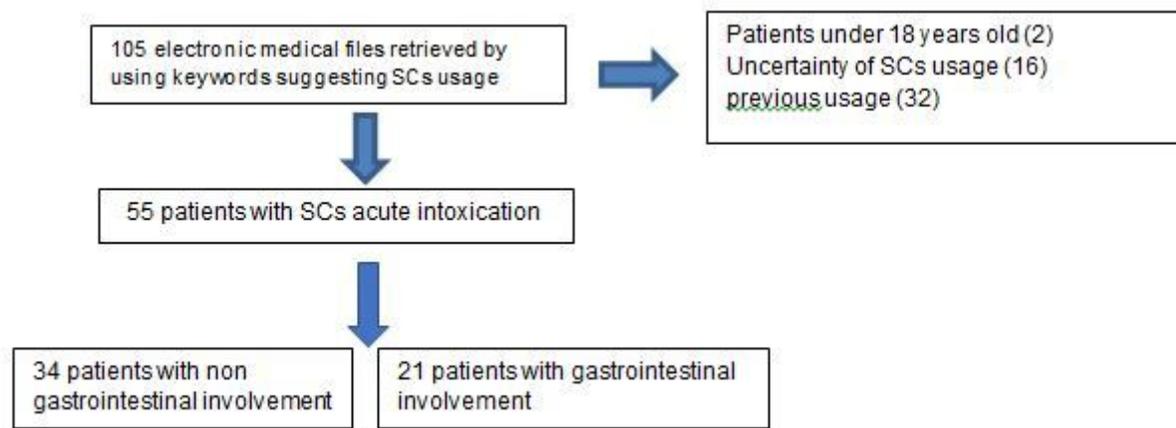
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## Figures



**Figure 1**

Study's patients flowchart