

Clinical Characteristics and Laboratory Test Results of Patients Admitted to Outpatient Clinic for Synthetic Cannabinoid Usage

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ABSTRACT

Clinical characteristics and laboratory test results of patients admitted to outpatient clinic for synthetic cannabinoid usage

Objective: Synthetic cannabinoids (SC) are psychoactive substances that have agonistic effects on cannabinoid receptors. The aim of this study was to investigate the sociodemographic variables, SC usage properties, clinical effects and withdrawal symptoms of SC in patients who admitted to Research, Treatment and Training Center for Alcohol and Substance Dependence (AMATEM) in Istanbul for SC usage, while analyzing the urine samples of the patients by an enzyme immunoassay screening test.

Methods: One hundred fifty eight patients who admitted to AMATEM outpatient clinic between 28.08.2013-13.02.2014 and reported that they had been using SC were enrolled in the study. Sociodemographic and clinical data form were applied to patients and their urine samples were investigated by a screening test.

Results: One hundred thirty five of the patients (86.0%) reported that they had been using cannabis before they started on SC, while 19 patients reported that the first substance they had used were SC. The reason to use SC was relaxation for 143 (92.3%) of the patients. One hundred eight (70.1%) of the patients had unsuccessful attempts to stop SC usage. One hundred four (86.7%) of the 120 patients whose urine samples could be analyzed, had positive screening test results for SC.

Conclusion: Our study is important because it is the first study that investigates the usage properties and clinical effects of SC with the screening test results for SC in Turkey.

Key words: Cannabis, laboratory, synthetic cannabinoids



ÖZET

Sentetik kannabinoid kullanımı nedeniyle polikliniğe başvuran hastaların klinik özellikleri ve laboratuvar sonuçları

Amaç: Sentetik kannabinoidler (SK) kannabinoid reseptörleri üzerinde agonistik etki gösteren psikoaktif maddelerdir. Çalışmamızın amacı SK kullanımı nedeniyle Alkol Madde Araştırma, Tedavi ve Eğitim Merkezi (AMATEM) İstanbul polikliniğine başvuran hastaların sosyodemografik özelliklerini, SK kullanım özelliklerini, SK'lerin klinik etkilerini ve yoksunluk bulgularını araştırırken aynı zamanda tarama (enzim immunoassay) yöntemi ile hastaların idrar örneklerinde SK'lerin analizini yapabilmektir.

Yöntem: AMATEM İstanbul polikliniğine 28.08.13-2013.02.2014 tarihleri arasında başvuran ve SK kullandığını bildiren ardışık 158 hasta çalışmaya dahil edildi. Hastalar sosyodemografik ve klinik veri formu ile birlikte değerlendirildi ve hastalardan idrar örneği alınarak SK için tarama testi uygulandı.

Bulgular: Hastaların 135'i (%86.0) SK kullanımından önce esrar kullandığını, 19 (%12.1) kişi ise ilk madde olarak SK kullanmaya başladığını bildirdi. Kullanım nedeni 143 (%92.3) kişi için SK'in yarattığı rahatlama hissiydi. Hastaların 108'inin (%70.1) daha önce başarısız bırakma girişimleri olmuştu. İdrar örneği alınabilen 120 hastanın 104'ünde (%86.7) SK için kullanılan tarama testi pozitif olarak saptandı.

Sonuç: Çalışmamız Türkiye'de SK'lerin kullanım özelliklerini ve klinik etkilerini araştırın ve SK tarama testi sonuçlarıyla birlikte değerlendiren ilk çalışma olması açısından önemlidir.

Anahtar kelimeler: Esrar, laboratuvar, sentetik kannabinoidler

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INTRODUCTION

Synthetic cannabinoids (SCs) are psychoactive substances that have agonistic effects on cannabinoid receptors, and similar effects like the Δ^9 -tetrahydrocannabinol (Δ^9 -THC) the active metabolite of cannabis (1). Products containing SCs are referred as "Spice" in Europe, "K2" in the United States, "Chronic" in Australia (2), and "Bonzai" or "Jamaika" in Turkey. SCs are generally produced in China and are distributed to the world in powder form (1). They are sprayed on herbal mixtures using solvents such as acetone or methanol, and then dried and sold in packages (1). The mixtures are usually consumed in cigarette form, like marijuana (3).

Over 140 products containing SCs have been identified (4), and they differ in terms of SC type and amount (5), and may contain other psychoactive substances psychoactively active apart from SCs (6-9). Although SCs' highly potent and short half-life creates a powerful effect (3), the heterogeneous structure of the mixture can lead to complicated clinical effects after use. Clinical conditions that include suicide or homicide risks, as well as the SC-related psychotic and affective symptoms, have been a serious problem for psychiatry clinics (10). In addition to the psychoactive effects of SCs, studies have revealed severe side effects such as seizures, myocardial infarction (MI) and kidney failure (11-13).

After being introduced to the market, the use of SCs spread quickly and became a serious problem, since they were legal, undetectable in substance screening tests and perceived to be safer than marijuana (3,14,15). Since 2009, SCs have constituted 24 percent of the 251 newly defined psychoactive substances (16), and today several legal regulations are currently being put in place to cover the use of SC, while screening test methods are being developed and disseminated (17). Furthermore, there are several ongoing studies looking to uncover the pharmacological features and clinical effects of SCs, although in Turkey studies regarding SCs are scarce, save for those of Gurdal et al. that include the results of analyses of SC-containing products (5).

Furthermore, routine screening tests cannot yet be applied in Ministry of Health-associated hospitals, among which our clinic can be counted.

The aim of this study is to investigate the sociodemographic features of the patients who were admitted to Bakirkoy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, Alcohol and Drug Research, Treatment and Training Center (AMATEM) for using SCs and features of SC usage (duration, amount, method), the clinical effects of SCs and details of the withdrawal among these patients. In addition, it is aimed to make SC analysis of the urine samples of patients using the screening (enzyme immunoassay) method that is planned to be adopted in our hospital.

METHOD

A total of 158 patients who were reported to have used SCs and were admitted to the AMATEM outpatient clinic between 28.08.2013 and 13.02.2014, were included in the study, and were evaluated using the sociodemographic data form. Urine samples were collected from the patients, and 120 were screened for SCs. Detailed information on the study was given to the patients, and informed consent forms were obtained from all patients.

The inclusion criteria was the patients' preference of SCs for the last 2 months, and the use of SCs in the last two weeks. Patients using substances other than SCs were excluded from the study.

All of the patients' sociodemographic and clinical features of SC use were evaluated using a semi-structured data form. The patients were asked about their duration of SC use, the number of attempts to quit, as well as the reasons for SC use, the negative effects of SC use and details of withdrawal. The majority of the questions included an 'other' option to allow the patients to respond personally.

For the laboratory analysis, urine samples were collected from 120 of the 158 patients, and SC screening was carried out using an enzyme immunoassay (Immunanalysis K2 Enzyme

Immunoassay) kit. The kit is able to detect JWH-018, JWH-073 and AM-2201 and its metabolites in urine, and had a positive cut-off value of 20ng/mL. The samples were analyzed twice in our laboratory, and 100 samples were analyzed in another laboratory for comparison as a control.

Statistical Analysis

The data was evaluated by using mean, standard deviation and percentages.

FINDINGS

Sociodemographic Features

Among the patients who were using SCs, 5.1% (n=8) were female, and the mean age was 26.1±7.1 years (18-53 years). Majority of the patients were single (67.1%, n=106), and were living with their families (96.2%, n=152). Among the patients, 42.4% (n=67) had a regular job, and 51.9% (n=82) had irregular work. The sociodemographic features of the participants are presented in Table 1.

Table 1: Sociodemographic features

Variables	(n=158)	%
Female	8	5.1
Age (Mean.±SS, min.-max.)	26.1±7.1 (18-53)	
Marital status		
Single	106	67.1
Married	48	30.4
Divorced	4	2.5
Living with	6	3.8
Family	152	96.2
Alone	6	3.8
Education		
No education	2	1.3
Primary school	54	34.2
Secondary school	61	38.6
High school	38	24.1
University	3	1.9
Employment		
Working	67	42.4
Working irregularly	82	51.9
Not working	9	5.7

Features of SC use

In our study, 70.3% of the patients (n=111) stated that they had used the "Bonzai"-type SC; 8.2% (n=13) stated that they had used "Jamaika"; and 21.5 percent (n=27) stated that they used both SCs. Among the patients, 91.8% had used SCs in the last 4 days, while 8.2% claimed that they had used SCs in the last 4 days to 2 weeks period. Among the patients, 69.6% (n=111) had consumed SCs by smoking, 56.3% of the patients (n=89) had consumed SCs when smoking pot and 3.2% (n=5) used SCs by foil. Eighty-seven patients (55.1%) stated that they had used SCs alone, 35 patients (22.2%) stated that they used SCs with a group and 34 patients (21.5%) used SCs in both ways. The average daily dose was 2.7±2.2 (0.5-18.0) grams, the mean duration of SC use was 22.0±11.9 (2-60) months, and the mean duration of regular SC use was 17.2±12.0 (2-48) months. The average last dose was 13.0±10.9 (1-48) grams. Of the total, 135 patients (86.0%) stated that they used

Table 2: Features of synthetic cannabinoid (SC) usage

Variables	(n=158)	%
Name of the brand		
Bonzai	111	70.3
Jamaika	13	8.2
Both	28	21.5
Last dose (day)		
In 4 days	145	91.8
In 2 weeks	13	8.2
Method		
Smoking	110	69.6
Pot	89	56.3
Folio	5	3.2
Environment		
Alone	87	55.1
With group	35	22.2
Both	34	21.5
Substance used before		
First substance	19	12.1
Cannabis	135	86.0
Others	8	5.1
Reasons to use SC		
Relaxation	143	92.3
Others	16	10.1
Attempt to quit	108	70.1
Daily dose (gram)	2.7±2.2 (0.5-18.0)	
Duration of usage (month)	22.0±11.9 (2-60)	
Duration of regular usage (month)	17.2±12.0 (2-48)	
Duration of the usage of last dose (month)	13.0±10.9 (1-48)	

marijuana before using SC; 19 (12.1%) stated that SCs were the first substance they had used, and eight patients (5.1%) stated that they had never used other substances before. Furthermore, 143 patients (92.3%) stated that they had used SCs due to the feeling of relief it brought, while 108 patients (70.1%) described their history of failed attempts to give up SCs (Table 2).

Adverse Effects due to SC use, and Withdrawal Symptoms

The most frequent withdrawal symptoms were anxiety (n=118, 75.6%), insomnia (n=96, 61.5%), lack of appetite (n=70, 44.9%), nausea (n=30, 19.2%) and nervousness (n=29, 18.6%), respectively. Of the total, 13 patients (9.5%) stated that they had experienced no withdrawal symptoms, although in the other patients, the following side effects appeared after SC use: feelings of thirst and hunger (n=90, 57.7%), palpitations (n=89, 57.1%), sensitiveness (n=79, 50.6%), nervousness (n=67, 42.9%), hallucinations (n=63, 40.4%), skin problems (n=54, 34.6%), delusions (n=25, 16.0%) and hair loss (n=19, 12.2%). The three individuals (1.9%) reported no adverse effects (Table 3).

Table 3: Withdrawal symptoms and negative effects after the usage of synthetic cannabinoids

Variables	(n=158)	%
Withdrawal symptoms		
Anxiety	118	75.6
Insomnia	96	61.5
Loss of appetite	70	44.9
Nausea	30	19.2
Nervousness	29	18.6
Other	18	11.5
None	13	9.5
Negative effects after use		
Thirst/Hunger	90	57.7
Palpitations	89	57.1
Sensitiveness	79	50.6
Nervousness	67	42.9
Hallucinations	63	40.4
Skin problems	54	34.6
Hair loss	19	12.2
Others	13	8.3
None	3	1.9

Other Features

Of the total, 75 patients (47.5%) stated that they had used marijuana in addition to SC, 46 (29.1%) claimed that they had used ecstasy, 12 stated that they had used alcohol (7.6%), 10 (6.4%) stated that they had used heroin and 9 (6.6%) stated that they had used cocaine. Furthermore, 11 patients (7.0%) stated that they had comorbid psychiatric disorders and 15 (9.5%) stated that they suffered from general medical disease. In addition, 20 (12.7%) had a family history of alcohol abuse and 11 (7%) had a family history of substance abuse. When asked about the negative effects they had witnessed in others due to the use of SC, 16 patients (10.3%) described mental disorders, 4 (2.6%) described neurological sequels and 67 (43.2%) reported no negative effects. Finally, 141 patients (91.0%) stated that they had first learned about SCs from friends, five (3.2%) stated that they had learned about SCs from the Internet, and six (3.9%) stated that they had learned about SCs from a dealer (Table 4).

Table 4: Clinical variables in synthetic cannabinoid users

Variables	(n=158)	%
Substance used together		
Cannabis	75	47.5
Ecstasy	46	29.1
Heroin	10	6.4
Alcohol	12	7.6
Cocaine	9	5.7
Psychiatric disease	11	7.0
Other medical disease	15	9.5
Family history of substance use		
Alcohol	19	13.9
Drug	11	8.1
Negative effects witnessed in others		
Neurological sequels	4	2.6
Mental illness	16	10.3
None	67	43.2
Other	3	1.9
Learned from		
Friend	141	91.0
Internet (Media is not included)	5	3.2
Dealer	6	3.9
Other	3	1.9

Laboratory Test Results

Urine samples were collected and tested from 120 of the patients, from which 104 (86.7%) tested positive in an SC screening test (>20 ng/mL) and 16 tested negative, although two of the negative samples tested positive upon retest, and one of these samples also tested positive in the reference laboratory. Of the 100 samples analyzed in the reference laboratory, 92 were found positive. Furthermore, the four samples that tested negative in the hospital, tested positive in the reference laboratory, which indicates an inconsistency. Additionally, 85 patients (70.8%) tested positive for tetrahydrocannabinol (THC), and among this group, 74 (87.1%) also tested positive for SC. Overall, 68 patients (56.7%) tested positive both for THC and SCs (three repetitions).

DISCUSSION

SCs are usually consumed by smoking or by hookah, but can also be used by evaporation, orally or via the rectal route (18). In our study, we found that SCs were most frequently consumed by smoking, although pot smoking (i.e. inhalation) was also quite common. Moreover, contrasting the finding of previous studies that SCs are mostly used in small groups (19), the majority of patients in the present study stated that they preferred to use SCs alone.

One of the most striking findings of our study was that the majority of patients had a history of marijuana use before SC. Moreover, approximately 50% of the patients stated that they continued to use marijuana, with 70.8% of the patients testing positive also for THC. According to an Internet-based study, 99.3% of SC users have used marijuana at least once, and 88.4% of individuals had used marijuana within the previous month (2). According to Vandrey et al. (18), the frequency of SCs and marijuana use is 40%, and it is possible that patients with a history of marijuana use started to use SCs to avoid legal problems, to evade the problems of routine urine tests, to experience a new substance or to obtain a more powerful effect than marijuana. In the course of the present study, the

patients were not asked to provide such details, which constitutes one of the limitations of the study. In addition, according to the statements of the patients who were admitted to our clinic, it is becoming difficult to access marijuana in Turkey, while access to SCs is becoming considerably easier. Considering the previous marijuana use in the majority of our patients, this change in the market may influence strongly the drift to SC use. This fact can be considered important, as it indicates that patients who use marijuana are at risk of switching to SC use.

Studies have shown that in addition to marijuana, substances such as alcohol, cigarettes, energy drinks and 3,4-methylenedioxi-N-methylamphetamine (MDMA) are used frequently in combination with SCs (2). Additional substance use (marijuana, ecstasy, heroin, alcohol or cocaine) was determined in almost all of the patients (96.2%), and so the presence of additional substances should be considered when treating patients identified with SC use, especially in cases of emergency interventions as a result of intoxication, and when developing treatment plans for substance abuse.

Previous studies have shown that the most common reasons for SC use are curiosity, enjoyment of the effects, the feeling of relief brought by SC use and using recreational substances while avoiding legal problems (18). On the other hand, the majority of patients in the present study stated that they used SCs due to the feelings of relief it gives, although this outcome may be a result of the study being made of patients who admitted themselves for treatment of SC-related problems. The leading reason for SC use in patients who were on probation was the lack of tests to detect the use of SC, as such patients were not expected to report their SC use.

According to the responses of patients to the Internet-based questions, 37% of SC users meet the criteria for abuse, and 12% meet the criteria for addiction according to the Psychiatric Disorders Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). In the same study, 38% of patients stated that they could not stop using SCs (18), while in the present study, it was determined that the majority of patients (70.1%) had a history of failed attempts to quit SCs. It is

suggested that the addiction potential of SC is high, based on the rapid development of tolerance (20,21), and this high rate in our study can be associated with the high addiction potential of SCs.

There are no randomized controlled studies on the clinical effects of SCs, and most of our current knowledge is based on case reports, admissions to emergency services, reports to poison control centers and Internet forums. Among the negative effects reported in our study, feelings of thirst and hunger, palpitations, sensitiveness, hallucinations, nervousness and delusions have also been reported in previous studies (17,18,22), while information on negative effects related to hair loss and skin problems can be found on Internet forums (23). Based on the knowledge garnered from our case reports, in addition to anxiety, nausea, nervousness, and insomnia, which are all observable in our study, symptoms including tachycardia, hypertension, hyperventilation, headaches, diarrhea, vomiting, diaphoresis, tremors, somatic pain, palpitations and depression can also be observed in SC withdrawal (18,21,24). Some of the patients in our study also reported a loss of appetite during withdrawal. The clinical effects of SCs, as well as withdrawal symptoms, should be defined for each type of SC to regulate treatments for SC use.

As is the case anywhere in the world, SC-containing products have different commercial names in Turkey, with the most common being “Bonzai Aromatic Potpourri” (64%) and “Bonzai Plant Growth Regulator” (26.8%) (5). In our study, we asked the patients what type of SC they had used, to which the majority stated they had used “Bonzai”, while a smaller group of patients stated that they had used “Jamaika” or both types of SCs. The patients stated that they had bought SCs from dealers in split doses rather than in closed packages, and that these doses had been packed by the dealer. This indicates that the patients cannot be sure of the commercial name of the substance they are using. When interpreting the results, it should be kept in mind that this is a patient-based classification, and perhaps patients are only giving information about different names of SCs.

In the present study we used a screening test that

was capable of detecting JWH-018, JWH-073, AM-2201 and its metabolites. Gurdal et al. (5) have reported that 32.9% of SC-containing products contain JWH-018, 65.9% contain JWH-018 and JWH-081, 1% contains CP 47,497 and 0.2% contains JWH-250. In other words the test was able to detect JWH-018 and metabolites, which are present in 98.8% of the products in Turkey. In our study, 104 (86.67%) of the 120 patients tested positive in the first SC screening test in our hospital, and 16 patients tested negative (<20 ng/mL). The patients who used products that contained SCs other than JWH-018, JWH-073 and AM-2201 can lead to observed negative results, or the last date of SC use for these patients may be less recent. It should be kept in mind that the last date of SC use depends on the personal reports of our patients, which has low reliability, and represents a limitation of our study. As such, when evaluating the results of our study, it should be noted that our study contains only SC users who seek treatment, and all of the information we have on these patients comes from personal statements. Considering the widespread use of SCs, the legal processes involved and the fact that routine SC screening tests are not carried out in any state hospital, it can be claimed that the findings could be acceptable as a screening test. Urine samples that test positive for SCs in screening tests can be further evaluated using advanced laboratory methods, such as gas chromatography-mass spectrophotometry (GC/MS).

The rampant growth in popularity of SCs, in addition their severe side effects, means that SCs are set to become a significant problem. Extensive epidemiologic studies are needed to elucidate the pharmacology, clinical effects and withdrawal symptoms of SCs and their features. Our study is the first to identify the features of SC use in Turkey and its clinical effects, and to evaluate these findings together with the results of SC screening tests. It is necessary to extend the use of laboratory tests to avoid problems in legal processes, to regulate intoxication and addiction treatment, and to follow up patients. However, given that new SCs are being continuously released into the market in order to avoid legal measures (24), choosing tests that can screen for various SCs will be advantageous.

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