T.C.
YEDİTEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES
DEPARTMENT OF PHARMACEUTICAL TOXICOLOGY

INVESTIGATION OF THE BRAIN INJURY IN SYNTHETIC CANNABINOID USERS

THE DOCTOR OF PHILOSOPHY THESIS

EDA YİĞİT, MD.

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THESIS APPROVAL FORM

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APPROVAL

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DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

28/06/2022

Signature

Eda Yiğit

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SYMBOLS / ABBREVIATIONS

2-AG	2-arachidonoylglycerol
AA	Arachidonic acid
AC	Adenylyl cyclase
ADC	Apparent diffusion coefficient
AEA	Anandamide
ALT	Alanine aminotransferase
ARF	Acute renal failure
AST	Aspartate aminotransferase
BBB	Blood-brain barrier
bpm	Beat per minute
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CB1R	Cannabinoid receptor 1
CB2R	Cannabinoid receptor 2
CBR	Cannabinoid receptor
CK	Creatine kinase
CK-MB	Creatinine kinase isoenzymes
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
CVE	Cerebrovascular events
CYP3A4	cytochrome P3A4
CYP450	Cytochrome P450

D2	Dopamine receptor 2
DAG	Diacylglycerol
DBP	Diastolic blood pressure
DTI	Diffusion tensor imaging
EAPCCT	The European Association of Poisons Centres and Clinical Toxicologists
EC	Endocannabinoid
ECG	Electrocardiography
ECS	Endocannabinoid system
ED	Emergency department
EMCDDA	The European Monitoring Centre for Drugs and Drug Addiction
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GC / MS	Gas chromatography-mass spectrometry
GCS	Glasgow coma scale
GPCR	G-protein coupled receptor
Hct	Hemotocrit
Hgb	Hemoglobin
HIMS	Hospital Information Management System
HR	Heart rate
ICU	Intensive care unit
IP3	Inositol-3-phosphate
LC-MS / MS	Liquid chromatography-tandem mass spectrometry
LTD	Long-term depression
MAGL	Monoacylglycerol lipase

MAPK	Mitogen-activated protein kinase
MCA	Middle cerebral artery
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean cell volume
NAc	Nucleus accumbens
NAPE	*N*-acyl-phosphatidylethanolamine
NAPE-PLD	*N*-acyl-phosphatidylethanolamine-specific phospholipase D
NMDA	N-methyl-D-aspartate
PI3K	Phosphatidylinositol-3-kinase
PLC	Phospholipase C
PLT	Platelet count
PPAR	Peroxisome proliferator activated receptor
PSS	Poisoning severity score
QTc	QT corrected for heart rate
RBC	Red blood cell count
RCVS	Reversible cerebral vasoconstriction syndrome
RDW	Red cell distribution width
SAH	Subarachnoid haemorrhage
SBP	Systolic blood pressure
SC	Synthetic cannabinoids
STD	Short-term depression
THC	*trans*-(-)-Δ^9-tetrahydrocannabinol
THCV	*trans*-(−)-Δ^9-tetrahydrocannabivarin
TRP	Transient receptor potential

TRPV1	Transient receptor potential vanilloid 1
UGT	5′-diphospho-glucuronosyltransferases
USA	United States of America
VILIP-1	Visinin like protein-1
VT	Ventricular tachycardia
WBC	White blood cell count
Δ^9-THC	*trans*-(-)-Δ^9-tetrahydrocannabinol

ABSTRACT

Yiğit, E. (2022) Investigation of the Brain Injury in Synthetic Cannabinoid Users, Yeditepe University, Institute of Health Science, Department of Pharmaceutical Toxicology, PhD thesis, İstanbul.

In this study, it was aimed to determine the clinical findings of the patients who admitted to the emergency department due to synthetic cannabinoid (SC) use, to investigate the clinical, radiological and blood parameters that can guide to differential diagnosis, and to identify the patients who may develop possible brain damage. In our study, the files of the patients who admitted to Şişli Hamidiye Etfal Training and Research Hospital Emergency Medicine Clinic between 01.01.2016 and 01.01.2021 after SC use were examined. 538 patients using SC were included in our study. The patients included in our study were divided into three groups as follows; Group 1: All SC users, Group 2: Patients who underwent brain imaging with suspicion of brain damage among SC users, Group 3: Control group patients who came to the emergency department with minor head trauma or headache and underwent brain imaging. In our study, a significant correlation was found between low Glasgow Coma Scale (GCS) score and group 2 in terms of consciousness. When the ECG was examined, a significant difference was found between groups 1 and 2 in terms of tachycardia and increased QTc length. When examined in terms of hospitalization in the ward and intensive care unit, it was seen that the hospital and intensive care hospitalizations of the patients in group 2 were ~2 and ~3 times higher, respectively, compared to group 1. When the patients were examined in terms of PSS, it was seen that PSS score was in severe and fatal scale in approximately half of the patients in group 2. In addition, there were nine patients with brain damage (ischemic/hemorrhagic cerebrovascular event (CVE)) in group 2. The potential of SCs to impair vital functions and cause life-threatening situations has become an important problem for clinicians and toxicologists. Our research supports a causal link between SCs and SVE. The use of SCs, especially in young patients with brain damage or suspicion, should be questioned in emergency departments, and toxicological screening should be performed, if necessary. Future studies will be needed to clarify the role of SCs in brain damage.

Key words: Brain imaging, Bonsai, Cerebrovascular event, Synthetic cannabinoid.

ÖZET

Yiğit, E. (2022). Sentetik Kannabinoid Kullananlarda Beyin Hasarının Araştırılması, Yeditepe Üniversitesi, Sağlık Bilimleri Enstitüsü, Farmasötik Toksiokoloji Anabilim Dalı, Doktora Tezi, İstanbul.

Bu çalışmada, sentetik kannabinoid (SK) kullanımı nedeniyle acil servise başvuran hastaların başvuru anındaki klinik bulgularını belirlemek, ayırıcı tanılara yol gösterebilecek klinik, radyolojik ve kan parametrelerini analiz etmek ve olası beyin hasarı gelişebilecek hastaları tanımlamak amaçlanmıştır. Araştırmamızda 01.01.2016-01.01.2021 tarihleri arasında Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi Acil Tıp Kliniği'ne SK alımı sonrası başvuran hastaların dosyaları incelendi. SK kullanan 538 hasta çalışmamıza dahil edildi. Araştırmamıza dahil edilen hastalar şu şekilde sınıflandırıldı; Grup 1: SK kullanan tüm hastalar, Grup 2: SK kullanıcıları arasında beyin hasarı şüphesiyle beyin görüntülemesi yapılan hastalar, Grup 3: Acil servise minor kafa travması veya baş ağrısı şikayeti ile gelip beyin görüntülenmesi yapılan kontrol grubu hastalar. Araştırmamızda bilinç durumu açısından düşük Glaskow koma skoru (GKS) puanı ile grup 2 arasında anlamlı ilişki bulundu. EKG incelendiğinde taşikardi ve uzun QTc süresi ile grup 1 ile 2 arasında anlamlı fark bulundu. Hastane ve yoğun bakım yatışları açısından incelendiğinde grup 2'deki hastaların hastane ve yoğun bakım yatışları grup 1'e göre sırasıyla ~2 ve ~3 kat fazla olduğu görüldü. Hastalar PSS açısından incelendiğinde grup 2'deki hastaların yaklaşık yarısında PSS şiddetli ve ölümcül skalada olduğu görüldü. Ayrıca grup 2 içerisinde beyin hasarı (iskemik/hemorajik serebrovasküler olay (SVO) tespit edilen 9 hasta bulunmaktadır. SK'lerin hayati fonksiyonları bozma potansiyeli ve yaşamı tehdit eden durumlara yol açması, klinisyenler ve toksikologlar için önemli bir sorun haline gelmiştir. Araştırmamız SK'ler ve SVO arasında nedensel bir bağlantıyı desteklemektedir. Acil servislerde beyin hasarı veya şüphesi bulunan özellikle genç hastalarda SK kullanımı sorgulanmalı gerekirse toksikolojik tarama yapılmalıdır. SK'lerin beyin hasarındaki rolünü netleştirmek için gelecek çalışmalara ihtiyaç duyulacaktır.

Anahtar kelimeler: Beyin görüntüleme, Bonzai, Serebrovasküler olay, Sentetik kannabinoid.

1. INTRODUCTION

Synthetic cannabinoids (SCs) that are known as "Bonsai" among the Turkish people [1] and presented in the market with the attractive names such as Herbal Dream, Moon Rocks, Spice Gold Spirit, K2, Yucatan Fire [1,2] are substances with addictive potential [1,3]. The rate of these psychoactive drugs' use has increased rapidly in Turkey as well as in the world in recent years [4]. The fact that several reports indicated that these substances are legal [5] caused an increase in the popularity and the number of users of these drugs [6,7]. Synthetic cannabinoids, either used alone or in combination with other drugs, cause various physiological effects including hot flushes, burning eyes, tachycardia, feeling sick, dry mouth, tiredness and reddened conjunctivae. [8] Physiological effects could range from mild symptoms to severe side effects in specific organs [9]. Although several case studies report health problems associated to synthetic cannabinoid abuse, the knowledge on the toxicity of synthetic cannabinoids, which are more potent than natural cannabinoids, is still very limited.

Cannabinoid receptors (CBRs) to which the SCs bind and exert their biological activities are members of G-protein coupled receptor (GPCR) family and constitute an important part of the endocannabinoid system (ECS) in the body [10]. The subtypes of CBRs are cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R). CB1R is more abundant in the nervous system, especially in central nervous system (CNS), while CB2R is reported to be expressed more in peripheral tissues [10,11]. Activation of CB1R and CB2R by their agonists leads to the inhibition of adenylyl cyclase (AC) leading to inhibition of cyclic adenosine monophosphate (cAMP) formation and protein kinase A (PKA) activity [10,12]. Activation of the CB1R on presynaptic neurons by its agonists inhibits the voltage-gated Ca^{2+} channels and activates K^{+} channels [13] leading to presynaptic hyperpolarization and inhibition of the neurotransmission [14]. In the CNS, CB1R is expressed in various regions including olfactory areas, neocortex, hippocampal formation, amygdala, basal forebrain, nucleus accumbens (NAc), thalamus, hypothalamus and substantia nigra [15]. Some studies suggest that activation of CB1R is the basis of the behavioural and neurological effects of cannabinoids as the CB1R that is localized in cortex and hippocampus is associated with the learning and memory functions [16,17], while the CB1R

localized in NAc and striatum is associated with the addiction [18] and CB1R localized in basal ganglia and cerebellum is associated with the regulation of the motor functions [19].

The annual report of The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) indicates that SCs have serious adverse health effects including death [20]. An other report published in 2018 states that the most common adverse effects of SCs include tachycardia, severe agitation and hallucinations [21]. Several case reports published in Turkey report that a synthetic cannabinoid, Bonsai, may induce myocardial infarction [22-24], indicating that they cause cardiovascular problems. Memory impairments, disorganized behaviour and hallucinations are among other side effects of SCs [25], along with respiratory depression [26,27].

There is limited information available on the pharmacokinetic properties of SCs. However, it is already known that the bioavailability of SCs largely depends on the administration route [28-30]. Although their pharmacokinetic characteristics are largely unknown, users report that following inhalation of SCs, the speed of onset to the peal effects are higher compared to natural cannabis [31]. In case of oral exposure, effects may be delayed due to presystemic and digestive activity and the duration of the effect may vary, but it can usually last for hours [32].

Major adverse health effects of SCs encountered in clinical practice are cardiovascular problems [33,34] and psychological disorders [35]. Hypertension, sudden cardiac arrest, convulsions, hallucinations, psychoses and paranoia are clinical symptoms that may result in death [36,37]. However, studies on brain damage caused by synthetic cannabinoids are limited.

Previous studies indicate that synthetic cannabinoid use can cause significant damage to the brain [38,39]. In addition, long-term cannabis use is shown to reduce the grey matter volume in the brain regions rich in CB1R that modulate the motivation, emotion and affection and that the duration and intensity of cannabis use is associated with those changes [40]. A study on rats finds that chronic SC administration leads to morphological changes in the hippocampal morphology and pattern of the changes are found to be akin to the alterations observed in the ischemic or toxic damage [41]. In another study in mice shows that administration SCs leads to tremor and traction and decreases locomotor activity, while no changes are observed with regards to learning and memory [42]. Same

study shows neurotoxic effects of SCs especially in the NAc [42]. Another study reveals structural abnormalities in the brain regions rich in CB1R including cingulate and prefrontal cortices and cerebellum in the subjects using cannabis [43].

The use of SCs increased drastically over the past few years since these are relatively cheap and easily accesible substances. The lack of proper diagnostic tests and the wide ranging adverse side effects of SCs, coupled with increased misuse, neccesiates further evaluation of the adverse effects of SCs abuse. This study covers the patient group with a plausible brain damage and investigates the relationship between diagnosis and clinical findings of patients who are admitted to the emergency department due to SC use. The study also outlines nine SC cases which present brain damage.

The remainder of this paper is organized as follows. Section 2 provides a brief discussion of SCs. The metarial and methodology is presented in Section 3 and Section 4 outlines the characteristics of the patients and presents the nine SC cases. Finally, Section 5 discusses the results and concludes.

2. GENERAL DESCRIPTION

2.1. Natural and Synthetic Cannabinoids

Cannabinoids are naturally occurring compounds and are originated from the plant *Cannabis sativa* (widely known as marijuana) which has been used in Asia for more than 5000 years for medical and religious purposes [44]. The first records on Cannabis (*Cannabis sativa*) were found in Taiwan and goes back to 10,000 years ago, the Stone Age [45]. Its first medicinal use is detected in ancient Indian and Chinese inscriptions from 5000 years ago. In 2737 BC, Chinese Emperor Shen Nung wrote in his monograph on healing properties of cannabis on migraine, asthma and some gynecological diseases [46,47].

The use of cannabis for medicinal purposes continued in the previous centuries. In 1842, army surgeon Dr W.B. O Shaugnessy presented to the British Medical Association the extensive medical use of cannabis as an analgesic, antispasmodic and anticonvulsant [48]. The use of cannabis dates back to ancient civilizations and today cannabis is still the most widely used illegal substance in the world. This substance, which has a wide production area in the world, outperforms amphetamine, opiate and cocaine in the list of the most consumed illegal substances [48].

Recreational uses, anti-nociceptive, anti-inflammatory, anticonvulsant and anti-emetic use are among the documented applications of cannabis [44,49]. The (-)-*trans*-Δ^9-tetrahydrocannabinol (THC) (Figure 1a) is the major psychoactive component of cannabis that contains more than 90 phytocannabinoids and their breakdown products [50]. Another one of the earliest molecule identified was cannabidiol (Figure 1b) and it lacks the psychotropic activities [51]. The other major natural cannabinoids present in *Cannabis* include cannabigerol [52,53], cannabichromene [52,53], *trans*-(-)-Δ^9-tetrahydrocannabivarin (THCV) [53] and *trans*-(-)-Δ^8-tetrahydrocannabinold (Δ^8-THC) [53] (Figure 1).

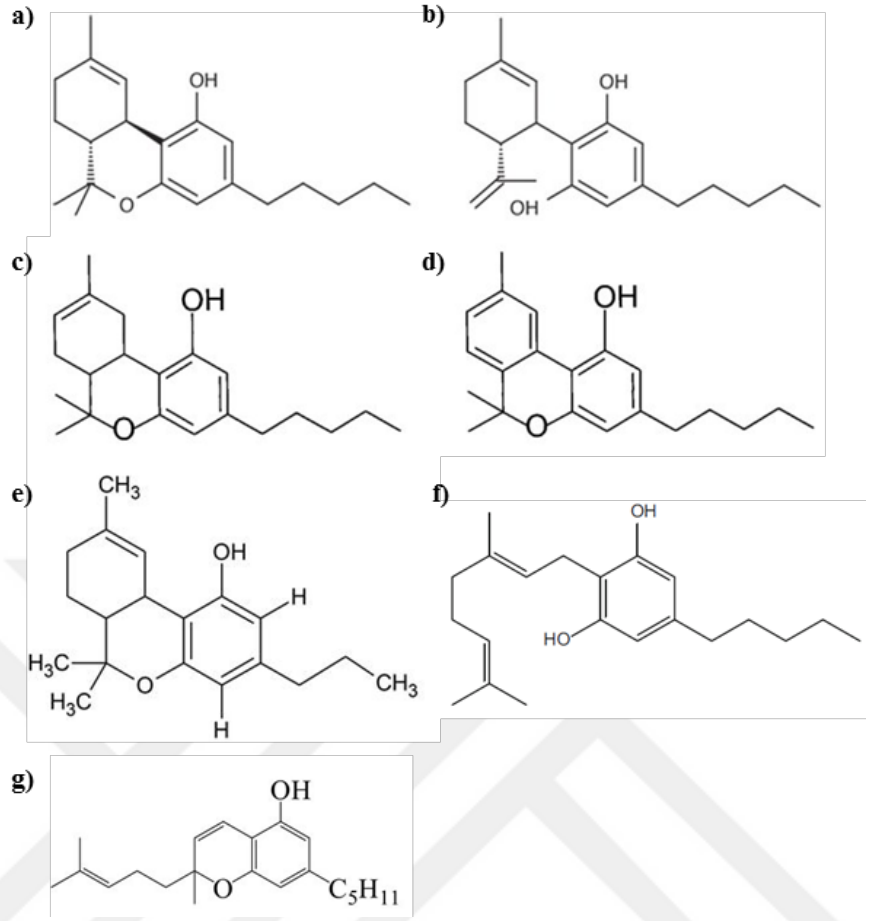

Figure 1. Chemical structures of **(a)** THC (Δ^9-THC), **(b)** cannabidiol [54], **(c)** Δ^8-THC, **(d)** cannabinol [55], **(e)** THCV [11], **(f)** cannabigerol [56] and **(g)** cannabichromene [57].

Despite the therapeutic potentials of cannabis- and cannabinoid-based drugs in various diseases including CNS diseases [58], psychosis [59], inflammatory bowel disease [60] and cancer [61], synthetic derivatives of cannabinoids have detrimental effects on human health. Cannabis is the major illicit drug that is used and abused worldwide [62]. The main reason of cannabis abuse is the psychoactive effects caused by THC [63]. The discovery of THC led to synthesis of various analogues of it with the purposes of using them as therapeutic agents in various diseases such as cancer and inflammatory diseases [8,64] and in endocannabinoid system research [10,63] (explained in section *2.2.1.* in detail), however, the recreational use and abuse of SCs has become a major concern [8].

Although the effects of SCs are similar to natural cannabis, the potency of the SCs has been indicated to be much higher than natural cannabis [6,8]. Due to the fact that they are more potent, lower doses are sufficient to observe a "high" effect of these drugs [65].

Additionally, due to the unexpected/unknown biological activities of SCs, poisonings and other serious adverse effects, including death, are more likely to occur [5,65]. SC products are solubilized in a solvent and then sprayed on the herbal material [8,66] and are distributed in the market as legal alternatives of cannabis [8]. In Europe and United States of America (USA), the first reports of SCs use were in early 2000s and 2008, respectively [67]. The K2 and Spice, are the two most common brand names of SCs in the market [68]. Nowadays, there are various SCs under different brand names such as Spice, K2, Moon Rocks and Black Mamba [69]. They can be found and purchased on the internet, head shops and convenience stores as harmless herbal mixtures, air-fresheners and incense as the legislations and laws about the production, distribution and use of SCs are not sufficient, although there are some attempts to control them [70].

The SCs synthesized until today can be grouped as adamantoylindoles, naphthoylindoles, naphthylmethylindoles, naphthylmethylindenes, naphthoylpyrroles, phenylacetylindoles, tetramethylcyclopropyl ketone indoles, quinolinyl ester indoles, and indazole carboxamide compounds according to their structural properties [8] (Figure 2). Cannabis exerts its activities through at least two receptors, CB1R and CB2R [5], as well as the SCs [6], and SCs are indicated to have higher potency and are generally more effective than THC [8,71-73].

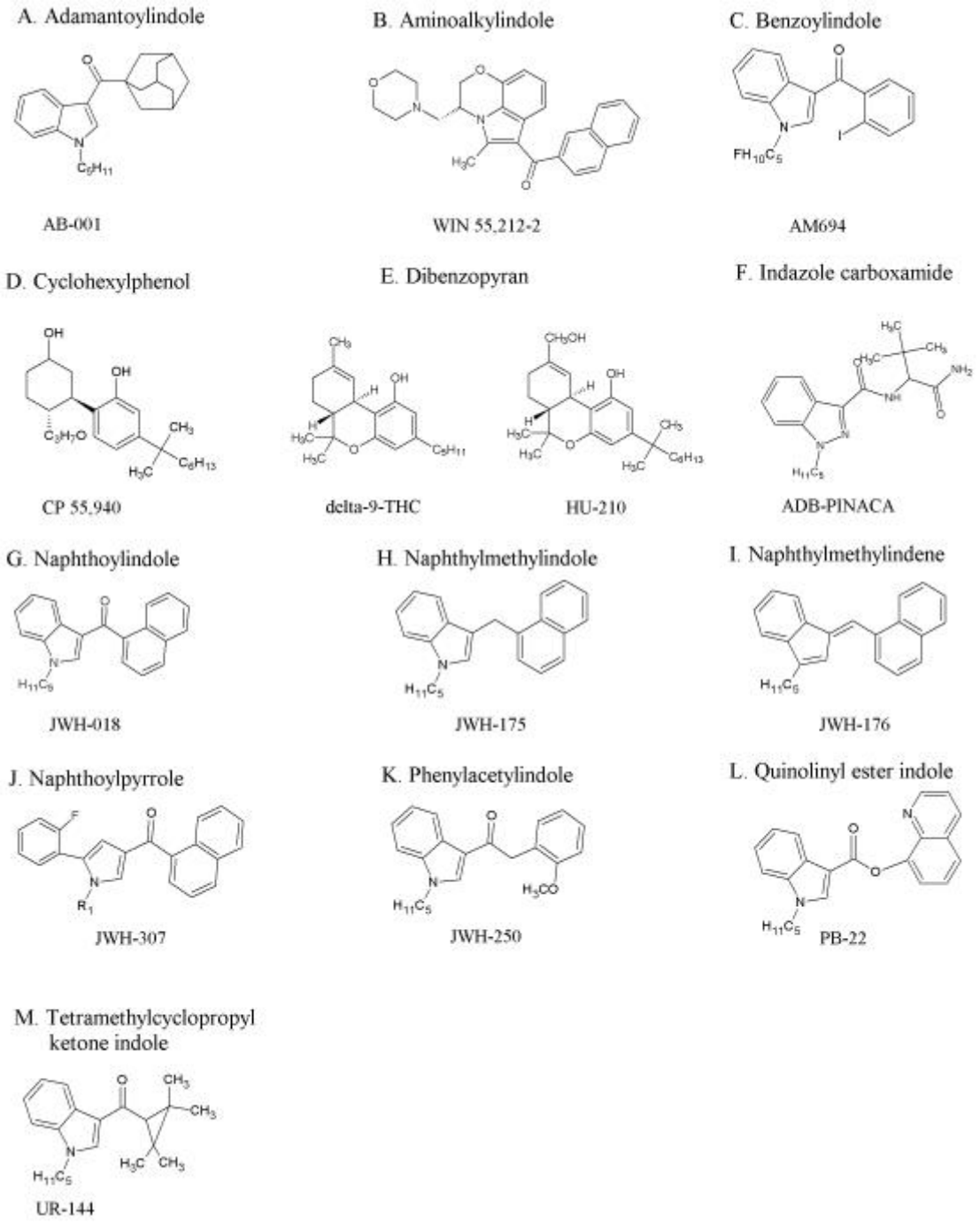

Figure 2. Classification of SCs according to their chemical structure [8]. One example for each class was indicated under the chemical structure.

The major administration route of SCs is smoking dried plant that was previously exposed to SCs by spraying [74]. On the other hand, for instance for Spice, it is reported that vaporization, oral and rectal ingestion are also among the administration routes [8,75]. Furthermore, an earlier study reports a case of ingestion of JWH-018, a napthoylindole

derivative of cannabinoids [8], in mixture with alcohol [76], while another study documents a cluster of 11 cases who unknowingly ingested SC receptor agonist AM-2201-laced brownies [77]. Last but not least, nasal insufflation of Synthacaine leads to intoxication of MAM-2201, which is another cannabinoid receptor antagonist [78].

Since at least 2008, European manufacturers imported cannabinoid powders in large quantities which will be then mixed with various dried plants and marketed as legal alternatives to cannabis. Hundreds of synthetic cannabinoid varieties launched onto the market as ready-made "herbal smoking mixtures". Synthetic cannabinoids remain the largest group of new substances monitored by The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and they are becoming more and more chemically diverse [79]. Since 2008, 169 different varieties have been detected, 11 of which were reported in 2016. This is lower than the level of 24 reported in 2015. In 2015, just over 22,000 cases of SCs were reported, and the five most commonly seized SCs in were ADB-FUBINACA, AB-CHMINACA, UR-144, 5F-AKB48, and ADB-CHMINACA [80,81].

2.2. Endocannabinoids, Endocannabinoid System and Their Physiological Roles

ECS is an extensive modulatory system not only in the CNS but also in the peripheral tissues [82] and plays a crucial role in the regulation of various physiological processes including brain development [83] and synaptic plasticity [84], gastrointestinal system activity [85], reproduction [86] and energy metabolism [87]. ECS comprises two major cannabinoid receptors, CB1R and CB2R, that are G-protein coupled receptors and endocannabinoids (ECs), cannabinoids and their derivatives exert their activities mainly by binding to and activating these receptors [88]. Subsections 2.1.1 and 2.2.2 provide detailed information on the ECS and its physiological .

2.2.1. Cannabinoid Receptors, Endocannabinoids and Endocannabinoid System

2.2.1.1. Cannabinoid Receptors

It was initially thought that the cannabinoids exert their activity on their downstream factors by non-specifically disturbing the cell membrane due to their hydrophobic nature [89]. Prior to the discovery of the CB1R [89], several studies suggested a mechanism in which a GPCR inhibiting AC is involved [90-92]. The discovery of CB1R, enabled the characterization of CB2R, the cannabinoid receptor found in the peripheral organs [93]. Although the first insights indicated that the CB2R is the peripheral receptor of

cannabinoids and initial studies failed to show its expression in brain [94-96], it has been recently detected in various regions of CNS with a lower expression level than CB1R [97-100]. In addition, CB2R expression is very low under physiological conditions and has been indicated to be inducible and its expression is elevated in the brain under various pathological conditions including inflammation, brain injury and neurodegeneration [101]. On the other hand, previous research identified another receptor for cannabinoids called G-protein coupled receptor 55 (GPR55) [102].

Human CB1R is a 472 amino acid protein and is encoded by *CNR1* gene and has 97-99% amino acid sequence homology with rat and mouse, while human CB2R consists of 360 amino acids and is encoded *CNR2* gene with an amino acid homology of around 80% with rat and mouse [10]. In addition, CB2R has two isoforms in humans, one of which (CB2A) is mainly expressed in testis in brain regions that is responsible for the reward response, while the second isoform, CB2B, is primarily expressed in spleen, as well as in the lower parts of the brain [103].

2.2.1.2. Endocannabinoids

Endocannabinoids are lipid, cannabis-like endogenous signalling molecules that are derivatives of arachidonic acid (AA) that is found in the lipid membranes [104]. The first endocannabinoid discovered after the discovery of CB1R is anandamide (AEA) [105] and this discovery was followed by identification of 2-arachidonoylglycerol (2-AG) [106,107]. Besides the two above-mentioned well-studied endocannabinoids, several peptides and AA derivatives that interacts with CB1R and exert endocannabinoid-like activities were identified [108]. Several other endocannabinoids are 2-arachidonylglyceryl ether, virodhamine [104,109], noladin ether, and N-arachidonoyldopamine (NADA), homo-linolenylethanolamide (HEA), docosatetraenylethanolamide (DEA) and oleoylethanolamide (OEA) [109] (Figure 3), however, they are less studied than AEA and 2-AG [104,109].

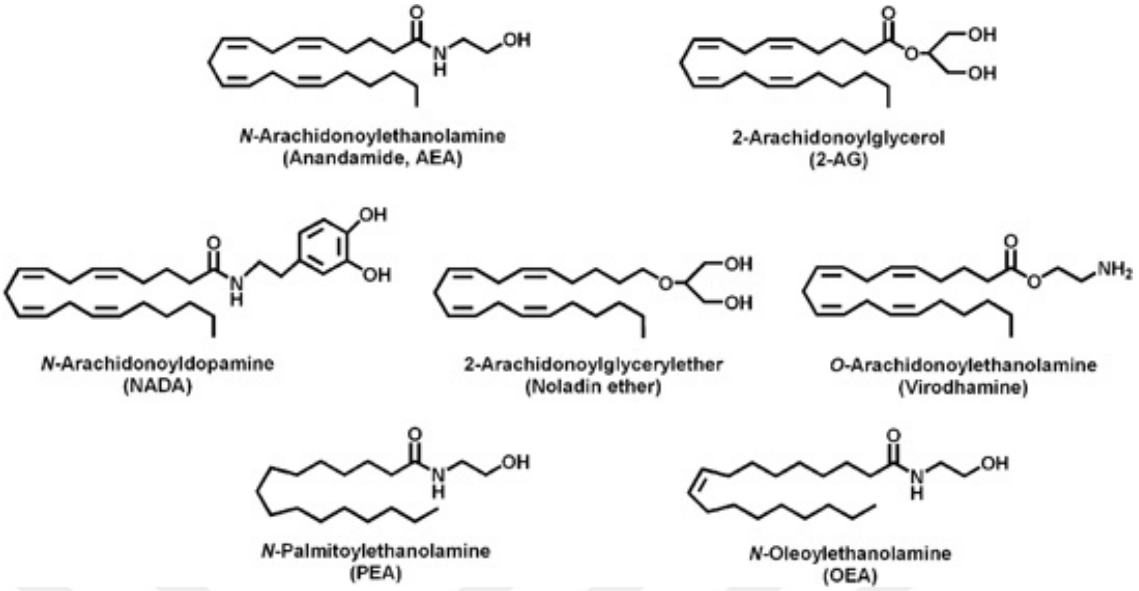

Figure 3. Chemical structures of endocannabinoids and endocannabinoid-like compounds [109].

Among these endocannabinoids and endocannabinoid-like compounds, two most-studied endocannabinoids, AEA and 2-AG, have different pharmacological characteristics as AEA was indicated to have high affinity for CB1R and is a partial agonist of it while 2-AG is a full agonist of both CB1R and CB2R and have moderate-to-low affinity for both receptors [108-110]. The production of both endocannabinoids is indicated to be on demand, despite the controversy regarding the case of 2-AG, in response to elevation of intracellular Ca^{2+} concentrations [111-113]. Nevertheless, synthesis, transport and inactivation of AEA and 2-AG vary depending on the target tissue [10]. Basically, catalysis of *N*-acyl-phosphatidylethanolamine (NAPE) by NAPE-specific phospholipase D (NAPE-PLD) or other mechanisms not involving NAPE-PLD result in AEA production, whereas diacylglycerol (DAG) is the precursor of 2-AG and either DAG lipase α or β are involved in the synthesis of it [10,108]. On the other hand, the rate limiting and Ca^{2+}-sensitive step in AEA and 2-AG synthesis is the conversion of phosphatidylethanolamine into NAPE and DAG by *N*-acyltransferase and phosphoinositides by phospholipase C, respectively [10,114,115]. Transportation of AEA was suggested via different mechanisms including simple diffusion due to concentration gradient, endocytosis and by binding carrier proteins [113]. On the other hand, transport mechanism of 2-AG is not clearly understood, however, it was suggested to share the

same transport mechanism with AEA [10]. Upon transportation into the cells, degradation of endocannabinoids occurs through hydrolysis and/or oxidation [113].

2.2.1.3. Endocannabinoid System (ECS)

ECS consists of the endocannabinoids, enzymes taking part in the synthesis and the degradation of the endocannabinoids and endocannabinoid receptors [104]. Endocannabinoids exert their activities mainly through the CB1R and CB2R [11], however, transient receptor potential (TRP) channels and peroxisome proliferator activated receptors (PPARs) were indicated to be targets of some cannabinoids [104] as AEA was shown to activate transient receptor potential vanilloid 1 (TRPV1) [116,117] and not only AEA but also several other cannabinoids were activates PPAR gamma and alpha [118].

At cellular level, cannabinoid binding to its receptors, CB1R and CB2R, regulates various intracellular targets and mediates the cellular fate (Figure 4). CB1R is coupled with $G_{i/o}$ and binding of a ligand such as endocannabinoid or its synthetic analogue to the receptor leads to inhibition of AC isoforms 1, 3 5, 6 and 8, which results in activation of several ion channels via PKA, activation of phosphatidylinositol-3-kinase (PI3K), mitogen-activated protein kinase (MAPK), ERK1/2 and calcineurin [119]. On the other hand, binding of a ligand to CB1R may lead to activation of $G_{\beta/\gamma}$ subunit leading to activation of AC isoforms 2, 4 and 7, activate nitric oxide synthase and increase the intracellular Ca^{2+} concentrations via activation of phospholipase C (PLC) / inositol-3-phosphate (IP3) cascade [119]. On the other hand, dimerization of CB1R and dopamine receptor 2 (D2) may induce PLC activation and increase Ca^{2+} concentrations via CB1R/$G_{q/11}$ [119]. In addition to these processes, upon binding of a ligand, CB2R may activate MAPKs, RAF1 and Krox-24 (Early growth response protein 1 (EGR-1)) and may inhibit cAMP/PKA, thereby its downstream factors Trk-A/Braf and Trk-A/Rap1, and AC isoforms 1, 3, 5, 6 and 8 via $G_{i/o}$ [119].

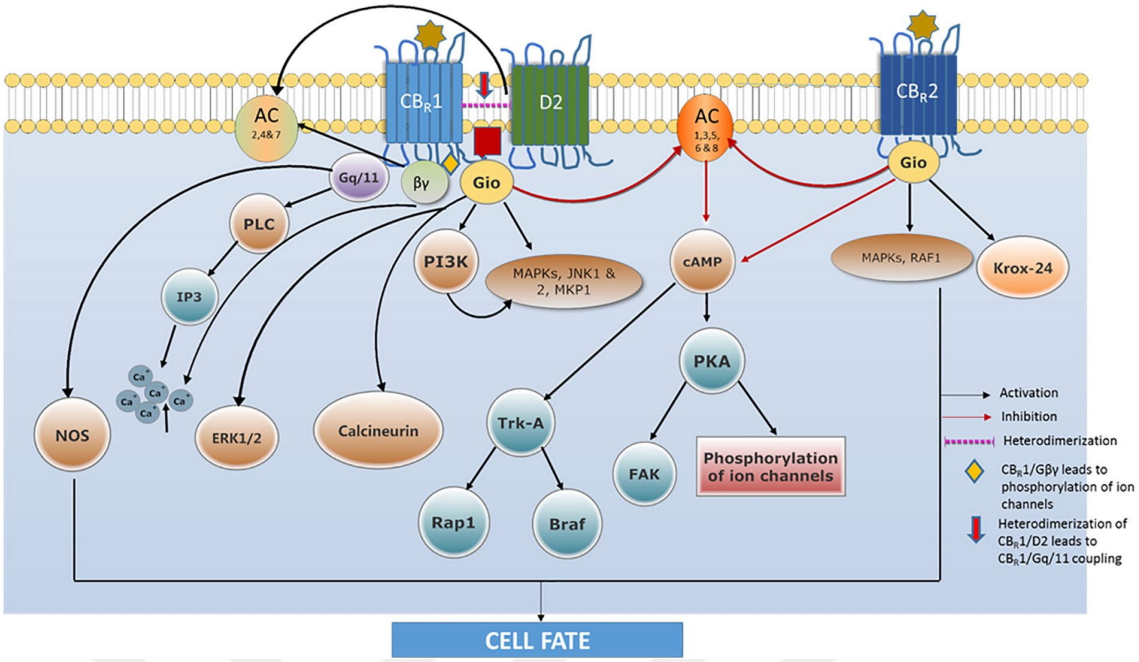

Figure 4. Regulation of cell fate. Intracellular signal transduction pathways by CB1R and CB2R-associated G proteins [119].

In the brain, basal levels of 2-AG are around 1000 times higher than the AEA and alterations in the 2-AG metabolism by pharmacological tools, but not AEA, lead to significant changes in the retrograde signalling regulated by endocannabinoids [10]. Although 2-AG is proposed to be the major endogenous ligand in CBR signalling in CNS due to its abovementioned features, AEA has been reported to have crucial roles in regulation of synaptic transmission via activation of TRPV1, inhibition of L-type Ca^{2+} channels, suppression of biosynthesis of 2-AG thereby inhibiting its physiological activities in striatum [10]. In 2001, endocannabinoid-mediated retrograde signalling that is the suppression of neurotransmitter release at the synaptic terminals of presynaptic neurons upon depolarization of the postsynaptic neurons were initially discovered in the hippocampus and cerebellum [120-122]. The widely accepted mechanism includes that depolarized and/or activated postsynaptic neuron releases endocannabinoid, which, in turn, binds to presynaptic CB1R and transiently supresses the transmitter release from both excitatory and inhibitory neurons (endocannabinoid-mediated short-term depression (STD)) [10,123]. On the other hand, subsequent studies revealed that ECS is not only involved in STD but also in long-term depression (LTD) on both excitatory and inhibitory presynaptic neurons [10,123].

In majority of the cases, the production of 2-AG in response to elevation in intracellular Ca^{2+} levels and/or $G_{q/11}$-coupled receptor activation is followed by release of it into and crosses the extracellular space via an unknown mechanism and binding of it to CB1R [10]. Activation of CB1R then leads to inhibition of neurotransmitter release via reduction of presynaptic Ca^{2+} influx through inhibition of voltage gated Ca^{2+} channels and suppression of AC/cAMP/PKA pathway [112,113,124]. Monoacylglycerol lipase (MAGL) that is expressed in specific synaptic terminals and glia then degrades 2-AG and signal is terminated [112,113,115]. AEA, on the other hand, play roles in the endocannabinoid-mediated synaptic transmission via different mechanisms including acting as an agonist on TRPV1 [108], contributing LTD [117,125,126] and negatively regulating 2-AG metabolism [127].

In addition, endocannabinoid-mediated communication between the neuron and microglia and astrocytes has been indicated [128-130]. Moreover, although the roles of CB2R in endocannabinoid-mediated synaptic transmission remains to be revealed [131-133], a recent study showed that CB2R plays a role in neuronal activity regulation through opening Ca^{2+}-activated chloride channels [134].

2.2.2. Physiological Roles of Endocannabinoid System

ECS has various important physiological functions not only in CNS but also in the peripheral tissues. In CNS, ECS plays important roles in pain perception [135,136], motor functions [137], cognitive functions [138,139], thermoregulation [140], sleep/wale cycle modulation [141], synaptic plasticity [142,143], neurogenesis [144], stress and anxiety responses [145], eating behaviour and appetite [146,147] and reproductive system [148,149]. In addition, ECS mediates transmissions that are regulated by the neurotransmitters dopamine, glutamate, gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA), as well as the secretion of gonadotropin-releasing hormone (GnRH) secretion [150,151]. In the periphery, on the other hand, cannabinoids have impacts on the various organ systems spanning from gastrointestinal to cardiovascular system and exerts their activities, however, the majority of the studies focused on the effects of ECS on the reproductive system as it has various effects on testis, ovary, both male and female reproductive tracts, as well as on gametes [152].

2.3. Pharmacology and Pharmacokinetics of Cannabinoids

Although the increasing interest of clinicians and public in use of cannabinoids in management of disease and symptoms, knowledge about the pharmacokinetics and pharmacodynamics of cannabinoids is very limited to be used as a guidance while prescribing [153].

Cannabinoids are generally either administered as inhalation, in form of capsulated dronabinol, the generic name for THC, orally or ingestion of baked foods or liquids, while other administration routes were reported [153]. In addition, pharmacokinetics of cannabinoids is similar in both men and women [154], as well as in frequent and infrequent consumers [155,156]. Depending on the route of absorption of THC, its bioavailability varies greatly [157]. The systemic bioavailability upon inhalation is usually between 10 and 35% and a peak plasma concentration is measured 3-10 minutes after smoking [157]. The average systemic bioavailability of inhaled cannabidiol was also indicated to be 31% with a similar kinetic profile with THC [153]. The peak plasma concentration of THC is reached generally 1-2 hours after ingestion [157]. On the other hand, oral bioavailability of cannabidiol was indicated to be very low (13 - 19%) by previous studies [158]. Due to their first-pass metabolism in liver after oral administration, its bioavailability is reduced before reaching the site of action [157]. Upon rectal administration, on the other hand, the bioavailability of THC varies with the formulation of the compound [157]. A small pilot clinical study revealed the bioavailability THC-hemisuccinate in Witepsol H15 that was administered via rectal route was two times higher than the bioavailability through oral administration [159]. No other study investigating the regarding the effects of other routes of administration of cannabidiol on bioavailability has been published yet [160].

Physicochemical properties of THC and its metabolites are believed to be the only factors affecting their tissue distribution and tissue concentration of the drugs is not affected by any transport mechanisms or barriers [161]. Most of the THC is found in plasma (~90%) [162], 95-99% of which is in bound form to plasma proteins, mainly to lipoproteins and, to a lesser extent, to albumin [156,162-164], while 10% is found in red blood cells [162]. Similarly, majority of cannabidiol is found to be bound to proteins in the circulatory system while the amount found in circulating red blood cell corresponds to 10% [165]. Upon

administration of THC, it is rapidly distributed in a variety of tissues including liver, lung, kidney, spleen and muscle and its plasma concentration rapidly decreases [166]. The similar pattern is also seen for cannabidiol [167]. In addition, cannabinoid accumulation in the adipose tissue may arise due to chronic use [30,168].

Cannabidiol and THC are metabolized mainly in the liver by the cytochrome P450 isozymes [153].

2.4. Pharmacology and Pharmacokinetics of Synthetic Cannabinoids

Both THC and SCs stimulate CB1R, however, THC is a partial agonist of the CB1R while synthetic cannabinoids are full agonists [169]. Castaneto et al. (2014) systematically reviewed animal and human studies and identified various pharmacological effects of SCs such as HU-210, WIN55,212-2 and CP-55,940 [8]. It was reported that those effects of SCs do not appear to be limited to their activties via CB1R or CB2R receptors. In adult rats, chronic exposure to HU-210 increased GABA binding to its receptors in the hippocampal region. However, the same study did not find a similar significant effect in the brains of adolescent rats. There are other studies showing that being exposed to CP-55,960 elevated self-administration of morphine and altered the density of μ-receptors in the rat brain [8].

SCs are not detected by common urine drug scans, and while gas chromatography/mass spectrometry are useful to detect some specific SCs, most of them cannot be detected due to unavailability of pure reference samples. Thus, patient's self-report or the use and identification of the packaging of the cross-referenced product referring to the common names of these products are crucial. In addition, different SCs may have different effects with varying duration. The pharmacological effects of SCs can vary with the presence of more than SCs in a single package of old product and the presence of other substances including nicotine, caffeine, harmaline, oleamide, and even O-desmethyltramadol, while some of these SCs are substrates of cytochrome P3A4 (CYP3A4), the chemical heterogeneity among the hundreds of products suggest it is not possible to assume that other compounds are also a substrate for this enzyme. Therefore, drug interaction potential of any product containing SCs cannot be predicted. The product with same name that is produced at different times can even have significant differences in ingredients, additives and potency. For instance, the amount of JWH-018 in “Spice”

ranged from 2 to 30 mg per gram of dried plant material [72]. Frequent "Spice" users report that when they use the same brand in different situations, variable and unpredictable effects occur, and the effects are either very similar or very different to those of cannabis. The most common street names are of the SCs are Fake Weed, K2, Scooby Snax, Synthetic Cannabis and Synthetic Marijuana. Cannabinoid components and concentrations referred to using the names below may vary from batch to batch [170].

2.5. JWH group of SCs and JWH-018

JWH group of SCs are a family of synthetic cannabinoids developed by chemist John W. Huffman at Clemson University in the United States in the 1990s and referred to by its initials. It is known that there are about 450 types of synthetic cannabinoids of the JWH group, but the metabolites JWH-18 and JWH-73 are widely used in the market. Similar to this story, the AM group of SCs was synthesized by Alexandras Makriyannis, and the HU group by the Hebrew University [171,172].

In 2010, the substance named “JWH-018” from the SCs was detected for the first time in our country with the street name of “Bonsai”. JWH-018 is the first synthetic cannabinoid reported by the EMCDDA with an early warning system [173]. The compound was first synthesized to research the activity of cannabinoid receptors; however, it later began to be synthesized by street chemists [174]. The chemical structure of lipophilic and non-polar JWH-018 is given in (Figure 5).

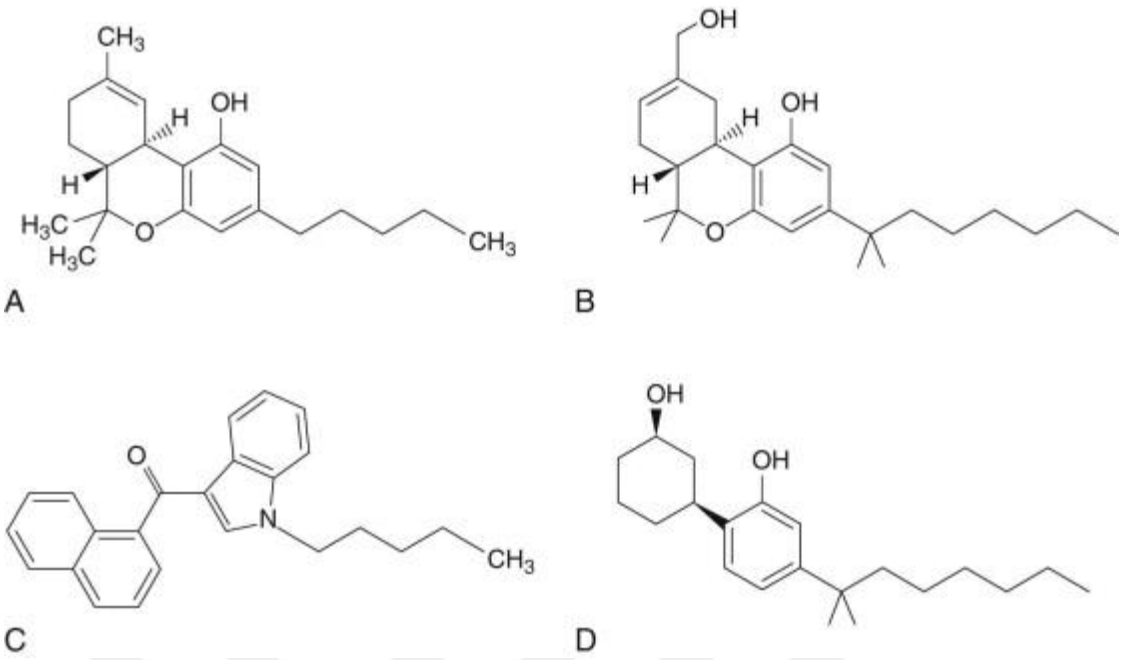

Figure 5. Chemical structures of synthetic cannabinoids of **(A)** THC, **(B)** HU-210, **(C)** JWH-018 and **(D)** CP-47,497 [175].

2.5.1. Pharmacokinetics of JWH-018

When JWH-018 metabolites in urine samples of mice exposed to JWH-018 were analysed and it was observed that traceable urinary metabolites of JWH-018 metabolites were monohydroxylated metabolites [176]. On the other hand, *in vitro* studies using liver microsomal enzymes revealed that metabolites observed in urine samples were similar to *in vivo* studies, and while phase I metabolites could be easily monitored, JWH-018 was not encountered [177]. Although the metabolites found in the study using CYP450 enzymes were compatible with previous studies, some differences were also found [178]. In an *in vitro* study by Chimalakonda et al., phase I carboxyl and hydroxyl metabolites of JWH-018 and JWH-073 were observed to be major excretion products in the urine [178]. On the other hand, Moran et al. stated that carboxyl and hydroxyl metabolites in urine can be used as fingerprints for the detection of substances [179]. In the study conducted by Sobolevsky et al. on urine samples collected from JWH-018 users, it was stated that the metabolites of JWH-018 formed as a result of hydroxylation in the indole ring and N-alkyl chain are the most suitable metabolites to be used in the screening method [180].

The pharmacokinetic and pharmacodynamic profiles of synthetic cannabinoids in humans have not been fully elucidated. It is generally thought to have pharmacokinetics,

which ends with hepatic CYP450 oxidation followed by glucuronic acid conjugation and renal excretion [181]. Although CYP450 isoenzymes responsible for SC metabolism have not been identified, the main uridine 5′-diphospho-glucuronosyltransferases (UGTs) responsible for conjugation have been identified as UGT1A1, UGT1A3, UGT1A9, UGT1A10 and UGT2B7 [178]. More than 90% of consumed JWH-018 is thought to be biotransformed within three hours of consumption [178]. The initial *in vitro* studies on a similar compound from this group revealed that the main substance was mainly converted N-dealkylated and hydroxylated metabolites. Moreover, there are opinions that one or more of these phase I metabolites that are excreted may be active [178]. This can be considered as an explanation for the more serious side effects of synthetic substances such as JWH-018. The chemical formulas of some of these compounds are shown in Figure 5 above.

2.5.2. Pharmacodynamics of JWH-018

Cannabinoid analogues have agonist effects on CB1R and CB2R. CB1Rs are the most abundant G-protein coupled receptors located in the brain and play an important role in the modulation of GABA and glutamate neurotransmission [182]. In addition, cannabinoid receptors often form heterodimers with other receptors [183]. This interaction, known to occur between cannabinoid and opioid receptors, led them as a target for the development of pharmaceutical strategies for effective pain control [184]. However, there is no information about the interactions of SCs and opiates, yet. Compared to THC, the affinity of JWH-018 for CB1R and CB2R is 4 and 10 times higher, respectively [185]. Studies on rodents reported that JWH-018 reduces locomotive activity and causes effects similar to those caused by THC, such as analgesia, hypothermia and catalepsy [186,187].

2.6. Acute Toxic Effects of SCs

In the literature, the incidence of side effects related to SC use is abundant [188]. Physical manifestations of acute SC intoxication include pupillary dilation, conjunctival hyperaemia, nausea, vomiting, slurred speech, shortness of breath, hypertension, tachycardia (>180 min), chest pain, muscle twitching, pallor or sweating [189].

2.6.1. Cardiological Side Effects

The cardiological side effects of SCs include tachycardia, cardiotoxicity, myocardial infarction, QTc prolongation due to potassium channel blockade and fatal

dysrhythmias such as polymorphic ventricular tachycardia (VT) and torsades de pointes [190-192]. When SCs are used in combination with other drugs, these effects are potentiated. While bradycardia as a cardiovascular side effect has been reported less frequently [193], hypertension and/or hypotension have also been reported [193,194].

2.6.2. Pulmonary Side Effects

Possible associations between lung injury and SC use have been reported [195]. Diffuse pulmonary infiltrates were reported with chronic inhalation of multiple SC-containing products and AM2201 [196,197]. Pneumonia associated with the use of ADB-PINACA have been reported [198].

2.6.3. Gastrointestinal Side Effects

A case of cannabinoid hyperemesis syndrome due to chronic heavy use of SCs (JWH-018, JWH-073, JWH-122, AM-2201 and AM694) was described by Hopkins and Gilchrist [199]. These effects should be supported by other studies as it is interpreted based on a single case study.

2.6.4. Nephrological Side Effects

SC use causes kidney damage in different ways. Acute renal failure has been reported due to the use of XLR-11 and other SCs [200,201]. Moreover, vomiting, flank pain, abdominal pain and increased urinary creatinine concentrations [202], as well as rhabdomyolysis have been reported [203].

2.6.5. Dermatological Side Effects

The most common dermatological side effects have been reported as periorbital darkening, sunken cheeks, wrinkles, hair loss, greying of hair, and acne [204].

2.7. Dependence and Addictive Potential of SCs

The addictive potential of SCs cannot be neglected [205]. Tolerance and withdrawal symptoms have been reported in the literature as a result of chronic use [206]. SC users constituted the third largest group of patients hospitalized in the detoxification service in Auckland, New Zealand between May 2013 and May 2014 [207].

Tolerance and withdrawal symptoms have been reported after long-term SC use. It has been reported that tolerance develops rapidly, and withdrawal symptoms are

internal restlessness, intense sweating, substance cravings, tremor, headache, nightmares, insomnia, irritability, concentration difficulties, and nausea [208,209]. Moreover, after discontinuation of SC use, withdrawal symptoms such as sleep disorders, anxiety, desire to use again, nausea, muscle twitches, cramps and tremors were reported [210]. Withdrawal symptoms of SCs detected in the study of Zimmerman et al. were excessive desire to reuse, restlessness, nightmares, tachycardia (max= 125/min), and hypertension (180/90 mmHg) [211]. Nacca et al. reported generalized anxiety, vivid dreams, headache, cramps, sweating, tremors, anorexia, and intense desire six days after SC use [212].

2.8. Imaging Methods for the Effects of SCs

Radiological imaging is a very important step on the way to diagnosis, very beneficial for patient care and diagnostic accuracy, and the use of methods such as CT and MRI has increased considerably in recent years [213]. The most common adverse effect of SCs on the CNS is embolic ischemic stroke, similar to natural cannabis [214]. The harmful effects of SCs are similar to those of natural marijuana, however, due to SCs contain a variety of compounds, they can cause higher toxicity than natural marijuana. Imaging methods in diagnosing ischemic and haemorrhagic cerebrovascular brain injuries are brain CT and MRI.

2.8.1. MRI: Diffusion Tensor Imaging and conventional MRI-T2/FLAIR

MRI findings of SC users basically appear with restricted diffusion and T2/FLAIR hyperintensity. Diffusion tensor imaging (DTI) is an MRI technique used to evaluate white matter microstructure and is an effective tool for assessing white matter damage by quantitatively assessing it as a fraction [215].

In cerebrovascular diseases, MRI is more sensitive than CT in the early stage of acute ischemic stroke, as well as the distinction between ischemic stroke and hemorrhagic stroke, which is often indistinguishable from each other. Clinical detection of acute and chronic extra-axial traumatic collections and haemorrhagic and non-haemorrhagic contusions, as well as stages of intracranial haemorrhages such as subdural and epidural hematomas, subarachnoid haemorrhage (SAH), contusions (especially those adjacent to bony surfaces), axonal injury and brainstem lesions are better detected with MRI thanks to being more sensitive than CT [216].

Neuroimaging methods can be safely employed to determine brain damage in traumatic brain injuries. While detecting brain lesions with better sensitivity compared to CT, the clinical decision on the use of MRI is important and may be indicated in patients with persistent neurological findings [216].

2.8.2. Computed Brain Tomography

CT imaging was first performed by Godfrey Hounsfield and James Ambrose in 1971 in England and provided the first brain scan of a patient with a brain cyst. The image proved that it is possible to obtain non-overlapped images of a slice of object. Since then, improvements in CT thanks to a number of significant technological advances has led to the ability to acquire thousands of sliced images. It is an essential tool for high resolution cross-sectional imaging and phenotyping in seconds with reduced radiation dose to reveal diseases and treatments. It is an alternative imaging technique for various clinical manifestations such as stroke, brain tumours and head traumas. In addition, CT has been used to evaluate the possible clinical benefits of pharmacological therapy at early stroke onset and to predict survival [217].

Cerebrovascular events (CVE) are one of the leading causes of death in the world. Immediate imaging in patients with suspected acute stroke is necessary because it can reveal other clinical conditions that can mimic stroke, as well as distinguishing between ischemic stroke and haemorrhagic stroke, which are often indistinguishable from each other clinically. Since it can show the area affected by acute stroke and the possible aetiology, radiology has a key role in determining and directing the treatment options of patients in the ED. Cranial CT without contrast is the first imaging modality to be applied in emergency radiology in suspected CVE cases. In the diagnosis of ischemic stroke, findings such as hyperdense middle cerebral artery (MCA) signs on the non-contrast CT, effacement of the cerebral sulcus and cisterns in the affected area, and inability to distinguish between gray matter and white matter can be seen [218].

The primary reason of that the emergency medicine professionals request a brain CT is to clarify the presence or absence of cerebral haemorrhage. The second reason is to investigate whether the patient has cerebrovascular ischemia.

2.9. Poisoning Severity Score

In 1990, the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) established a working group to consider a system for defining the clinical severity of poisoning. A poisoning severity score (PSS) including collecting observational data on poison centres and cases of poisoning was developed. PSS aims to provide a simple but relatively reliable system for describing a poisoning in qualitative terms to describe its eventual severity [219]. A five-level poisoning severity classification scale and PSS are used to classify poisoning severity in clinical toxicology and emergency medicine departments [219].

The scale consists of twelve systems (gastrointestinal system, respiratory system, nervous system, cardiovascular system, metabolic balance, liver, kidney, blood, muscle system, local effects on the skin, local effects on the eye, and local effects from bites and stings) [219,220]. The PSS rates the severity of poisoning at three levels: (1) minor, (2) moderate, and (3) severe poisoning [219,220]. On either side of these grades are extremes, (0) cases with no symptoms of poisoning, and (4) fatal cases [219,220]. Signs and symptoms are given as examples and do not cover all possibilities (Table 1) [219,220]. Although very strict criteria are not useful in this type of chart, some numerical values are provided to aid in the evaluation [219,220].

Table 1. Summary of the Poisoning Severity Score. The most severe symptom determines severity scoring [219,220].

Organ	***Minor:1***	***Moderate:2***	***Severe:3***
Nervous System	Drowsiness, vertigo, ataxia, restlessness, paraesthesia, mild visual or auditory disturbances	Unconsciousness with appropriate response to pain, brief apnoea, bradypnea, confusion, agitation, hallucinations, delirium, infrequent, generalized, or local seizures, visual and auditory disturbances	Deep coma with inappropriate response to pain or unresponsive to pain, respiratory depression within sufficiency,

			extreme agitation frequent, generalized seizures, status epilepticus, opisthotonos, generalized paralysis, blindness, deafness
Muscular System	Mild pain, tenderness CK~250–1500 IU/l	Pain, rigidity, cramping, and fasciculations. rhabdomyolysis, CK~1500–10 000 IU/l	Intense pain, extensive cramping, and fasciculations, rhabdomyolysis with complications, CK>10 000 IU/l
Cardiovascular System	Isolated extrasystoles, sinus tachycardia (HR<140 in adults), mild and transient hypo/hypertension	Sinus bradycardia (HR~40–50 in adults), sinus tachycardia (HR:140–180 in adults), frequent extrasystoles, AV-block I-II, prolonged QRS and QTc-time, repolarization abnormalities, more pronounced hypo/hypertension	Severe sinus bradycardia (HR<40 in adults), severe sinus tachycardia (HR>180 in adults), life threatening ventricular dysrhythmias, AV block III,

			asystole shock, hypertensive crisis
Respiratory System	Irritation, coughing, breathlessness, mild dyspnoea	Prolonged coughing, bronchospasm, dyspnoea, hypoxaemia requiring extra oxygen	Manifest respiratory insufficiency
Gastrointestinal Tract	Vomiting, diarrhoea, pain	Pronounced or prolonged vomiting, diarrhoea, and/or pain, dysphagia	Massive haemorrhage, perforation, severe dysphagia
Metabolic Balance	Mild electrolyte and fluid disturbances (K^+3.0–3.4 mmol/l), mild hypoglycaemia (~50–70 mg/dl in adults), hyperthermia of short duration	More pronounced electrolyte and fluid disturbances (K^+2.5–2.9 mmol/l), more pronounced hypoglycaemia (~30–50 mg/dl in adults). Hyperthermia of longer duration	Severe electrolyte and fluid disturbances (K^+<2.5 mmol/l) severe hypoglycaemia (~<30 mg/dl or 1.7 mmol/l in adults), dangerous hypo- or hyperthermia

AV: Atrioventricular; CK: Creatine kinase; HR: Heart rate

3. MATERIAL & METHOD

3.1. Patients and Study Design

This retrospective study was approved by the Yeditepe University Clinical Research Ethics Committee (Date: 30.06.2021; No: 1460). The files of the cases who admitted to the ED at Şişli Hamidiye Etfal Training and Research Hospital between 01.01.2016 and 01.01.2021 and Sarıyer Etfal Training and Research Hospital, which is connected to Şişli Hamidiye Etfal Training and Research Hospital, between 01.07.2018 and 01.01.2021 were investigated with regards to SC use in the Hospital Information Management System (HIMS). After analysis of the anamnesis and examination findings in the files of the cases, cases who were older than 18 years, had a history of using synthetic cannabinoids for at least one year and admitted to the ED after taking synthetic cannabinoids within the last eight hours and toxicology panel (SC urine test) results were positive were included in the study (Group 1). Moreover, particular cases with at least one sign or suspicion of brain damage (neurological finding) were identified in HIMS and included in the study (Group 2) and the diagnosis of these cases were made by using imaging methods (CT / MRI). The neurological symptoms and symptoms related with other systems are summarized as follows: consciousness (blurring), confusion, amnesia, headache, speech disorders, visual disturbances or diplopia, psychosis, paranoia, depressed mood and aggression, disorientation, sensory disorders, tingling sensation, pain or loss of pain sensation, motor weakness (stroke), difficulty swallowing, urinary and fecal incontinence, dizziness, tremor, syncope, seizure, balance disorders, hallucination, gastrointestinal system disorders (nausea, vomiting, abdominal pain, appetite disorders, etc.), circulatory and respiratory system disorders (tachycardia, hypotension, hypertension, chest pain, heart attack, shortness of breath, air hunger etc.), neurological findings of other systems (cramp, widespread muscle pain, fasciculation, fatigue, loss of reflexes, coordination disorders, gait-balance-posture disorders, etc.).

The data of the patients admitted to Şişli Hamidiye Etfal Training and Research Hospital between 01.01.2016-01.01.2021 and to Sarıyer Etfal Training and Research Hospital, which is under Şişli Hamidiye Etfal Training and Research Hospital, between 01.07.2018-01.01.2021 were examined. Among the patients who admitted to the ED with the consumption of SCs defined by the International Statistical Classification of Diseases

and Related Health Problems (ICD) codes registered in HIMS, 993 patients who met the inclusion criteria were identified.

A total of 2.211.922 admissions were made to the ED. A total of 993 patients were detected to use SCs from the HIMS. The inclusion criteria were being 18 years or older, using SCs for one year or longer and admission to the ED with various complaints due to SC use within the last 8 hours were investigated. Patients with toxicology panel (SC urine test) results were positive were included in the study. The exclusion criteria were being younger than 18 years old, readmission to the hospital within 24 hours, negative results of the toxicology panel and missing data of patients. In total, 455 patients was excluded from the study, as a result, 538 patients were determined as the patient group who admitted to the ED due to using SCs.

The patients were classified as follows: Group 1: all patients using SC, Group 2: patients among SC users underwent brain imaging with the suspicion of brain damage, Group 3: control group patients who admitted to the ED with minor head trauma or headache and underwent brain imaging.

3.2. Patient Examinations

Vital signs and neurological examination findings were obtained from the files of cases and Glasgow Coma Scale (GCS) scores were determined. The five basic vital signs (body temperature, pulse, blood pressure, respiration rate and oxygen saturation) were recorded. GCS is a basic and indispensable criterion of neurological examination and brain damage [221]. It is a criterion developed for the neurological assessment of the person in general and for the determination of the level of consciousness [221]. When the patient is evaluated according to the criteria of the scale, the patient is given scores between 3 (deep unconsciousness) and 15 (normal level of consciousness) [221]. The total GCS score is determined and scaling is as follows: 15, oriented; 13 – 14, confused; 8 – 13, stupor; 3 – 8, precoma; 3, coma.

Glasgow Coma Scale (GCS) [222]: By using GCS criteria, clinicians can assess the general neurological condition of a person. Initially, the GCS was used to determine the level of consciousness in head injury cases, and it is now employed as a crucial element of neurological examination. Chronic patients are also monitored in intensive care units in hospitals by using GCS, and prediction of the neuronal dysfunction and life-threatening

condition can be done by 85% confidence within two weeks after injury. Quality of motor and verbal responses, as well as, eye opening response are used in the evaluation and the three attributes are evaluated both separately and together.

Routine laboratory and imaging test results of the patients were examined for each patient included in the study. Hemogram and blood biochemistry, complete urinalysis tests of the patients were evaluated. CT and MRI results of the patients were examined.

Patients also underwent urine toxic substance screening test by using Triage® TOX Drug Screen Panel (94400EU, Quidel; USA). It is a rapid and new test panel developed for simultaneous screening of 11 different drugs (paracetamol, tetrahydrocannabinol, amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, opiates, tricyclic antidepressants, phencyclidine and methadone) and their toxic doses from urine samples [223].

3.3. Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS statistics 21.0 (IBM Corp. Armonk, NY, USA). Distribution of the data was analyzed using Kolmogorov-Smirnov test. Continuous parameters were stated as mean ± standard deviation (SD), and numerical variables without normal distribution were shown as median (minimum-maximum) values. Normally distributed data were compared with Student's t-test, whereas parameters without normal distribution were compared by using Mann-Whitney U test. Associations between PSS, GCS and hospitalization status of the patients were evaluated with the Pearson and Spearman correlation tests. A $p < 0.05$ was considered statistically significant.

4. RESULTS

4.1. Demographical and Clinical Characteristics of the Patients

When we evaluated all 538 patients who admitted to hospitalized in the ED after using SCs, it was detected that 17 of them were diagnosed with acute renal failure, 11 of them were diagnosed with myocardial infarction (MI) (one with ST elevation MI), 9 of them were diagnosed with cerebrovascular disease (ischemic / hemorrhagic) and 2 of them were diagnosed with pulmonary thromboembolism. Patients diagnosed with acute renal failure underwent hemodialysis. Apart from these, 4 patients were admitted to psychiatry clinics and 18 patients were admitted to other relevant clinics and intensive care unit for diagnosis, treatment and follow-up (seizure follow-up, syncope etiology, hypertension treatment, etc.). Four of patients diagnosed with acute renal failure underwent hemodialysis. Evaluation of the files revealed that 5 patients among all patients died.

Among 538 patients who admitted to ED after using SCs (group 1), 114 patients underwent brain imaging (group 2). Evaluation of patients in group 2, nine patients patients had cerebrovascular disease (ischemic / hemorrhagic), five patients had acute renal failure, five patients had acute MI, and two patients were diagnosed with pulmonary thromboembolism. It was determined that 10 patients were hospitalized in the relevant clinics and intensive care unit for diagnosis, treatment and follow-up (seizure follow-up, syncope etiology, hypertension treatment, etc.). In addition, it was determined that five patients who died in the whole patient population (group 1) were evaluated as patients in group 2, as brain imaging was performed considering possible brain damage.

The mean age of the patients in group 1 was significantly lower compared to groups 2 ($p = 0.049$; **Table 2**). Among the patients in group 1, 94 patients (17.47%) were female and 444 patients (82.53%) were male, while in group 2, 16 patients (14.04%) were female and 98 (85.96%) were male.

Table 2. Distribution of all patients using SC by age

	Age			n	p
	Mean ± SD	**Median**	**Min – Max**		
Group 1	29.30 ± 9.34	26.5	18-55	538	0.049
Group 2	32.65 ± 9.03	32	18-55	114	

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage, Statistical analysis: Mann-Whitney U test, Min: minimum, Max: maximum, sd: standard deviation, n; the total number * *p=sig<0.05.*

In all patients in group 1, the total number of patients who used only SCs was 195 (36.25%), the total number of those who used alcohol together with SCs was 190 (35.32%), the total number of those who used other psychoactive/recreational substances together with SCs was 52 (9.66%) and the total number of people who consumed alcohol and other psychoactive/recreational substances together with SC was 101 (18.77%). On the other hand, in group 2, the total number of patients who used only SCs was 29 (25.44%), the total number of patients who used alcohol together with SCs was 42 (36.84%), the total number of patients who used other psychoactive/recreational substances with SC was 14 (12.28%) and the total number of patients who consumed alcohol and other psychoactive/recreational substances together with SC was 29 (25.44%).

While there were no significant differences in systolic blood pressure (SBP), respiratory rate and body temperature between group 1 and group 2 ($p<0.01$; **Table 3**), diastolic blood pressure (DBP) and HR were significantly higher ($p<0.01$; **Table 3**) and SpO_2 was significantly lower in patients in group 2 ($p<0.01$; **Table 3**) compared to group 1.

Table 3. Vital signs of the patients in group 1 and group 2.

Vital Signs	Group 1 (n=538)		Group 2 (n=114)		p
	Median (Min-Max)	Mean ± SD	Median (Min-Max)	Mean ± SD	
SBP	122 (67-254)	123.96±19.07	124 (67-254)	130.06±26.57	0.073
DBP	82 (38-176)	82.31±13.64	87 (38-176)	89.81±19.85	**0.00***
HR	85 (55-226)	90.20±24.74	90 (55-226)	103.90±35.80	**0.00***
Respiratory rate	16 (12-32)	15.73±2.06	16 (12-32)	16.34±3.21	0.190
Body temperature (°C)	37 (35-38.2)	36.97±0.42	37 (35-38.2)	36.96±0.47	0.848
SpO_2	96 (66-100)	94.90±3.43	92 (66-100)	91.75±4.99	**0.00***

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. DBP: Diastolic blood pressure; HR: Heart rate; SBP: Systolic blood pressure. Statistical analysis: Mann-Whitney U test, Min: minimum, Max: maximum, sd: standard deviation, n; the total number, ***** *p=sig<0.01.*

The most common symptoms on the admission in patients in group 1 were tachycardia (149; 28.76%) and hallucinations (111; 20.63%), while in group 2, the most common symptoms were tachycardia (53; 46.40%), somnolence (39; 34.21%), seizures (35; 30.70%), confusion (31; 27.19%) and agitation (25; 21.92%). All symptoms were detected in both groups are indicated in **Table 4**.

Table 4. Distribution of the symptoms of SC users on admission to ED in group 1 and group 2.

Symptoms	Group 1		Group 2		p-value
	n=538	%	n=114	%	
Unrest	84	15.61	13	11.40	0.252
Agitation	74	13.75	25	21.92	**0.027***
Irritability	96	17.84	11	9.64	**0.032***
Hallucination	111	20.63	10	8.77	**0.003***
Vertigo	38	7.06	12	10.52	0.207
Anxiety	63	11.71	8	7.01	0.144
Seizures	35	6.50	35	30.70	**0.000***
Somnolence	103	19.14	39	34.21	**0.000***
Numbness-tingling (paresthesia)	69	12.82	21	18.42	0.116
Psychosis	3	0.55	3	2.63	**0.035***
Paranoia	6	1.11	1	0.87	0.823
Confusion	91	16.91	31	27.19	**0.011***
Self-harm	9	1.67	0	0	0.165
Speech disorder	29	5.39	6	5.26	0.956
Depressed mood	20	3.7	2	1.75	0.282
Aggression	27	5.01	13	11.40	**0.010***
Laughing attacks	4	0.74	0	0	0.356
Myoclonia	34	6.31	19	16.61	**0.000***
Tremor	13	2.41	1	0.87	0.303
Fatigue	91	16.91	9	7.89	**0.015***
Myalgia-muscle cramps	51	9.47	7	6.14	0.256
Motor fatigue	9	1.67	9	7.89	**0.000***
Headache	32	5.94	9	7.89	0.437
Sweating	17	3.15	1	9.87	0.177
Tachycardia	149	28.76	53	46.49	**0.000***
Bradycardia	20	3.71	5	4.38	0.736
Hypertension	53	9.85	18	15.78	0.065

Hypotension	14	2.60	4	3.50	0.592
Chest pain	30	5.57	6	5.26	0.894
Syncope	16	2.97	9	7.89	**0.013***
Dyspnea	75	13.94	19	16.66	0.562
Abdominal pain	61	11.33	8	7.01	0.173
Dry mouth	47	8.73	6	5.26	0.218
Nausea-vomiting	69	12.82	14	12.28	0.874
Urinary and fecal incontinence	19	3.53	19	16.66	**0.00***
Sensation of thirst	61	11.33	5	4.38	**0.025***
Red eyes	77	14.31	20	17.54	0.379
Areflexia	3	0.55	3	2.63	**0.035***
Hyperreflexia	26	4.83	4	3.50	0.540
Diarrhea	18	3.34	0	0	**0.048***
Mydriasis	49	9.10	15	13.15	0.187
Miosis	7	1.30	4	3.50	0.097

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. Statistical analysis: Mann-Whitney U test, n; the total number, %; percentile, ***** *p=sig<0.05.*

It was determined that the GCS scores, which was initially evaluated on admission to the ED, ranged between 3 -15. When evaluated, a statistically significant correlation was found between patients with low GCS scores and grup 2 (p<0.01; **Table 5**).

Table 5. Distributions of the patients in group 1 and group 2 with regards to GCS score.

GCS score	**Group 1**		**Group 2**		**p**
	n=538	**%**	**n=114**	**%**	
3-8	19	3.53	19	16.66	**0.00***
9-12	37	6.88	25	21.93	
13-14	103	19.14	43	37.72	
15	379	70.45	27	23.69	

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. Statistical analysis: Kruskal Wallis test/Chi-square test, n; the total number, %; percentile, ***** *p=sig<0.01.*

Electrocardiography (ECG) findings showed that there was a significant relationships in patients who undergoing brain imaging with the suspicion of brain damage and tachycardia findings in ECG ($p<0.01$; **Table 6**).

Table 6. Distribution of ECG findings of the patient in group 1 and group 2.

ECG finding	Group 1		Group 2		p
	n=538	%	n=114	%	
Normal sinus rhythm	369	68.58	56	49.12	
Tachycardia	149	28.76	53	44.49	**0.00***
Bradycardia	20	3.71	5	4.38	

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. ECG: Electrocardiography. Statistical analysis: Kruskal Wallis test/Chi-square test, n; the total number, %; percentile, * *p=sig<0.01.*

When the pupil diameters were examined, most of the patients in both groups were observed isochoric (n=482 (89.60%) and n=95 (83.35%) in group 1 and group 2, respectively; **Table 7**). There were no significant associations between patients' pupil diameter in group 1 and group 2 ($p>0.05$).

Table 7. Distributions of the patients in group 1 and group 2 with regards to pupil diameter.

Pupil Diameter	Group 1		Group 2		p
	n=538	%	n=114	%	
Isochoric	482	89.60	95	83.35	
Mydriasis	49	9.10	15	13.15	0.052
Miosis	7	1.30	4	3.50	

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. Statistical analysis: Kruskal Wallis test/Chi-square test, n; the total number, %; percentile, p=sig<0.05.

QT corrected for heart rate (QTc) values calculated from the ECG showed that group 2 had significantly higher QTc values compared to the group 1 ($p=0.024$; **Table 8**).

Table 8. QTc values of the patients in group 1 and group 2.

	Group 1 (n=538)		Group 2 (n=114)		p
	Median (Min - Max)	**Mean ± SD**	**Median (Min - Max)**	**Mean ± SD**	
QTc value (msec)	416 (379-581)	424.91 ± 33.59	428 (379-581)	436.44 ± 40.15	**0.024***

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. Statistical analysis: Mann-Whitney U test, Min: minimum, Max: maximum, sd: standard deviation, n; the total number, * *p=sig<0.05.*

When the hospitalization/discharge status of the patients were examined, it was found that most of the patients in both groups were discharged (**Table 9**). However, it was observed that hospitalization in ward and intensive care unit (ICU) were ~2 and ~3 times higher, respectively, in group 2 compared to group 1 (**Table 9**), In the light of these data, it was determined that there was a significant difference between group 2 and group 1 when the hospitalization/discharge status of the patients was examined (p<0.01; **Table 9**)

Table 9. Distribution of the patients according to their discharge and hospitalization status in group 1 and group 2.

	Group 1		Group 2		p
	n=538	**%**	**n=114**	**%**	
Discharge	436	81.04	76	66.67	
Refusing treatment	41	7.62	7	6.14	
Hospitalization in ward	29	5.39	12	10.53	**0.00***
Hospitalization in ICU	32	5.95	19	16.66	

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. Statistical analysis: Kruskal Wallis test/Chi-square test, %; percentile, n; the total number, * *p=sig<0.01.*

When the groups were evaluated according to their PSS, a significant difference was observed between group 1 and group 2. It was observed that PSS progressed on a severe and fatal scale in approximately half of Group 2 patients (p<0.01; **Table 10**).

Table 10. Distribution of the patients according to PSS in group 1 and group 2.

PSS	Group 1		Group 2		p
	n=538	%	n=114	%	
None	0	0	0	0	
Mild	208	38.66	27	23.68	
Moderate	273	50.74	34	29.82	**0.00***
Severe	52	9.67	50	43.86	
Fatal	5	0.93	3	2.64	

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. Statistical analysis: Kruskal Wallis test/Chi-square test, %; percentile, n; the total number, * p=sig<0.01.

When group 1 SC users who admitted to the ED were evaluated, there was a significant and moderate negative relationship between PSS and GCS (r=-0.476, p<0.01; **Table 12**). There was a significant and moderately positive relationship between hospitalization status and PSS (r=0.594, p<0.01; **Table 12**). Moreover, there was a significant and strong negative correlation between hospitalization and GCS (r=-0.806, p<0.01; **Table 11**).

Table 11. Associations between PSS, GCS and hospitalization status of the patients in group 1.

		GCS	Hospitalization
PSS	r	**-0.476***	**0.594***
	p	**0.00****	**0.00****
	n	538	538
GCS	r		**-0.806***
	p		**0.00****
	n		538

Group 1: all patients using SC, *r: Spearman's Rho Corelation test, n; the total number, * p=sig<0.05, ** p=sig<0.01.

When group 2 SC users who admitted to the emergency department were evaluated, there was a significant and strong negative relationship between PSS and GCS (r=-0.913, p<0.01; **Table 12**). There was a significant and strong positive relation between hospitalization and PSS (r=0.706, p<0.01; **Table 12**). In addition, there was a significant and strong negative correlation between hospitalization and GCS (r=-0.940, p<0.01; **Table 12**).

Table 12. Associations between PSS, GCS and hospitalization status of the patients in group 2.

		GCS	Hospitalization
PSS	r	**-0.913***	**0.706***
	p	**0.00****	**0.00****
	n	114	114
GCS	r		**-0.940***
	p		**0.00****
	n		114

Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. *r: Spearman's Rho Corelation test, n; the total number, * p=sig<0.05, ** p=sig<0.01.

Blood pH and HCO_3^- levels of the patients in group 2 was significantly lower than group 1 ($p<0.0001$; **Table 13**). On the other hand, COHg and lactate levels were significantly higher in group 2 of patients compared to group 1 ($p<0.05$; **Table 13**).

Troponin-T, creatinine kinase isoenzymes (CK-MB), Na^+ and C-reactive protein levels were significantly higher in patients in group 2 compared to group 1 ($p<0.05$; **Table 14**), while blood urea nitrogen (BUN) was significantly higher in group 1 compared to group 2 of patients $p<0.05$; **Table 14**). On the other hand, hemoglobin (Hgb), hematocrit (Hct), mean cell volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and mean corpuscular hemoglobin (MCH) levels were significantly higher in group 1 compared to group 2 ($p<0.05$; **Table 15**), while white blood cell counts (WBC) were significantly higher in group 2 compared to group 1 ($p<0.0001$; **Table 15**).

Table 13. Blood gas parameters of the SC patients admitted to ED in group 1 and group 2.

	Group 1 (n=538)		Group 2 (n=114)		P
	Median (Min-Max)	**Mean ± SD**	**Median (Min-Max)**	**Mean ± SD**	
pH (range: 7.35-7.45)	7.37 (6.70-7.51)	7.32 ± 0.47	7.23 (6.70-7.51)	7.21 ± 0.13	**0.000***
PCO_2 (range: 35-45 mmHg)	43 (34-78)	44.3 ± 11.73	52 (36-78)	56 ± 20.3	0.790
PO_2 (range: 70-100 mmHg)	91 (48-100)	89.7 ± 10.02	79 (48-100)	78 ± 10.4	0.790
BE (mmol/L)	-1.00 (-17.90-11.40)	-2.40 ± 3.53	-4.03 (-17.90-9.80)	-9.39 ± 4.24	0.885
HCO_3^- (mmol/L)	24.80 (16.60-35.70)	25.57 ± 3.68	22.20 (16.60-29.80)	21.78 ± 2.87	**0.000***
COHg (range: 0-3 %)	3.40 (0.10-29)	5.47 ± 4.31	5.50 (0.50-29)	7.93 ± 6.20	**0.000***
Lactate (range: 0-0.2 mmol/L)	2.30 (0.10-18)	3.21 ± 3.45	3.70 (0.54-18)	5.09 ± 6.20	**0.011***

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. BE: Blood base excess. Statistical analysis: Mann-Whitney U test, Min: minimum, Max: maximum, sd: standard deviation, n; the total number, * p=sig<0.05.

Table 14. Cardiology parameters and blood biochemistry results of the SC users in group 1 and group 2.

	Group 1		Group 2		
	Median (Min - Max)	**Mean ± SD**	**Median (Min - Max)**	**Mean ± SD**	**p**
Troponin T (n=305, n=69) (range: <14 ng/L)	3.60 (0.10-1297)	24.38 ± 116.71	6.04 (1.10-987)	37.79 ± 144.16	**0.014***
CK-MB (n=311, n=82) (range: 0.6-6.3 ug/L)	4 (0.70-52)	4.57 ± 5.63	3.75 (0.70-31)	4.40 ± 4.13	0.986
CK (n=247, n=57) (range: 26-192 U/L)	162 (40-1626)	224.46 ± 266.31	170 (58-1626)	355.17 ± 357.09	**0.005***
BUN (n=517, n=114) (range: 10.7-38.52 mg/dL)	30 (8,80-91)	31.55 ± 12.40	28.40 (11-91)	29.33 ± 13.77	**0.024***
Creatinine (n=517, n=114) (range: 0.50-1.30 mg/dL)	0.80 (0.30-8.59)	0.89 ± 0.49	0.80 (0.40-8.59)	0.95 ± 0.82	0.990
Na^+ (n=517, n=114) (range: 136-145 mmol/L)	139 (118-150.5)	139.69 ± 5.14	139 (123-150.5)	140.06 ± 4.89	**0.007***
K^+ (n=517, n=114) (range: 3.5-5.1 mmol/L)	3.36 (2.44-5.89)	3.71 ± 0.55	3.66 (2.84-5.89)	3.77 ± 0.53	0.572
Ca^{2+} (n=517, n=114) (range: 8.4-10.2 mg/dL)	9.30 (7.50-10.30)	9.03 ± 0.62	9.26 (7.50-9.82)	8.98 ± 0.64	0.499
Cl^- (n=517, n=114) (range: 101-109 mmol/L)	104 (83-117)	104.03 ± 3.87	104 (89-112)	103.95 ± 3.97	0.955
ALT (n=517, n=114) (range: 0-50 U/L)	21 (6-127)	26.23 ± 20.56	21 (11-123)	26.06 ± 18.76	0.844
AST (n=517, n=114) (range: 0-40 U/L)	26 (8-688)	32.33 ± 35.39	26 (9-208)	30.77 ± 21.55	0.600
Glucose (n=538, n=114) (range: 80-110 mg/dL)	118 (61-387)	127.55 ± 45.21	118 (69-306)	129.73 ± 40.15	0.275
CRP (n=519, n=114) (range: <5 mg/L)	2.60 (0.20-156)	8.13 ± 15.77	8.60 (0.60-156.30)	24.51 ± 35.02	**0.000***

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CK: Creatinine kinase; CK-MB: Creatinine kinase isoenzymes;

CRP: C-reactive protein. Statistical analysis: Mann-Whitney U test, Min: minimum, Max: maximum, sd: standard deviation, n; the total number, * p=sig<0.05.

Table 15. Hematology results of the SC users in group 1 and group 2.

	Group 1		**Group 2**		**p**
	Median (Min - Max)	**Mean ± SD**	**Median (Min - Max)**	**Mean ± SD**	
Hgb (n=517, n=114) (range: 11.5-15.5 g/dL)	13.90 (7.58-18.90)	13.59 ± 1.44	13.40 (8.90-16.10)	13.10 ± 1.48	**0.004***
Hct (n=517, n=114) (range: 35.5-48%)	41 (22.83-57.70)	40.88 ± 4.40	40.50 (26.90-49.60)	39.75 ± 4.46	**0.036***
MCV (n=517, n=114) (range: 75-90 fL)	90.30 (67.30-106.5)	90.39 ± 6.26	88.90 (71-105.90)	88.61 ± 6.35	**0.008***
MCHC (n=517, n=114) (range: 310-370 g/L)	338 (296-379)	335.32 ± 12.66	334 (303-369)	332.43 ± 12.37	**0.043***
MCH (n=517, n=114) (range:25-34 pg)	30.50 (22.20-36.20)	30.53 ± 2.46	30.50 (22.20-34.40)	30.09 ± 2.29	**0.042***
WBC (n=517, n=114) (range: 4.5-10.5 x 10^9/L)	11.17 (4.70-33.02)	12.11 ± 3.75	14.47 (5.23-26.59)	14.47 ± 4.52	**0.000***
PLT (n=517, n=114) (range:180-400 x10^9/µL)	276 (106-749)	283.11 ± 94.57	287.50 (106-557)	300.23 ± 97.96	0.086
RBC (n=517, n=114) (range: 3.8-5.6 x 10^{12}/L)	4.58 (2.34-5.90)	4.47 ± 0.52	4.59 (3.42-5.09)	4. 53 ± 0.43	0.506
RDW (n=517, n=114) (range: 11.2-15%)	13.30 (9.80-20.70)	13.80 ± 1.77	13.30 (11.90-19.30)	13.59 ± 1.54	0.456

Group 1: all patients using SC, Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage. Hct: Hemotocrit; Hgb: Hemoglobin; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; MCV: Mean cell volume; PLT: Platelet count; RBC: Red blood cell count; RDW: Red cell distribution width; WBC: White blood cell count. Statistical analysis: Mann-Whitney U test, Min: minimum, Max: maximum, sd: standard deviation, n; the total number, * p=sig<0.05.

To examine brain damage associated with SC use, patients undergoing brain imaging that could show possible brain damage among the SC users were evaluated. The control group of group 2 was group 3. The mean age of group 2 and group 3 were similar (p=0.896; **Table 16**), as well as gender (p=0.977; **Table 17**).

Table 16. Age distribution of the patients in group 2 and group 3.

	Age			n	P
	Mean ± SD	**Median**	**Min – Max**		
Group 2	32.65 ± 9.03	32	18-55	114	0.896
Group 3	32.21 ± 9.01	31	18-54	120	

Group 2: patients among SC users undergoing brain imaging with the suspicion of brain damage, Group 3: control group patients who admitted to the ED with minor head trauma or headache and underwent brain imaging. Statistical analysis: Mann-Whitney U test, Min: minimum, Max: maximum, sd: standard deviation, n; the total number, p=sig<0.05.

Table 17. Gender distribution of the patients in group 2 and group 3.

	Group 2		Group 3		P
	n	**%**	**n**	**%**	
Female	16	14.04	17	14.16	0.977
Male	98	85.96	103	85.84	
Total	114	100	120	100	

Group 2: patients among SC users underwent brain imaging with the suspicion of brain damage with the suspicion of brain damage, Group 3: control group patients who admitted to the ED with minor head trauma or headache and underwent brain imaging. Statistical analysis: Mann-Whitney U test, %; percentile n; the total number, p=sig<0.05.

In group 2 patients who underwent brain imaging a total of 114 brain CT scans and 53 brain MRI were performed. In group 3, a total of 120 brain CT scans were performed. A brain damage diagnosis were made for nine patients in group 2, while none of the patients in group 3 were diagnosed with any kind of brain damage.

The ages of patients with brain damage in SC users ranged between 21 and 54 years, with a mean age of 37.22 ± 9.53 years, of which two patients (22.22%) were female

and seven patients (77.88%) were male. When the diagnoses of these patients were examined, one patient had hemorrhagic cerebrovascular disease (SAH), four patient had was ischemic CVE, and four patients had lacunar infarct.

4.2. Presentation of the Cases with a Diagnosis of Brain Damage

4.2.1. Case 1

A 36-year-old female patient was brought to the ED with slurred speech. In her history, while drinking alcohol and smoking "bonsai" with two of her friends, she began to have nausea-vomiting deteriorate in speech and unable to move her left arm. When paramedics arrived, the patient had somnolence and agitated, and required physical restraints to avoid self-harm. She would not talk, but she had echolalia. Her vital findings were as follows: GCS= 7 BP= 201/147 mmHg, HR= 114 beat per minute (bpm), and respiratory rate= 24 min. The grade of muscle strength was 3/5. ECG finding was sinus tachycardia. There was no chronic disease in her history and she did not use regular medication. She had been a synthetic cannabinoid user for five years. Brain MRI revealed ischemia and apparent diffusion coefficient (ADC) equivalent of the lesion were found in the cortical area of right MCA (**Figure 6**). She was consulted with neurologist and admitted to the neurology clinic with the diagnosis of acute ischemic cerebrovascular disease.

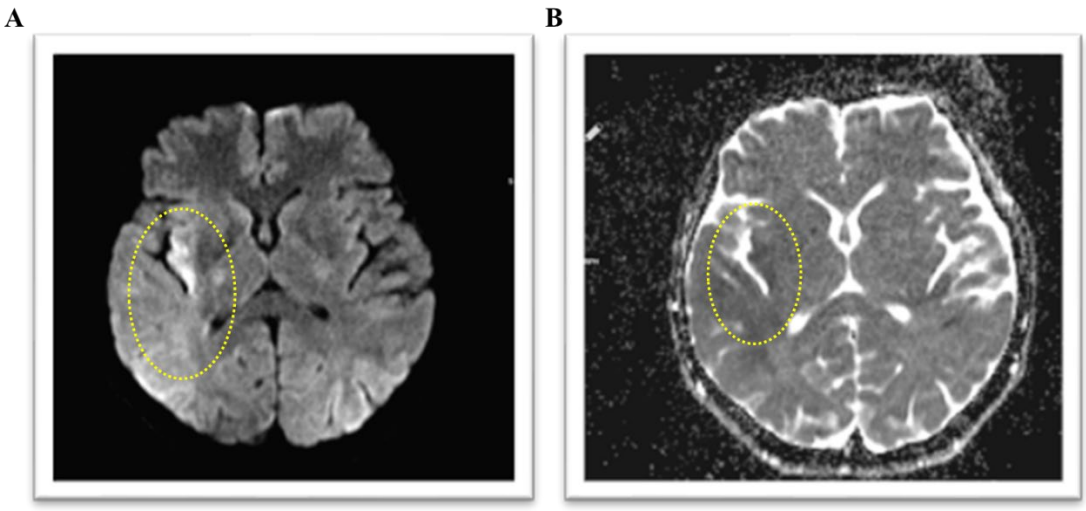

Figure 6. Brain MRI of Case 1 (A) Diffusion and (B) ADC scans showing right MCA stroke and right MCA M1 oclusion (as high lighted by yellow dotted circle).

4.2.2. Case 2

A 45-year-old male patient was brought to the ED after reportedly having a seizure. In his history, while he and his friend were drinking alcohol, using psychoactive substance and smoking "bonsai" cigarettes, irritability before seizure, drowsiness and slurred speech had begun. He was brought to the ED by his family. Vital signs were as follows: BP= 171/126 mmHg, HR= 110/min and respiratory rate= 18/min. In the physical examination, it was revealed that he was disorriented with regards to place and time, he was confused, there were symptoms of sweating, vomiting, redness of the eyes and mydriasis, and GCS score was 11. There was frust hemiparesis and dysarthria in the left upper and lower extremities. ECG finding was sinus tachycardia. There was no chronic disease in his medical history and he was not using any regular medication. He had been a SC user for six years In brain MRI diffusion imaging, right MCA infarction was diagnosed in diffusion-weighted sections and ADC images were found in parallel (**Figure 7**). He was consulted with neurologist and admitted to the neurology clinic with the diagnosis of acute ischemic cerebrovascular disease.

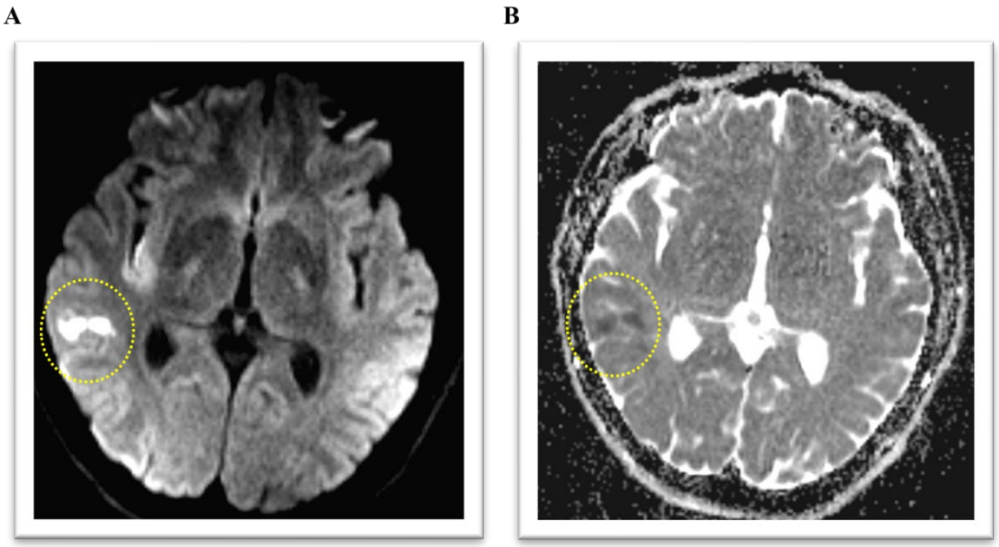

Figure 7. Brain MRI of Case 2 (A) Diffusion and (B) ADC scans showing right MCA stroke and right MCA M1 oclusion (as high lighted by yellow dotted circle).

4.2.3. Case 3

A 21-year-old male patient was brought to the ED accompanied by witnesses, considering that he had been inactive (syncope) for a long time alone in the park. According to the information received from his relatives, it was learned that he used alcohol and SC. In his physical examination he was found confused, unrest and his GCS= 8, BP: 164/116 mmHg, HR= 124 bpm, respiration rate= 14/min and body temperature was 38.2 °C. The grade of muscle strength on the left arm was 3/5. Slurred speech and mydriasis were present. ECG findings were sinus tachycardia. It was learned in his history that he did not have a chronic disease and had been a synthetic cannabinoid user for three years. In laboratory parameters, troponin T levels increased as high as 35.4 ng/L during the follow-up. There was no acute pathology apparent in brain CT. In the diffused brain MRI sections, a hyperintense lesion was observed in the vicinity of the anterior horn of the left lateral ventricle, and a hypointense lesion in the ADC (**Figure 8**). He was consulted with anesthesiologist and admitted to the ICU due to unconsciousness and respiratory support requirement.

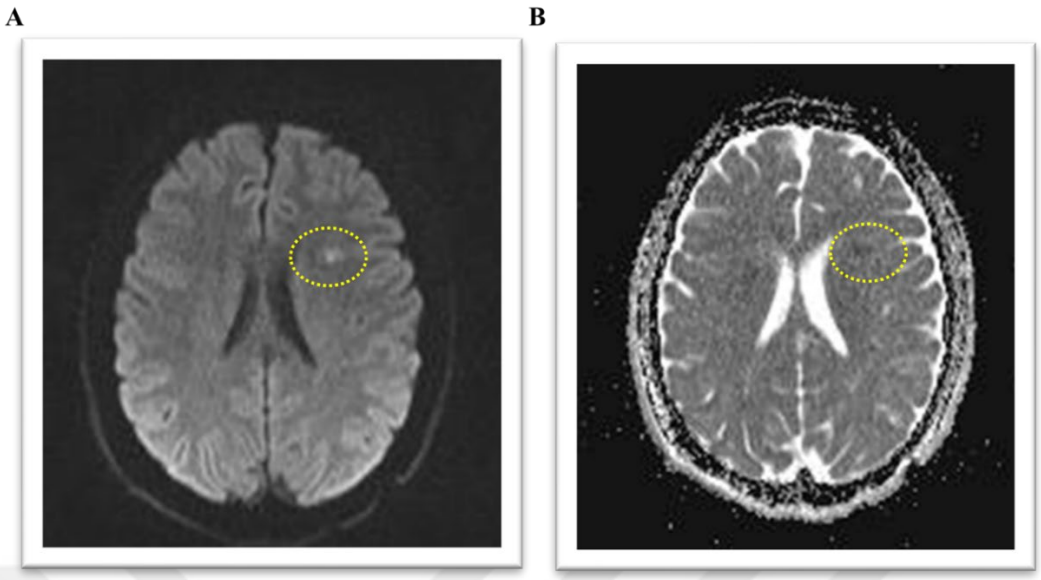

Figure 8. Brain MRI of Case 3 (A) Diffusion and (B) ADC scans showing the anterior horn of the left lateral ventricle lacunar infarct (as high lighted by yellow dotted circle).

4.2.4. Case 4

A 39-year-old male patient was brought to the ED by his relatives, in an unconscious state with seizure, in an 112 ambulance. In his story, it was learned that he was drinking alcohol heavily for the last 2 days and consumed drugs called "jamaica gold". Also it was learned that he had complaints of headache and vertigo. He had been addicted to SCs for 3 years and had no known chronic disease. In the physical examination, it was observed that he had urinary and fecal incontinence, seizures and vomiting. His GCS score was 3 and vital signs were as follows: BP= 254/176 mmHg, HR= 138 bpm and respiratory rate= 22/min. He had mydriasis and metabolic acidosis. The patient was intubated in the ED. Diffuse edema and bilateral periventricular and intracranial hemorrhage were detected on brain CT (**Figure 9**). He was consulted with anesthesiologist and admitted to the ICU. Antiedema treatment and hemodialysis were started in the ICU as intubated. He died on the 5th day of ICU stay.

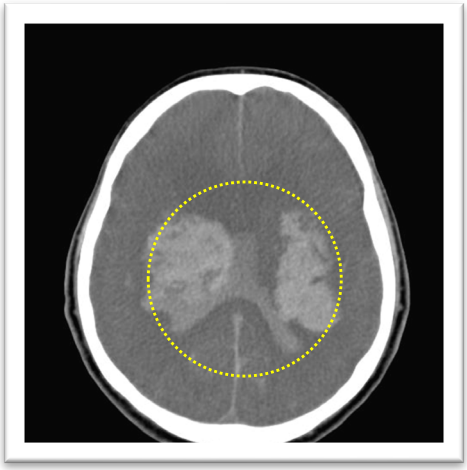

Figure 9. Brain CT of Case 4 shows bilateral periventricular and intracranial hemorrhage (as high lighted by yellow dotted circle).

4.2.5. Case 5

A 54-year-old male patient admitted to the ED with his relatives because of right-sided weakness after SC use and pscyhoactive substance. He became unconscious shortly after he was admitted to the hospital with symptoms of agitation, restlessness and nausea-womitting were detected on physical examination. It was learned in his history that he did not have a chronic disease and he was not using any regular medication. He had been a synthetic cannabinoid user more than three years. His GCS score was 5 and his vital signs were as follows: BP= 174/128 mmHg, BP= 135 bpm and respiratory rate= 18/min. No intraparenchymal hemorrhage was observed in the brain CT, and an appearance compatible with acute infarction was observed in the lentiform nucleus, head and body of caudate nucleus on the left side in the brain diffusion MRI (**Figure 10**). He was consulted with neurologist and admitted to the neurology clinic with the diagnosis of acute ischemic cerebrovascular disease.

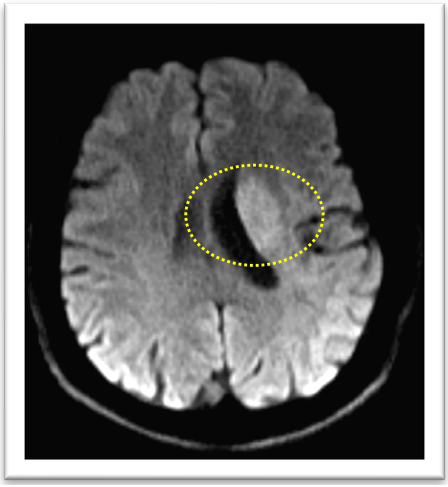

Figure 10. Brain diffusion MRI of Case 5 showing infarct in the left lentiform nucleus, head and body of caudate nucleus (as high lighted by yellow dotted circle).

4.2.6. Case 6

A 32-year-old male patient admitted to the ED because of the sudden onset of right-sided weakness after SC use as indicated by his family. According to the information received from his family, he had been addicted to SC for the last 2 years. In his history that he did not have a chronic disease and he was not using any regular medication. On physical examination, he was unconscious and agitated, and had a GCS score of 8. His vital signs were as follows: BP= 132/99 mmHg, HR= 98 bpm, and respiratory rate= 16/min. No intraparenchymal hemorrhage was detected in brain CT, while an appearance compatible with lacunar infarction was observed in the vicinity of the left lateral ventricle in diffusion MRI (**Figure 11**). He was consulted with anesthesiologist and admitted ICU with the diagnosis of acute ischemic cerebrovascular disease.

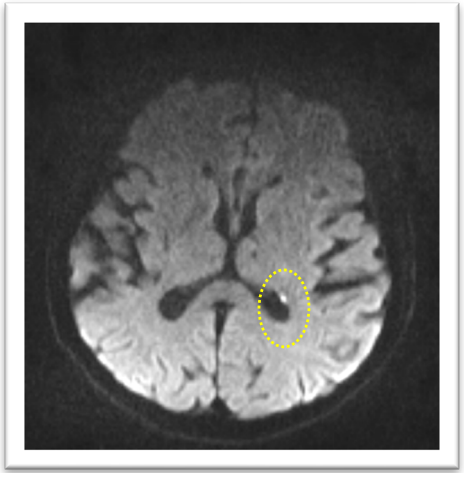

Figure 11. Brain diffusion MRI of Case 6 showing lacunar infarct (as high lighted by yellow dotted circle).

4.2.7. Case 7

A 37-year-old male patient admitted to the ED with his relatives because of the sudden onset of left-sided weakness after SC use as reported by his family. It was learned in his history that he did not have a chronic disease and he was not using any regular medication. He had been addicted to SC for the last 4 years. On physical examination, he was unconscious and had a GCS score of 3. His vital signs were as follows: BP= 158/115 mmHg, HR= 115 bpm, and respiratory rate= 16/min. No intraparenchymal hemorrhage was observed in the brain CT, and an appearance consistent with acute infarction extending to the posterior of the lentiform nuclei adjacent to the right lateral ventricle was observed in the diffusion MRI (**Figure 12**). He was consulted with anestesiologist and admitted ICU with the diagnosis of acute ischemic cerebrovascular disease.

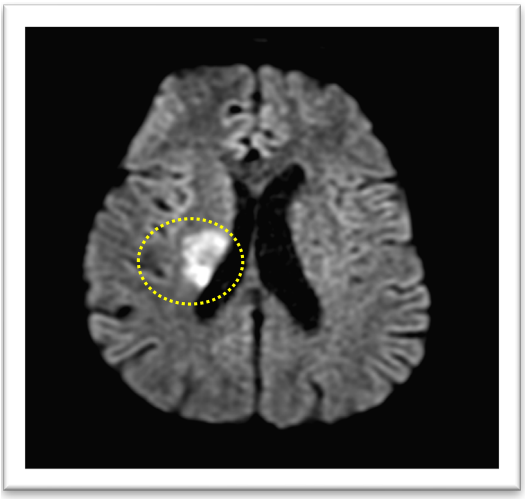

Figure 12. Brain diffusion MRI of Case 7 showing right lateral ventricle lentiform nuclei infarct (as high lighted by yellow dotted circle).

4.2.8. Case 8

A 42-year-old female patient was brought to the ED accompanied by an 112 ambulance with the complaint of motor weakness in the left arm. Emergency paramedics at the scene were told that she had used “bonsai” and a psychoactive substance. In his history it was learned that he did not have a chronic disease and he was not using any regular medication. He had been a synthetic cannabinoid user more than five years.She lost consciousness shortly after her admission to the hospital, and had symptoms of redness of the eyes and somnolence on physical examination. Her GCS score was 7 and vital signs were as follows: BP= 184/92 mmHg, HR= 106 bpm, and respiratory rate= 16/min. Intraparenchymal hemorrhage was not observed in brain CT, while an appearance consistent with an acute infarction in right internal capsule was observed in diffusion MRI (**Figure 13**). He was consulted with neurologist and admitted to the neurology clinic with the diagnosis of acute ischemic cerebrovascular disease.

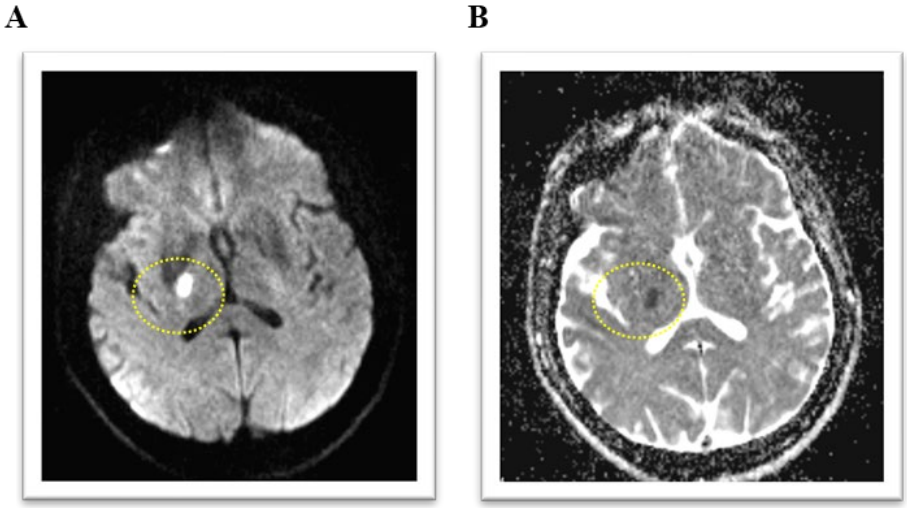

Figure 13. Brain diffusion MRI of Case 8 (A and B) showing right internal capsule infarct (as high lighted by yellow dotted circle).

4.2.9. Case 9

A 29-year-old male patient was brought to the ED in an unconscious state accompanied by an 112 ambulance. His friends told the emergency medical staff at the scene that he had been using SC regularly for 5 years and he had been using SC together with alcohol during the day. In his history that he did not have a chronic disease and he was not using any regular medication. Physical examination revealed symptoms of sweating, vomiting, myoclonus, urinary incontinence and unconsciousness. His GCS score was 5 and vital signs were as follows: BP= 177/99 mmHg, HR= 126 bpm, and respiratory rate= 18/min. No intraparenchymal hemorrhage was observed in the brain CT, while millimetric point diffusion restriction was observed in the left MCA area in the diffusion MRI examination, and an appearance compatible with the cortico subcortical branch was observed in the left MCA irrigation area in the perfusion MRI (**Figure 14**). He was consulted with neurologist and admitted to the neurology clinic with the diagnosis of acute ischemic cerebrovascular disease.

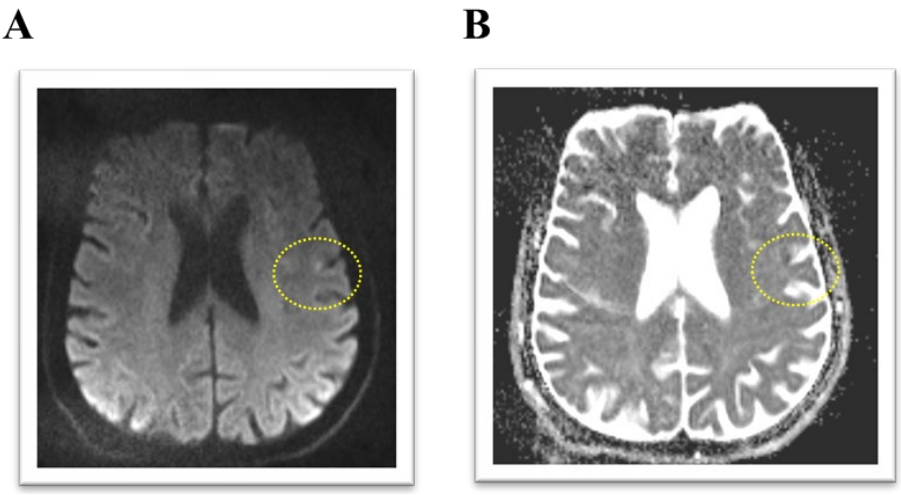

Figure 14. Brain diffusion MRI of Case 9 (A and B) showing left cortical lacunar infarct (as high lighted by yellow dotted circle).

5. DISCUSSION & CONCLUSION

SC use has increased in recent years as they are affordable and easily accessible. The SC users are usually admitted to the ED and the symptoms vary considerably depending on the chemical composition and concentration of the compound, as well as the other substances consumed together with SCs such as psychoactive compounds and alcohol. On the other hand, the lack of a standard detection method for SCs due to absence of practice in routine analyses, differences in the chemical composition and sytnhesis methods, as well as their diverse side effects make it hard to detect SCs in the samples. Moreover, the major target of diagnostic tests are mostly the primary compounds and the detection of the metabolites are difficult. Growing evidence suggests that natural or synthetic cannabinoid use may lead to ischemic cardiovascular or cerebrovascular events. In our study, we investigated the acute toxic effects in the patients using SCs who are admitted to ED by analyzing the clinical and demographical parameters and presented the cases diagnosed with CVE.

In recent years, the abuse of narcotic drugs such as SCs has been increasing. In particular, SC use is increasing among adolescents and young adults [224]. In a study conducted by Bozkurt et al. included 158 patients whose mean age was 26.1±7.1 years and 94.9% of the patients were male [225]. In the 2-year long retrospective study performed by Aksel et al. on 197 patients, 190 patients (96.4%) were male and 7 (3.6%) were female, and the mean age was 22 [226]. In a 6-month study by Kucuk et al., 111 of 112 patients were male, only one patient was female, and the mean age was 23.32 ± 6.14 years (min – max = 15 – 48). 64.28% of the patients were between the ages of 18-24 years [227]. In a study conducted by Dogan et al. between October 15, 2011 and March 20, 2013, all 30 patients were male and the mean age was 24.27 (min – max = 16 – 40) [228]. Similar to the study by Dogan et al, in the study conducted by Altinisik et al. between 2014 and 2015, all of the cases were male and between the ages of 16 – 41 years, with a mean age of 23.5 years [229]. In a study of 852 cases conducted by Hu et al. on college students in 2011, they found that the mean age of SC users was 20.6 years, and the majority of them were male [230]. Hoyte et al., on the other hand, determined that the mean age for SC use is 22.5 years and that 74.3% of the users are male [231]. In another study by Barratt et al., it was determined

that the average age for SC use in Australia was 27 and 77% of users were male [232]. Similarly, in the study conducted by Castellanos et al. in 2011, 91% of SC users were male and 9% female [209]. Moreover, in the study conducted by Dresen et al. in 2009, it was observed that the majority of SC users were more frequently used in male and young age groups [233]. In our study, when we examined the age of the whole patient population who admitted to the ED after taking synthetic cannabinoids, we observed that the ages ranged between 18 and 55 with the mean age of 29.30±9.34 years. Moreover, 94 of them were female (17.47%), 444 of them were male (82.53%). The fact that the patients who applied to ED using SCs in our study were mostly male and in young patient population was found to be compatible with the literature.

In a study, eleven different SCs were found in different combinations and rates varying in many brands and series [234]. Therefore, it can be said that it is very difficult to predict the clinical effects of SC-containing substances. Symptoms of SC toxicity may mimic the sympathomimetic effects such as sweating, agitation, and restlessness in addition to the euphoric and psychoactive effects of marijuana [235]. Recently, various reports regarding the effects such as rhabdomyolysis, renal failure, acute myocardial infarction, respiratory depression after SC use have been published [236]. Although similar to cannabis, SCs do not give positive results in toxicological examinations for THC [235,237]. In addition, SCs are not easy to detect today, since they are not registered in any mass spectrometer system and there are no reference standards [235,237]. In order to diagnose the toxicity due to SCs, the symptoms and signs should be well defined and this toxicity should be suspected [235,237]. A case in which SC toxicity is considered in the ED can be regarded as a disease that is not easy to manage for an ED. Among the reasons for this changes in consciousness, loss of place and time orientation, lack of communication, even when there is a relative, the lack of anamnesis and information, and the necessity of making the right decision in a short time in this very difficult patient group can be indicated. Mostly, patients present with neurological, psychiatric, cardiological and respiratory findings. SCs are not innocent chemicals. Serious clinical conditions such as seizures, cerebrovascular diseases (stroke), acute coronary syndrome, rhabdomyolysis, acute renal failure, respiratory depression were reported in our cases. A significant number of cases were referred to ICU for further examination and treatment. Cases of death after SC administration were also reported.

The symptoms of the patients who used SCs also differ considerably. The report, published annually by the EMCDDA, states that the serious adverse health effects of SCs including death [238]. A 2015 review in the same report indicated that the most common adverse health effects associated with SCs were tachycardia, extreme agitation, and hallucinations [238]. When we look at the publications presented as case reports, especially from our country, it has been claimed that Bonzai, a synthetic drug, can develop myocardial infarction (heart attack) [239]. As can be understood from some studies, it has been observed that it has a negative effect on the circulatory system [228]. Sensory impairments, learning difficulties, memory disorders, hallucinations and sleep disturbances are among other effects [228]. In the multicenter retrospective study of Kamijo et al. in Japan, 24.9% of patients presented vomitting, 23.6% of patients presented restlessness, 15.6% of patients presented nausea, 14.5% of patients presented palpitation, 10.4% of patients presented anxiety, 9.3% of patients presented confusion, 6.4% of patients presented feeling of abnormal behaviour, 5.8% of patients presented feeling of sickness, 2.7% of patients presented panic attack, 1.7% of patients presented psychosis and chest pain, 1.5% of patients presented fainting and 1.0% of patients presented tremor [240]. In the study conducted by Küçük et al., 25% of the patients developed sudden aggression and meaningless movements, 16.96% of the patients complained of chest tightness and shortness of breath, 16.07% of them complained of palpitation, 13.39% of them complained of fainting, and confusion, 14.28% of them complained of nausea and vomiting, 10.7% of them complained of drowsiness and dizziness, and 3.57% them complained of various hallucinations [227]. It was observed that cardiac side effects such as chest tightness, shortness of breath and palpitation were significantly higher with a rate 33.03% in the patients [227]. In the study conducted by Hoyte et al. on 1353 patients exposed to a single SC compound, the most common symptoms were tachycardia (40%), agitation (23.4%), vomiting (15.3%), drowsiness/lethargy (13.5%), confusion (12%), nausea (10%), hallucination (9.4%), hypertension (8.1%), dizziness (7.3%), chest pain (4.7%), syncope (2.1%), hypotension (1.3%) and bradycardia (1.3%) [231]. Barratt et al. reported that 68% of people using SCs experienced at least one side effect [232]. The most frequently reported adverse effects were decreased motor coordination (39%), dissociation (22%), dizziness (20%), paranoia (18%), and psychosis (4%) [232]. On examination, on the other hand, sweating, nausea, vomiting, tremor, mydriasis, tachycardia and hypertension are

among the most observed side effects [233]. In another study conducted by Forrester et al., cardiac symptoms such as palpitation and chest pain were found most frequently (48.5%), followed by drowsiness and dizziness (24.3%) [241]. In the study of Altinisik et al., they observed confusion, sleepiness, restlessness-agitation, hallucinations, anxiety-panic, acute psychosis, amnesia, tachycardia, bradycardia, hypertension, hypotension and arrhythmia [229]. In our study, in line with other similar studies, tachycardia was observed in 149 (28.76%) patients and hallucinations in 111 (20.63%) patients were observed most frequently in group 1 patients who admitted to ED after using SCs. In addition to other studies, tachycardia was the most common in 53 (46.4%) patients, agitation in 25 (21.92%) patients, after exposure to the active substance in group 2 patients who applied to the ED using SC after making a separate evaluation in the group thought to have brain damage. Seizures were observed in 35 (30.70%) patients, somnolance in 9 (34.21%) patients, and confusion in 31 (27.19%) patients.

There are numerous of reports indicated cardiovascular side effects including tachycardia, hypertension, palpitation, chest pain and arrythmias [231,235,242-244], neurological side effects [185,235,241,242,245,246], gastrointestinal side effects [242,244], as well as other side effects including mydriasis, photsensitivity and pulmonary side effects [74,196,241,245]. In our study, cardiological symptoms and findings such as tachycardia, hypertension, chest pain and bradycardia were commonly encountererd. It was seen with a high rate in our patients, especially in group 2 with a frequency of 46.49%, compared with other patient groups. All these results show that the examination findings in our study are compatible with the literature, and that we may encounter psychological, neurological, cardiac, metabolic, gastrointestinal, muscular and ocular examination findings in patients who use bonsai on admission to ED.

When the vital signs of all patients in the ED were evaluated after taking SCs, the mean SBP was 122 mmHg, the mean DBP was 82 mmHg, the HR was 85 per minutes, the respiratory rate was 16 per minutes, the body temperature was 37°C and O_2 saturation was 96%. In the group of patients among SC users underwent brain imaging with the suspicion of brain damage (group 2), mean DBP was 87 mmHg, HR was 90 minutes, and O_2 saturation was 92%. The number of severe patients according to GCS score in group 2 was higher than group 1. For these reasons, GCS also created differences in vital

parameters. In the study conducted by Aksel et al., the mean systolic blood pressure of the non-intubated patients was 120 mmHg, the mean DBP was 70 mmHg, the saturation was 98%, the HR was 89, and the GCS score was 15, while in intubated patients, mean SBP was 110 mmHg, mean DBP was 68 mmHg, saturation was 41%, HR was 71, and GCS score was 3 [226]. In our study and literature review, it has been shown that respiratory acidosis due to hypoventilation in patients using SC may occur and result in respiratory depression. In our study, although the HCO_3^- and BE values were within normal limits in both groups, the HCO_3 and BE values were found to be significantly lower than the non-risk group (group 1). In the literature, there are studies with HCO_3^- and BE in the blood gas measurements and it has been suggested that one of the metabolic effects of SCs is acidosis [247]. This suggests that blood gas measurements may be useful to distinguish the patients at high risk of brain damage compared to patients at not risk. Moreover, patients who admited to the ED after SC use HR values measured in the first evaluation in ED, respiratory rate, oxygen saturation, GCS score, PSS calculation, Na^+ levels, pH value, PCO_2 values, HCO_3^- levels should be considered when determining the referral to the ICU.

Previous studies investigated the effect of long-term cannabis use on cognitive performance. In 90s, case-controlled studies reported that regular cannabis use leads to poorer cognitive performance [248]. The challenge in this issue was to determine whether the cannabis use leads to poor cognitive performance, subjects with porrer cognitive function are the regular cannabis users or both [248]. Since then, accumulating reports consistently indicated deficit in memory, verbal learning and attention in subjects who are regular cannabis users [249-252]. Other studies reported that these deficits are usually in correlation with the duration and frequency of cannabis use, as well as the age of cannabis use onset and estimated cumulative dose of THC [252-254]. In the following discussion, we summarized the results of these studies in relation to the findings of this thesis.

Possible recovery of altered cognitive function after cessation of cannabis is debatable due to conflicting results in the literature [249,254]. Using Dunedin's birth cohort covering 1037 New Zealanders born in 1972 or 1973, a longitudinal study investigated the changes in IQ over 25 years. Meier et al. (2012) compared the IQ level before the start of cannabis use (age 13) and the IQ level after decades long sustained cannabis exposure

(age 38) and showed substantial decline in cognitive performance. The decline was not reversible over time either [255]. Early and persistent cannabis users also manifested an average decline of eight IQ points compared to the control subjects who had not used cannabis, and cannabis-using subjects who had not used cannabis continuously. Rogeberg (2013) related the finding of lower IQ in sustained cannabis to socioeconomic status variables that are not accounted for [256]. This suggestion of socioeconomic status effects, however, were not supported by following analyses of the Dunedin data [257]. On average an 8 point decline is observed in the IQ of participants who started cannabis use at an early age and whose cannabis use was persistent over time. Meier et al.'s findings are consistent with a later study conducted by Auer et al. (2005)[255], where the researchers find an association between sustained daily use of cannabis throughout adult life and poorer verbal memory [258]. The studies on brain structure and function in cannabis users supported these epidemiological findings. MRI studies indicated structural alterations in different brain regions including hippocampus, prefrontal cortex and cerebellum in chronic cannabis users, especially at a higher rate in persons have been using cannabis the longest [259]. Moreover, a systematic review reported a consistent decrease in hippocampal volume in long-term consistent cannabis smokers [260].

We think that the poorer cognitive performance shown in these studies may be due to brain damage (micro). Therefore, in our study, we presented 9 patients diagnosed with cerebrovascular disease (brain damage) after admitting to the ED with various symptoms, in SC users for at least one year or more. It will be useful to prospectively examine the alterations in hippocampus, prefrontal cortex and cerebellum morphology in chronic and/or acute cannabis smokers. Excluding the possibility of reverse causation as an explanation for these findings has been difficult as younger individuals with poorer cognitive performance are more likely to use cannabis more regularly. Also, shared risk factors for regular cannabis use and poor cognitive performance have been implicated.

Case reports of stroke in cannabis indicated an increasing number of strokes in recent years [261]. As an example, Wolff reported only 59 cases of cannabis-associated strokes in the literature up to 2013, namely ischemic strokes or transient ischemic attracks [261]. By 2015, this rate has increased up to 100 cases of cannabis-related ischemic stroke [262-264]. There have also been studies identifying smoking cannabis as a stroke risk factor

in young adults [265], moreover, several cases documented ischemic stroke in SCs users [266-268]. The case of 21-year-old male who had a cerebellar ischemic stroke following smoking cannabis illustrates such an example. Wolff et al. attributed his stroke to multifocal intracranial arterial stenosis [214]. A potentially important factor in cannabis-associated strokes is tobacco smoking concomitantly [261].

Orthostatic hypotension, altered cerebral vasomotor function, supine hypertension, blood pressure swings, cardio-embolism, vasculopathy, vasospasm, and reversible vasoconstriction cerebral syndrome are considered possible mechanisms for cannabis-related strokes among cannabis users [261]. Moreover, a study conducted young adults (<45 years) who had an ischaemic stroke within a two-year period reported that in 13 of 48 were cannabis users and in 10 of the 13 patients, stroke was caused arose from multifocal intracranial arterial stenosis [214]. In another study, the cerebral vasoconstriction was reversed in all patients after stopping cannabis use [264]. Thus, it is suggested that cannabis use may cause ischemic stroke in young adults by promoting reversible cerebral vasoconstriction. These findings were justified with a five-year follow-up of cases of reversible cerebral vasoconstriction syndrome (RCVS) in 159 young ischemic stroke patients. RCVS is found to be the cause of 13% stroke cases, most often in young adult males with a mean age of 32 [264]. In 67% of these cases the precipitant was smoking cannabis resin [264]. The cerebral vasoconstriction is reversed within 3−6 months in case of quitting smoking cannabis [264]. The cerebral vasoconstriction induced by cannabis is likely the mechanism for these strokes [264]. In our study, when other differential diagnoses that may cause brain damage in patients diagnosed with stroke are excluded, the use of SC should be considered as a risk factor for stroke (especially in young patients), and the brain damage it causes should be explained by the mechanisms that may develop due to SC use. However, these mechanisms should be better elucidated by experimental and molecular studies.

Various studies reported cases who developed rhabdomyolysis and/or acute renal failure (ARF) associated with SC use [202,203,269]. Bhanushali et al. reported that all patients recovered with hydration and there was no need for renal replacement therapy in a case series involving four cases of ARF due to SC use [269]. In this study, ARF developed in 17 patients and hemodialysis was performed on four patients. Other ARF patients

improved with hydration and renal replacement therapy. While cases of renal failure due to SC use have been reported in the literature [2,199,269], creatinine levels, which is a marker for renal injury, did not increase statistically in our study.

Concomitant use of other psychoactive substances or alcohol is another issue in the SC users. In a study conducted by Bozkurt et al., 47.5% of SCs users used SCs together with cannabis, 29.1% with ecstasy, 7.6% with alcohol, 6.4% with heroin and 6.6% with cocaine [225]. In the same study, it was reported that 86% of the cases used cannabis before using SC [225]. It was reported that the first substance used by 12.1% was SC, while 5.1% had used another substance initially [225]. Winstock et al. found that 99.3% of SC users used cannabis at least once in their lives, and the rate of those who used cannabis in the last month was 88.4% [31]. Vandrey et al. also found the rate of cannabis use together with SC to be 40% [75]. Studies have shown that together with SC, besides cannabis, substances such as alcohol, cigarettes, energy drinks and 3,4-methylenedioxy-N methylamphetamine are frequently used [31] This shows us that SCs can cause toxicity when taken alone or together with alcohol and other psychoactive substances. Studies have shown that patients using SCs tend to use alcohol and other recreational drugs as well. The presence of additional substance use with SCs should be considered in ED, especially in cases of intoxication, during the emergency response and when making a treatment plan for psychoactive substance use. When the SCs that the patients used were evaluated according to their use with either alcohol or other psychoactive substances, it was observed that in most of the patients in all patients using SC (group 1) only SC was used. In patients among SC users undergoing brain imaging with the suspicion of brain damage (group 2), SC and alcohol were used together in most of the patients.

The PSS with a four-scale severity classification scale was used to classify the severity of poisoning in the Clinical Toxicology and Emergency Department [270]. Hermanns-Clausen et al., in their studies, found most SC users with moderate PSS score [244]. Similarly, in our study, 50.74% of all patients were found to be with moderate PSS score and 9.67% severe PSS score. For patients among SC users undergoing brain imaging with the suspicion of brain damage (group 2), 29.82% of them were found to have moderate PSS score and 43.86% were found to have severe PSS score.

While there is no similar study in the literature examining the correlation between hospitalization, GCS, and PSS scores, as in our study, when all patients using SC (group 1) who were admitted to the ED were evaluated, a significant and moderately positive and negative relationship was found between PSS and GCS, respectively. In addition, there was a significant and moderately positive relationship between hospitalization and PSS, and a significant and strong negative relationship between hospitalization and GCS. When group 2 (patients among SC users undergoing brain imaging with the suspicion of brain damage) was evaluated, there was a significant and strong negative relationship between PSS and GCS, and a significant and highly positive relationship between hospitalization and PSS. Moreover, there was a significant and strong negative relationship between hospitalization and GCS.

Commonly used synthetic cannabinoid derivatives such as JWH-018, JWH-073, AM-2201 can be detected with tests that can be used as a screening test [271]. However, screening tests are not yet widely used in our country and the data in our study were based on urine toxicology tests and patients' statements. A total of 993 patients were detected to use SCs from the HIMS. In our study, urine toxicology test, which can detect SC, was not found positive in all patients, which were examined in the laboratory of our hospital. These patients were excluded from the study due to exclusion criteria (being younger than 18 years old, readmission to the hospital within 24 hours, negative results of the toxicology panel, and missing data of patients). The inclusion criteria were being 18 years or older, using SCs for one year or longer, and admission to the ED with various complaints due to SC use within the last 8 hours. Since it is known that synthetic cannabinoid derivatives can have very different effects from each other, one of the most important limitations of our study is that it is not known which derivative the patients used and the duration and frequency of use were recorded according to the statements of the patients. However, the heterogeneity of past substance use in the patient group may also have affected the results. In our study, the presence of control group patients who were admitted to the ED with minor head trauma or headache and underwent brain imaging (group 3), is the part that makes a difference compared to other studies.

Diffusion MRI and brain CT are used in many studies to define the structural features of the brain and to determine the effects of diseases and various conditions

including substance use and psycho-neurological diseases. The changes in the brain caused by alcohol, natural cannabinoids and many other substances have been shown in different studies. However, to the best of our knowledge, there is no such study yet for synthetic cannabinoids. Thus our study, in chronic synthetic cannabinoid users; is aimed to observe neurological changes, especially brain damage, due to acute synthetic cannabinoid intake. Various studies investigated the neurological effects of cannabinoids and their derivatives. In one of these studies, to evaluate the association between cannabis use and ischemic stroke in the young adult population, 48 young patients who presented with acute ischemic stroke participated were included [214]. In our study, group 2 is also important in this respect. Moreover in our study; vital signs and cardiovascular and neurological examination findings were obtained from the files of cases and GCS scores were determined. Routine laboratory and imaging test results of the patients were examined for each patient included in the study. Hemogram and blood biochemistry, and complete urinalysis tests of the patients were evaluated . CT and MRI results of the patients were examined [214]. In this series, 21% (n = 10) had multifocal intracranial stenosis associated with cannabis use [214]. In our study, there are 9 patients with brain damage (ischemic-hemorrhagic cerebrovascular event). In another study of case series related to SC intoxication, it was observed that one patient was admitted to the ED with seizures and one patient with hemiparesis, but after the necessary follow-up period, the effect of the substance wore off and they were discharged [2]. Although our cases with CVE have symptoms of seizures and hemiparesis, these effects can be seen without any neurological sequelae as seen in this study. Indeed, these symptoms of seizure, lethargy and hemiparesis were frequently observed in all of our SC cases. In conclusion, multifocal angiopathy and other causes; associated with SC consumption may be an important cause of ischemic stroke in young people.

As a result of the case study consisting of several independent cases in which patients were admitted with different neurological symptoms, it was emphasized that there was a significant increase in morbidity and psychotic symptoms after SC use [272]. In the same study, it was observed that one case “barked like a dog” periodically, while the other “walked naked and strayed” [272]. In our study, psychosis was observed in three cases, when all SC users were evaluated, and case 1 had echolalia.

While evaluating the results of our study, it is necessary to consider its limitations. Due to the large number of derivatives of SCs, the amount that can be detected in body fluids is limited. It is known that the emergence of new varieties every day is one of the factors that complicates the analysis. SCs can be detected in serum and urine by liquid chromatography-tandem mass spectrometry (LC-MS / MS) and gas chromatography-mass spectrometry (GC / MS), but these methods have not yet become widespread enough to enter routine practice.

The findings and conclusions of our study can be summarized as follows:

1. The use of synthetic cannabinoids is an important public health problem, especially affecting the young adult population. SC use is more common in men. The most common symptom in patients admitted to the ED due to SC use is altered consciousness.
2. More scientific research and controlled studies are needed to elucidate the toxicological and pharmacological effects of synthetic cannabinoids. In this study, SCs and their toxic effects were evaluated in the light of current literature. We show the possible brain damage that SCs can cause with the simultaneous routine blood and urine analyzes and radiological imaging (Brain CT and MRI) of the patients included in our study.
3. When we evaluated 538 patients who were admitted to the ED due to SC use, among the inpatients, two were hospitalized due to pulmonary thromboembolism, seventeen were hospitalized due to acute renal failure, nine were hospitalized due to brain damage (ischemic-hemorrhagic cerebrovascular event) and eleven were hospitalized acute coronary syndrome. Five patients died. When considering all these results, it was concluded that SC use for ED physicians is an important marker that should be questioned in the anamnesis.
4. It was observed that our patients did not have significant risk factors for CVE such as known diabetes, hypertension, hyperlipidemia, and family history. Chronic SC use should be considered a risk factor for the etiology of stroke, based on the fact that the patients did not have a history of drug use and 9 cases of brain damage (ischemic-hemorrhagic cerebrovascular event). Future research should attempt to determine whether there is an independent association between synthetic

cannabinoid use and stroke. Given the ethical constraints of examining an illegal substance in countries, this can be difficult. However, the follow-up of patients admitted to the ED with the diagnosis of ischemic stroke makes this study necessary. This study provides evidence of an association between a lifestyle including SC use and ischemic stroke. However, finding a relationship is not the same as proving causation. Since SC and cannabinoids have cardiovascular effects, a causal relationship with cerebral ischemia is plausible.

5. Patients presenting to the ED due to SC use is one of the situations that are difficult to manage and require quick and correct decisions for emergency physicians. Factors such as patients coming with changes in consciousness due to SC use, mostly not having a relative and thus taking insufficient anamnesis, concealing SC use, and lack of diagnostic kits that recognize all SCs create problems for physicians in making the right decision for treatment. First of all, the correct diagnosis should be made in patients who apply to the emergency department after SC intake. For this, new and safe diagnostic kits are needed. New algorithms should be developed to determine the prognosis of SC toxicity (for detection of brain damage and especially the prevention of neurological damage). Future studies and further field studies are needed on these issues
6. The most common symptoms of SC intoxication are tachycardia and agitation. There is a significant relationship between low GCS scores and high PSS scores in SC intoxication cases. In the light of these data; considering Group 2, which has low GCS scores and high PSS scores, the most common symptoms are tachycardia, agitation, somnolence, confusion, hallucination, paresthesia, red eyes, dyspnea, and seizure. Although some mechanisms have been proposed to explain the cause of symptoms such as dyspnea and seizures in SC intoxications, this relationship cannot be defined clearly. New and prospective studies are needed to scientifically explain the causes of symptoms common in SC intoxications (especially in life-threatening cases).
7. Cardiovascular and neurological side effects are common in SC intoxication. At the time of admission, tachycardia and impaired consciousness are found most frequently. Since the use of SCs is increasing day by day, it can be understood that it will be one of the most problematic substances and will continue to be a

problem. Therefore, the need for equipment and experience required for the identification and reporting of the chemicals in these substances will increase day by day. Considering the results obtained from this study, more comprehensive, nationwide, prospective studies should be conducted. Results from future studies (contributing to the literature) will help to identify new SCs and to better understand the toxic effects of SCs. In conclusion, there is a need for new studies across the country in the fight against SC.

SC use history is; serious public health and social issue worldwide, as it is quite difficult to determine which SC is being consumed that is a necessary step to link the adverse health effects to the toxicity of the new drug. There are several case series that not only describe the association of neurological problems with SC toxicity, but also confirm the presence of specific SCs in some cases. With our study, we hope to contribute to these case series with a systematic and large number of cases Our study aimed not only to describe the clinical features, vital parameters, ECG findings, laboratory results, GCS and PSS of all patients who applied to the emergency department with the use of SC, but also to determine the relationship between neurological problems and SC toxicity in our case series. As observed in our case series, the patient group may present a variety of neurological manifestations that may prompt physicians for extensive investigations and unnecessary procedures. Routine tests, both blood parameters and radiological brain imaging, to confirm or refuse the diagnosis are costly and time consuming. Reducing unnecessary costs is important. In our study, we examined the emergency applications of SC users for various reasons after acute SC intake and tried to analyze the clinical, radiological and blood parameters that will guide the differential diagnosis. It is important for clinicians to follow current SC trends closely and collaborate with toxicologists when necessary. To address the uptake of SCs and their resulting toxicities, pharmacists, law enforcement, toxicologists, emergency physicians and mental health practitioners should work together. In-hospital assessment of SC toxicity and faster results will help reduce unnecessary testing and procedures.

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7. APPENDICES

7.1. Ethical Approval

T.C. YEDİTEPE ÜNİVERSİTESİ

Sayı : 37068608-6100-15- 2175
Konu: Klinik Araştırmalar
Etik Kurul Başvurusu hk.

01/07/2021

İlgili Makama (Eda Yiğit)

Yeditepe Üniversitesi Eczacılık Fakültesi Farmasötik Toksikoloji AD. Doç. Dr. Muhammed Hamitoğlu'nun proje koordinatörü olduğu, Marmara Pendik Eğitim ve Araştırma Hastanesi Adli Tıp AD. Dr. Eda Yiğit'in sorumlu araştırmacı olduğu **"Sentetik Kanabinoid Kullananlarda Beyin Hasarının Retrospektif Olarak Değerlendirilmesi"** isimli araştırma projesine ait Klinik Araştırmalar Etik Kurulu (KAEK) Başvuru Dosyası **(2218)** kayıtlı Numaralı KAEK Başvuru Dosyası, Yeditepe Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından **30.06.2021** tarihli toplantıda incelenmiştir.

Kurul tarafından yapılan inceleme sonucu, yukarıdaki isim belirtilen çalışmanın yapılmasının etik ve bilimsel açıdan uygun olduğuna karar verilmiştir. **(KAEK Karar No: 1460)**

Prof. Dr. Turgay ÇELİK

Yeditepe Üniversitesi
Klinik Araştırmalar Etik Kurul Başkanı

7.2. Curriculum Vitae

Kişisel Bilgiler

Adı	Eda	**Soyadı**	Yiğit

Öğrenim Durumu

Derece	Alan	Mezun Olduğu Kurumun Adı	Mezuniyet Yılı
Doktora	Pharmaceutical Toxicology	Yeditepe Univercity	2015-
Tıpta Uzmanlık	Forensic Science	Marmara Univercity Medical Faculty	2019-
Tıpta Uzmanlık	Emergency Medicine	Bezmialem Vakıf Univercity Medical Faculty of Hospital	2010-2015
Lisans	Sociology	Anadolu Univercity	2015-2020
Lisans	Faculty of Medicine	İstanbul Univercity Cerrahpaşa Medical Faculty	2002-2008
Lise	BSc degree (scientific phase)	Kocaeli Körfez Science High School	2000

Bildiği Yabancı Dilleri	Yabancı Dil Sınav Notu (#)
English	78-YDS

İş Deneyimi (Sondan geçmişe doğru sıralayın)

Görevi	Kurum	Süre (Yıl - Yıl)
Medical Doctor	Kocaeli Körfez İl Sağlık Müdürlüğü Toplum Sağlığı Merkezi	2008-2009
Research Assistant Doctor	Bezmialem Vakıf Univercity Medical Faculty of Hospital-Emergency Medicine Department	2010-2015
Specialist Doctor	Univercity of Health Science Şişli Hamidiye Etfal Training and Research Hospital-Emergency Medicine Department	2015-2019
Research Assistant Doctor	Marmara Univercity Pendik Training and Research Hospital-Forensic Science	2019-2022

Bilgisayar Bilgisi

Program	Kullanma becerisi
Microsoft programs	İyi

Bilimsel Çalışmaları

SCI, SSCI, AHCI indekslerine giren dergilerde yayınlanan makaleler

1. Yiğit, Mehmet, Özgür Söğüt, Özlem Tataroğlu, Adnan Yamanoğlu, Eda Yiğit, Eray Metin Güler, Ömer Faruk Özer, And Abdürrahim Koçyiğit. 2018. "Oxidative Antioxidative Status Lymphocyte DNA Damage and Urotensin-2 Receptor Level in Patients with Migraine Attacks." Neuropsychiatric Disease and Treatment 14 (January). Neuropsychiatric Disease and Treatment: 364–74.
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4. Yiğit, Mehmet, Özgür Söğüt, Eda Yiğit, Kenan Ahmet Türkdoğan, Onur Kaplan, Ali Dur, Ertan Sönmez, and Bulut Demirel. 2016. "The Relationship between Anemia and Recurrence of Ischemic Stroke in Patients with Trousseau S Syndrome A Retrospective Cross-Sectional Study." *Turkish Journal of Emergency Medicine* 16 (January). Turkish Journal of Emergency Medicine: 65–68.
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8. Yiğit, Eda, Özgür Söğüt, And Mehmet Yiğit. 2015. "Luxatio Erecta Humeri Hands-Up Dislocation." *The Journal Of Emergency Medicine* 49 (2). The Journal Of Emergency Medicine.
9. Karabacak, Mustafa, Mehmet Yiğit, Kenan Ahmet Türkdoğan, Eda Yiğit, And Şehabettin Selek. 2014. "Is Signal Peptide Cub Egf Domain Containing Protein1 A Diagnostic Biomarker In Patients With Hypertensive Crises." *Clinical Hemorheology And Microcirculation*, January. Clinical Hemorheology And Microcirculation
10. Yiğit, Mehmet, Kenan Ahmet Türkdoğan, Emin Uysal, Özgür Söğüt, Şevki Hakan Eren, Eda Yiğit, And Veysel Kenan Çelik. 2015. "Impact of C EBP Homologous

Protein in the Diagnosis of Acute Pancreatitis." *Biomedical Research-INDIA* 26 (1). Biomedical Research-INDIA: 131–34.

11. Olgularla Adli Psikiyatri ve Davranış BilimleriBölüm Adı:Çekişmeli Boşanma ve Velayet Davalarında Ortaya Atılan İstismar İddialarının Değerlendirilmesi: Olgu Sunumu, Usluoğullari Fatih Hitami, Yiğit Eda, İnanici Mehmet Akif, Yayın Yeri:Akademisyen Kitapevi, Editör: Oral Gökhan, Basım sayısı:1, Sayfa sayısı:7, ISBN:978-625-7451-68-0, Bölüm Sayfaları:197 -203

Diğer dergilerde yayınlanan makaleler

Uluslararası bilimsel toplantılarda sunulan ve bildiri kitabında (*Proceedings*) basılan bildiriler

1. M. Yiğit, Ö. Söğüt, K. A. Türkdoğan, And E. Yiğit, "A Vasculitis Case In Ed Drug Induced Leucocytoclastic Vasculitis," Presented At The 1st Intercontinental Emergency Medicine Congress , 2014
2. M. Yiğit, K. A. Türkdoğan, Ö. Söğüt, E. Yiğit, And A. Yaman, "Co Occurrence Of Acute Coronary Syndrome And Stroke Trousseau S Syndrome ," Presented At The 1st Intercontinental Emergency Medicine Congress , 2014
3. E. Sönmez, K. A. Türkdoğan, M. Karabacak, M. Yiğit, E. Yiğit, And Ö. Söğüt, "Scube1 Has Diagnostic Value In Patients
4. With Hypertensive Crises," Presented At The 8th European Congress On Emergency Medicine , 2014.
5. Ö. Söğüt *Et Al.*, "The Predictive Value Of Signal Peptide Cub Egf Domain Containing Protein1 Scube1 In Terms Of The Duration Of Peripheral Ischemia And Exposure To Reperfusion," Presented At The 3 Rd International Critical Care And Emergency Medicine Congres , 2016.
6. E.Yiğit, M.Mollaoğlu, M.Hamitoğlu, 'Cardiac Arreset Presented With Brugada Syndrome Due To Bonzai Abuse; A Case' Report Presented 10th International Congress Of The Turkish Society Of Toxicology Antalya, Turkey 16 - 19th October, 2019

Hakemli konferans/sempozyumların bildiri kitaplarında yer alan yayınlar

Diğer (Görev Aldığı Projeler/Sertifikaları/Ödülleri)

Degree of Doctor of Medicine
Certificate in Laboratory Animal Science