Review
Eurasian Journal of Toxicology

The Synthetic Cannabinoids

Cengizhan KESKI[1]

[1]University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Emergency Medicine, Bursa, Türkiye

Abstract

Synthetic cannabinoids are defined as psychoactive substances that trigger the endocannabinoid system. Despite attempts to utilize some of their effects for therapeutic purposes, they are predominantly used as recreational drugs. In the past decade, their recreational use has increased more than other psychoactive substances in Europe and the United States. In Turkey, they are referred to as "Bonzai" or "Jamaika." Additionally, factors such as stronger effects compared to cannabis, cost-effectiveness, easy accessibility, and evasion of standard drug tests contribute to the growing use of synthetic cannabinoids. This paper aims to examine the structure and toxicology of synthetic cannabinoids, along with diagnosis and treatment, in line with current literature.

Keywords: poisoning; emergency medicine; synthetic cannabinoids; Δ9-THC; tetrahydrocannabinol

Introduction

Natural cannabis (Δ9-THC, tetrahydrocannabinol) is derived from the Cannabis Sativa plant[1]. Δ9-tetrahydrocannabinol (Δ9-THC), the main psychoactive component of marijuana, binds to endocannabinoid system receptors. Synthetic cannabinoids (SCs) stimulate the endocannabinoid system more intensely and briefly than natural cannabinoids[2].

Δ9-THC was first synthesized by Gaoni and Mechoulam in 1964 (3). Since 2008, 209 species of SCs have been identified in European Union (EU) countries. In 2019, they accounted for 60% of the psychoactive substance market. SC consumption is common among individuals aged 15-34 in the EU[2].

Due to structural differences among SCs and their short plasma half-lives, their detection is challenging. Continuous emergence of new SCs often leads to underestimation of their prevalence, posing a problem for countries[4].

SCs dissolve in organic solvents. It can be mixed with herbs such as mint and thyme. It is sold on the internet or other means under various packaging and names[2]. SCs are usually inhaled. It can also be consumed orally as a tablet powder herbal mixture[5,6].

Physicochemical Properties

In their pure form, synthetic cannabinoids (SCs) are odorless and appear as white or yellowish crystalline powders. They are soluble in organic solvents and alcohols (such as ethanol, methanol, acetone, isooctane, ethyl acetate, acetonitrile) but have low solubility in water[7].

Structurally, they are generally divided into four components: nucleus, tail, binder, and attached groups. Various analytical methods can be employed to detect and quantify SCs. The gold standard method combines gas chromatography-mass spectrometry (GC-MS). Techniques such as nuclear magnetic resonance (NMR) or infrared spectroscopy, gas chromatography combined with flame ionization detection, and liquid chromatography-mass spectrometry (LC-MS) can also be utilized[7,8].

The chemical classification of SCs can be as follows[9];

1. Classic cannabinoids: Tetrahydrocannabinol, other chemical components of marijuana, and their structurally similar synthetic analogs (e.g., AM-411, AM-906, HU-210, O-1184).

Corresponding Author: Cengizhan KESKI **e-mail:** cengizhankeski@gmail.com
Received: 03.04.2024 • **Accepted:** 28.04.2024
Cite this article as: Cengizhan KESKI. The Synthetic Cannabinoids. Eurasian J Tox. 2024;6(1): 6-11

2. Non-classic cannabinoids: Cyclohexylphenols or 3-aryl-cyclohexanols (e.g., CP55,244, CP-55,940, CP-47,497).
3. Hybrid cannabinoids: Combinations of structural features of classic and non-classic cannabinoids (e.g., AM-4030).
4. Aminoalkylindoles, further categorized into: (a) Naphthoylindoles (e.g., JWH-015, JWH-018, JWH073, JWH-081, JWH-122, JWH-200, JWH-210, JWH398) (b) Phenylacetylindoles (e.g., JWH-250, JWH-251) (c) Benzoylindoles (e.g., pravadoline, AM-694, RSC-4) (d) Naphthylmethylindoles (e.g., JWH-184) (e) Cyclopropylindoles (e.g., UR-144, XLR-11) (f) Adamantylindoles (e.g., AB-001, AM-1248) (g) Indole carboxamides (e.g., APICA, STS-135) (h) Indole carboxylates.
5. Eicosanoids: Endocannabinoids like anandamide and their synthetic analogs (e.g., Metanandamide).
6. Others: Encompasses other structural types such as diarylpyrazoles (e.g., RimonabantR), naphthoylpyrroles (e.g., JWH-307), naphthylmethylindenes (e.g., JWH176), and indazole carboxamides (e.g., APINACA).

Pharmacodynamic Effects

The main receptors of the endocannabinoid system are G protein-coupled receptors. The pharmacology of synthetic cannabinoids (SC) is similar to Δ9-THC, and they similarly affect cannabinoid receptors 1 and 2 (CB1R and CB2R). While Δ9-THC exhibits partial agonist effects on receptors, SCs exert full agonist effects. For this reason, SCs lead to higher psychoactive effects and more undesirable effects[10].

Activation of CB1R inhibits adenylate cyclase activity, leading to a decrease in cyclic adenosine monophosphate (cAMP)10. Additionally, CB1R activation induces the activation of the mitogen-activated protein kinase (MAPK) family, including signal-regulated extracellular kinases 1 and 2 (ERK1/2), by the βγ subunits. Phosphorylation of CB1R by G protein receptor kinases (GRKs) following activation may induce the translocation of β-arrestin 1 and 2 to the cell membrane, leading to desensitization and internalization of CB1R, which has been reported to be associated with the development of tolerance[11].

SCs can also modulate signaling pathways independently of CBRs. For example, it has been reported that aminoalkylindole derivatives, arylpyrazole derivatives, and synthetic analogs of phytocannabinoids target transient receptor potential cation channel subfamily V member 1 (TRPV1). It has been found that the desensitization of these channels by WIN55,212-2 promotes analgesic effects[12].

SCs primarily target the brain and modulate neurotransmitter signaling along with other processes.

Ossato and colleagues have shown that SCs facilitate dopamine release in the striatum and nucleus accumbens, resulting in a psychostimulant effect in mice dependent on CB1R activation. Since the ventral tegmental area and nucleus accumbens, along with the medial forebrain bundle connecting both regions, are key structures of the brain's reward circuitry, dopamine neural firing induced by SCs in these regions enhances reward response, thus explaining the addictive potential of these substances[13].

It has also been reported that SCs are more effective than Δ9-THC in inhibiting glutamatergic synaptic transmission14.

It has been shown that SCs suppress glutamate and γ-aminobutyric acid (GABA) release in mice by activating presynaptic CB1Rs in Purkinje cells[15].

Yano and colleagues have shown that SCs may target serotonin receptors independently of CBR activation[16].

Clinical and Therapeutic Aspects

SCs are primarily consumed via inhalation, resulting in rapid absorption by the alveoli. They quickly reach peak concentrations in the blood, and their effects are immediately noticeable. Their half-lives are short[10]. The high lipophilicity of most SCs allows them to bind extensively to plasma proteins, which can lead to increased distribution volumes[17].

SCs are also metabolized to more hydrophilic compounds via conjugation with sulfate and/or glucuronic acid to facilitate renal excretion. The presence of SC metabolites in urine makes it a preferred sample for SC detection. However, before analysis, urine must undergo β-glucuronidase treatment to separate conjugate metabolites10.

SC users often seek some of the known psychotropic effects of the drug, such as increased relaxation, heightened well-being, and social disinhibition, which typically occur immediately after consumption.

Considering the widespread distribution of cannabinoid receptors in the body, SCs can target different organs. They can trigger adverse effects in cardiovascular, digestive, dermatological, ophthalmological, neurological, pulmonary, and hepatic systems. Acute poisonings have been particularly associated with neurological perturbations, including short-term memory loss, flashbacks, and suicidal ideation, among other cognitive impairments[5].

Neurological symptoms include delirium, confusion, hallucinations, agitation, panic attacks, and convulsions. Chronic SC consumption is also associated with an increased risk of developing neuropsychiatric disorders.

Psychotic symptoms are common following SC use. While these are typically transient (lasting only a few hours), they can lead to prolonged psychotic episodes in individuals with no history of psychosis.

New third-generation fluorinated SCs have been shown to induce reduced motor activity and impaired sensorimotor responses, hypothermia, and increased pain threshold against harmful mechanical and thermal stimuli in mice[18].

SCs also target the human cardiovascular system, leading to increased heart rate, tachycardia, and, in the most severe cases, myocardial infarction or stroke[19].

Severe poisonings have been associated with rhabdomyolysis, liver and kidney toxicity, and failure.

Lung injuries (e.g., pneumothorax, pneumomediastinum) are also common and can be attributed to direct local injuries caused by SCs or impurities in SC mixtures, often requiring oxygen support[4,20].

SC withdrawal can also lead to adverse symptoms such as restlessness, headache, irritability, drug cravings, hypertension, nausea, tremors, diaphoresis, and nightmares. Seizures and cardiovascular arrest may occur in more severe cases[21,22].

Poisonings from SCs, whether taken alone or in conjunction with other recreational substances or prescription drugs, are often observed. Fatal poisonings resulting in cardiac arrest, drowning, multiple organ failure, suicide, or traumatic accidents can also occur.

Emergency indoles, indole carboxylates, and indazole carboxamides are the SCs most frequently mentioned in death reports.

Establishing a direct correlation between SCs and cause of death is often challenging because the lack of appropriate reference standards generally hinders the accurate identification and quantification of SCs found in biological samples. Additionally, post-mortem blood concentrations can vary depending on factors such as the type of SC, individual characteristics, and the time elapsed since death.

Most mild SC poisonings require only symptomatic treatment on an outpatient basis, while severe poisonings (e.g., seizures, severe agitation, neuropsychiatric complaints, arrhythmias, stroke, severe dyspnea) result in hospitalization.

The treatment of acute SC poisoning typically involves intensive monitoring and supportive therapy[23-26].

Intravenous fluids are commonly administered to expand the circulatory system volume, control vomiting, and prevent dehydration and renal failure.

Benzodiazepines are the first-line treatment to reduce sedation, anxiety, and agitation, although psychiatric evaluation and antipsychotic administration are often necessary[26,27].

Intubation and mechanical ventilation may be required in severe cases.In cases of oral ingestion, gastric lavage and ingestion of activated charcoal may be necessary depending on the amount of SC ingested and the time elapsed since ingestion[22].

Aksel and colleagues have identified a new treatment called intravenous lipid emulsion (ILE) for SC poisonings, showing promising results as an effective antidote for lipophilic drugs such as SCs, improving recovery from cardiovascular collapse and reversing neurological symptoms caused by these drugs[28]. ILE sequesters drugs in the intravascular space and distributes lipid-soluble drugs into the circulation phase, reducing their concentrations and toxicities.

Withdrawal symptoms from SCs are managed with benzodiazepines, antiemetics, and other symptomatic treatments[29].

Because adolescents and young adults (including women of reproductive age and pregnant women) are the primary users of SCs, the impact of SC use on neurodevelopment represents a fundamental concern. SCs modulate the endocannabinoid system, which is involved in various biological processes, including cell fate and neurogenesis mechanisms (e.g., neuronal differentiation, migration, maturation, synaptic pruning)[30,31].

Due to their high lipophilicity, SCs can easily pass through the placental barrier and reach embryonic tissues[32]. The connection between exposure to SCs prenatally and postnatally and neurogenesis dysfunction is strongly supported by preclinical studies.

Mereu and colleagues demonstrated that daily administration of the CB1R agonist WIN55,212-2 (0.5 mg/kg) to pregnant rats resulted in impaired memory retention capacity in offspring aged 40 and 80 days. These effects were accompanied by a decrease in presynaptic glutamate release in the hippocampus and changes in hippocampal long-term potentiation associated with learning and memory consolidation[33].

Pinky and colleagues reported that the same SC (WIN55,212-2) administered to pregnant rats at a dose of 2 mg/kg body weight daily significantly altered various biochemical markers in adolescent offspring, including a reduction in oxidative stress and apoptotic marker levels and an increase in mitochondrial function in the cerebellum (a brain region playing a significant role in learning and motor function). Interestingly, while GluA1 levels (a significant subtype of glutamate receptor) and tyrosine hydroxylase activity were unaffected, total monoamine oxidase (MAO) activity decreased significantly in the cerebellum, supporting the idea that SCs affect monoamine neurotransmitter levels in this brain region[34].

Numerous in vitro studies have also revealed the crucial role of CBR stimulation in modulating neurogenic processes[35,36]. Kim and colleagues observed that the SC (300 nM WIN55,212-2) significantly inhibited new synapse formation in rat hippocampal neurons obtained from 17-day-old embryos by inhibiting forskolin-induced cAMP elevation. Interestingly, WIN55,212-2 did not block effects induced by a membrane-permeable cAMP analog, suggesting that it inhibits new synapse formation by preventing cAMP synthesis rather than actions downstream of cAMP (e.g., neurotransmitter release)[37].

Jiang and colleagues reported that chronic treatment of neural stem cells isolated from E17 Long Evans rat embryos with 100 µg/kg HU-210 supported neuronal proliferation via ERK pathway activation but did not support differentiation. They associated this effect with the anxiolytic and antidepressant-like effects of HU-210[38].

Miranda and colleagues demonstrated that chronic exposure to SCs during neurogenesis promoted early neuronal and glial differentiation in human-induced pluripotent stem cells and led to abnormal functioning of voltage-gated calcium channels in newborn neurons when stimulated by extracellular potassium[39].

Evaluating the consequences of prenatal and postnatal SC exposure on human neurodevelopment is challenging. This is because cognitive, motor, and behavioral parameters can only be evaluated retrospectively, and various confounding factors can lead to significant differences in outcomes. Thus, isolating the direct consequences of SC use without interpretational bias is hindered[39-41]. Therefore, data on perinatal SC-associated toxicity are limited to only a few case studies reporting no mortality or morbidity characteristics in newborns.

Epigenetic disturbances have been reported in the brain and peripheral organs following exposure to Δ9-THC[42]. Several studies have reported the epigenetic mechanistic consequences of SC exposure[43]. Ibn Lahmar Andaloussi and colleagues observed an increase in global DNA methylation in the prefrontal cortex and transcription of DNA methyltransferase 1 (DNMT1) and 3 (DNMT3) in adolescent male rats exposed to WIN55,212-2 for one week. They suggested that these epigenetic modifications contributed to the anxiogenic-like effects observed in exposed rats and their offspring[44].

Tomas-Roig and colleagues observed that long-term administration of WIN55,212-2 during adolescence increased anandamide levels and promoted DNA hypermethylation in the intragenic region of the intracellular signal modulator Rgs7 (an intracellular antagonist of GPCR signaling). It was found that this altered the expression of Rgs7 in adulthood45. Application of HU-210 to female rats during pregnancy and for 14 days after birth has been shown to alter microRNA expression in the left hemisphere of the entorhinal cortex, a brain region associated with schizophrenia[46].

Therapeutic Potential

Accumulated findings have revealed the therapeutic potential of the endocannabinoid system, leading to the consideration of cannabinoids as candidate agents for treating various disorders[47]. Indeed, synthetic analogs of Δ9-THC, such as dronabinol and nabilone (Marinol and Cesamet, respectively), have been approved by the U.S. Food and Drug Administration as adjunct analgesics for alleviating chemotherapy-induced nausea and vomiting or chronic pain when first-line antiemetics fail[48]. Additionally, nabiximols, marketed as Sativex, which is a standardized combination of synthetic Δ9-THC and cannabidiol in equal amounts, has shown moderate evidence for treating spasticity associated with multiple sclerosis[47]. However, efforts to develop SC-based therapeutic agents have largely been halted due to adverse events associated with CB1R activation triggered primarily in the central nervous system[49].

The ability of SCs to bind to CB2Rs suggests the safe targeting of the endocannabinoid system due to its potential to modulate inflammatory processes. For instance, it has been shown that WIN55,212-2 suppresses nitric oxide production, TNF-α release, and the formation of CXCL10, CCL2, and CCL5 chemokines in IL-1-stimulated astrocytes[50]. However, the discovery of the endocannabinoidome has further complicated the signaling events triggered by SCs, thus limiting their potential therapeutic applications[49].

Conclusions

Research on the biological significance of the endocannabinoid system has greatly expanded in recent years, with synthetic cannabinoids (SCs) playing an important role as research tools to understand how this system regulates fundamental biological processes. However, the widespread recreational use of SCs has become a significant public health and social concern.

The ability of SCs to interact with cannabinoid receptors (CBRs), namely CB1R, CB2R, and non-CBRs (e.g., TRPV, GPR55, PPARs, 5-HT receptors), and the biased agonism of SCs upon binding to CBRs, increase the complexity of the signaling pathway network modulated by these substances, hindering the understanding of such signal modulation.

Furthermore, since the targets of SCs are widespread throughout the body, their effects and adverse outcomes extend to all major organs and tissues. The toxicology of SCs is generally uncertain because (a) toxic effects may be associated not only with SC itself but also with other toxic substances present in SC herbal mixtures; (b) various confounding factors (e.g., genetic, environmental, frequency/type of SC used) can influence their effects; (c) in vitro effects vary depending on the cell model and experimental design (e.g., concentration, time point, exposure protocol); and (d) only a few studies have addressed the toxicological effects of SCs at biologically relevant concentrations.

Modulation of mitochondrial function and activity by SCs and induction of apoptotic signaling have been shown as significant mechanisms underlying the toxicity of these substances.

Additionally, the contribution of SC-associated neurodevelopmental/neuropsychiatric disorders to neurogenesis is likely, which is particularly concerning given that adolescents and young adults are the main users of SCs. SCs may also interfere with epigenetic mechanisms and promote epigenetic changes that can predispose individuals to different pathologies inherited by their offspring. Interestingly, while the therapeutic value of SCs has been demonstrated with the clinical use of synthetic Δ9-THC analogs to treat chemotherapy-induced nausea and vomiting, evidence for their potential use in other

therapeutic applications remains lacking. Understanding the pharmacological and toxicological mechanisms underlying the short- and long-term consequences of SC use and how they may affect consumers' health and quality of life, as well as improving the interpretation of clinical/pathological findings related to SCs, is of great importance, and further research in this area is warranted.

Synthetic cannabinoids (SCs) are designed to mimic the effects of Δ9-tetrahydrocannabinol (Δ9-THC) but exhibit stronger potency and efficacy at cannabinoid receptors.

Recreational SC use is globally prevalent and often associated with acute poisoning and death reports.

SCs trigger a complex signaling pathway network contributing to the modulation of fundamental biological processes by targeting both cannabinoid and non-cannabinoid receptors.

Given their high metabolic rates and the lack of appropriate reference standards for main compounds and related metabolites, timely detection and quantification of SCs in biological samples continue to be a challenge for forensic toxicologists/pathologists.

SCs induce numerous adverse outcomes that are more severe and longer-lasting across different organ systems than those induced by Δ9-THC.

Chronic SC use and/or use, particularly by vulnerable groups (e.g., adolescents and young adults), may promote the onset of neurodevelopmental/neuropsychiatric disorders (e.g., psychosis, autism spectrum) in the long term, for example, by disrupting proper neurogenesis or causing epigenetic changes.

SCs have been proposed as candidate agents for several different therapeutic applications, but there is currently little evidence regarding their therapeutic potential beyond the treatment of chemotherapy-induced nausea and vomiting.

Further research is needed to elucidate the key mechanisms underlying the short- and long-term effects mediated by SCs, which will help reduce the misuse of SCs by high-risk groups.

References

1. Aşıcıoğlu FJYNP-AMSK. Yeni nesil psiko-aktif maddeler. 2013:3-5.
2. Drugs EMCf, Addiction D. Perspectives on drugs: synthetic cannabinoids in Europe. Publications Office of the European Union Luxembourg; 2017.
3. Gaoni Y, Mechoulam RJJotAcs. Isolation, structure, and partial synthesis of an active constituent of hashish. 1964;86(8):1646-7.
4. Mills B, Yepes A, Nugent KJTAjotms. Synthetic cannabinoids. 2015;350(1):59-62.
5. Lafaye G, Karila L, Blecha L, Benyamina AJDicn. Cannabis, cannabinoids, and health. 2017;19(3):309-16.
6. Solimini R, Busardo FP, Rotolo M, Ricci S, Mastrobattista L, Mortali C, et al. Hepatotoxicity associated to synthetic cannabinoids use. 2017;21.
7. Tettey JN, Crean C, Rodrigues J, Yap TWA, Lim JLW, Lee HZS, et al. United Nations Office on Drugs and Crime: recommended methods for the identification and analysis of synthetic cannabinoid receptor agonists in seized materials. 2021;3:100129.
8. Liu CM, Jia W, Meng X, Hua ZDJJoFS. Identification and quantification of 10 indole/indazole carboxamide synthetic cannabinoids in 36 herbal blends by gas chromatography□mass spectrometry and nuclear magnetic resonance spectroscopy. 2021;66(6):2156-66.
9. Tettey JNA, Crean C, Rodrigues J, Angeline Yap TW, Lee Wendy Lim J, Shirley Lee HZ, et al. United Nations Office on Drugs and Crime: Recommended methods for the Identification and Analysis of Synthetic Cannabinoid Receptor Agonists in Seized Materials. Forensic Science International: Synergy. 2021;3:100129.
10. Alves VL, Gonçalves JL, Aguiar J, Teixeira HM, Câmara JSJCRiT. The synthetic cannabinoids phenomenon: from structure to toxicological properties. A review. 2020;50(5):359-82.
11. Patel M, Manning JJ, Finlay DB, Javitch JA, Banister SD, Grimsey NL, et al. Signalling profiles of a structurally diverse panel of synthetic cannabinoid receptor agonists. 2020;175:113871.
12. Ruparel NB, Patwardhan AM, Akopian AN, Hargreaves KMJMp. Desensitization of transient receptor potential ankyrin 1 (TRPA1) by the TRP vanilloid 1-selective cannabinoid arachidonoyl-2 chloroethanolamine. 2011;80(1):117-23.
13. Oleson EB, Cheer JFJCSHpim. A brain on cannabinoids: the role of dopamine release in reward seeking. 2012;2(8):a012229.
14. Brown TM, Brotchie JM, Fitzjohn SMJJoN. Cannabinoids decrease corticostriatal synaptic transmission via an effect on glutamate uptake. 2003;23(35):11073-7.
15. Irie T, Kikura-Hanajiri R, Usami M, Uchiyama N, Goda Y, Sekino YJN. MAM-2201, a synthetic cannabinoid drug of abuse, suppresses the synaptic input to cerebellar Purkinje cells via activation of presynaptic CB1 receptors. 2015;95:479-91.
16. Yano H, Adhikari P, Naing S, Hoffman AF, Baumann MH, Lupica CR, et al. Positive allosteric modulation of the 5-HT1A receptor by indole-based synthetic cannabinoids abused by humans. 2020;11(10):1400-5.
17. Lobato-Freitas C, Brito-da-Costa AM, Dinis-Oliveira RJ, Carmo H, Carvalho F, Silva JP, et al. Overview of synthetic cannabinoids ADB-FUBINACA and AMB-FUBINACA: clinical, analytical, and forensic implications. 2021;14(3):186.
18. Canazza I, Ossato A, Vincenzi F, Gregori A, Di Rosa F, Nigro F, et al. Pharmaco-toxicological effects of the novel third-generation fluorinate synthetic cannabinoids, 5F-ADBINACA, AB-FUBINACA, and STS-135 in mice. In vitro and in vivo studies. 2017;32(3):e2601.
19. Gurney S, Scott K, Kacinko S, Presley B, Logan BJFSR. Pharmacology, toxicology, and adverse effects of synthetic cannabinoid drugs. 2014;26(1):53-78.
20. Tatusov M, Mazer-Amirshahi M, Abbasi A, Goyal MJTAJoEM. Clinical effects of reported synthetic cannabinoid exposure in patients admitted to the intensive care unit. 2019;37(6):1060-4.
21. Martinotti G, Santacroce R, Papanti D, Elgharably Y, Prilutskaya M, Corazza OJC, et al. Synthetic cannabinoids: psychopharmacology, clinical aspects, psychotic onset. 2017;16(5):567-75.

22. Cooper ZD. Adverse Effects of Synthetic Cannabinoids: Management of Acute Toxicity and Withdrawal. Current psychiatry reports. 2016;18(5):52.
23. Mills B, Yepes A, Nugent K. Synthetic Cannabinoids. The American journal of the medical sciences. 2015;350(1):59-62.
24. Riederer AM, Campleman SL, Carlson RG, Boyer EW, Manini AF, Wax PM, et al. Acute Poisonings from Synthetic Cannabinoids - 50 U.S. Toxicology Investigators Consortium Registry Sites, 2010-2015. MMWR Morbidity and mortality weekly report. 2016;65(27):692-5.
25. Armenian P, Darracq M, Gevorkyan J, Clark S, Kaye B, Brandehoff NP. Intoxication from the novel synthetic cannabinoids AB-PINACA and ADB-PINACA: A case series and review of the literature. Neuropharmacology. 2018;134(Pt A):82-91.
26. Müller HH, Kornhuber J, Sperling W. The behavioral profile of spice and synthetic cannabinoids in humans. Brain Research Bulletin. 2016;126:3-7.
27. Tsatsakis A, Docea AO, Calina D, Tsarouhas K, Zamfira LM, Mitrut R, et al. A Mechanistic and Pathophysiological Approach for Stroke Associated with Drugs of Abuse. Journal of clinical medicine. 2019;8(9).
28. Aksel G, Güneysel Ö, Taşyürek T, Kozan E, Çevik Ş E. Intravenous Lipid Emulsion Therapy for Acute Synthetic Cannabinoid Intoxication: Clinical Experience in Four Cases. Case reports in emergency medicine. 2015;2015:180921.
29. Armenian P, Darracq M, Gevorkyan J, Clark S, Kaye B, Brandehoff NP. Intoxication from the novel synthetic cannabinoids AB-PINACA and ADB-PINACA: A case series and review of the literature. Neuropharmacology. 2018;134:82-91.
30. El Marroun H, Brown QL, Lund IO, Coleman-Cowger VH, Loree AM, Chawla D, et al. An epidemiological, developmental and clinical overview of cannabis use during pregnancy. Preventive Medicine. 2018;116:1-5.
31. Cristino L, Bisogno T, Di Marzo V. Cannabinoids and the expanded endocannabinoid system in neurological disorders. Nature reviews Neurology. 2020;16(1):9-29.
32. Dong C, Chen J, Harrington A, Vinod KY, Hegde ML, Hegde VL. Cannabinoid exposure during pregnancy and its impact on immune function. Cellular and molecular life sciences : CMLS. 2019;76(4):729-43.
33. Mereu G, Fà M, Ferraro L, Cagiano R, Antonelli T, Tattoli M, et al. Prenatal exposure to a cannabinoid agonist produces memory deficits linked to dysfunction in hippocampal long-term potentiation and glutamate release. Proceedings of the National Academy of Sciences of the United States of America. 2003;100(8):4915-20.
34. Pinky PD, Majrashi M, Fujihashi A, Bloemer J, Govindarajulu M, Ramesh S, et al. Effects of prenatal synthetic cannabinoid exposure on the cerebellum of adolescent rat offspring. Heliyon. 2021;7(4):e06730.
35. Alexandre J, Carmo H, Carvalho F, Silva JP. Synthetic cannabinoids and their impact on neurodevelopmental processes. Addiction biology. 2020;25(2):e12824.
36. Oudin MJ, Gajendra S, Williams G, Hobbs C, Lalli G, Doherty P. Endocannabinoids regulate the migration of subventricular zone-derived neuroblasts in the postnatal brain. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2011;31(11):4000-11.
37. Kim D, Thayer SA. Cannabinoids inhibit the formation of new synapses between hippocampal neurons in culture. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2001;21(10):Rc146.
38. Jiang W, Zhang Y, Xiao L, Van Cleemput J, Ji SP, Bai G, et al. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. The Journal of clinical investigation. 2005;115(11):3104-16.
39. Miranda CC, Barata T, Vaz SH, Ferreira C, Quintas A, Bekman EP. hiPSC-Based Model of Prenatal Exposure to Cannabinoids: Effect on Neuronal Differentiation. Frontiers in molecular neuroscience. 2020;13:119.
40. Scheyer AF, Melis M, Trezza V, Manzoni OJJ. Consequences of Perinatal Cannabis Exposure. Trends in neurosciences. 2019;42(12):871-84.
41. Wu CS, Jew CP, Lu HC. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. Future neurology. 2011;6(4):459-80.
42. Szutorisz H, Hurd YLJN, Reviews B. High times for cannabis: Epigenetic imprint and its legacy on brain and behavior. 2018;85:93-101.
43. Gomes TM, da Silva DD, Carmo H, Carvalho F, Silva JPJPR. Epigenetics and the endocannabinoid system signaling: An intricate interplay modulating neurodevelopment. 2020;162:105237.
44. Andaloussi ZIL, Taghzouti K, Abboussi OJIJoDN. Behavioural and epigenetic effects of paternal exposure to cannabinoids during adolescence on offspring vulnerability to stress. 2019;72:48-54.
45. Tomas-Roig J, Benito E, Agis-Balboa R, Piscitelli F, Hoyer-Fender S, Di Marzo V, et al. Chronic exposure to cannabinoids during adolescence causes long-lasting behavioral deficits in adult mice. 2017;22(6):1778-89.
46. Hollins S, Zavitsanou K, Walker F, Cairns MJTp. Alteration of imprinted Dlk1-Dio3 miRNA cluster expression in the entorhinal cortex induced by maternal immune activation and adolescent cannabinoid exposure. 2014;4(9):e452-e.
47. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. 2015;313(24):2456-73.
48. de Vries M, van Rijckevorsel DC, Wilder-Smith OH, van Goor HJEoop. Dronabinol and chronic pain: importance of mechanistic considerations. 2014;15(11):1525-34.
49. Cristino L, Bisogno T, Di Marzo VJNRN. Cannabinoids and the expanded endocannabinoid system in neurological disorders. 2020;16(1):9-29.
50. Sheng WS, Hu S, Min X, Cabral GA, Lokensgard JR, Peterson PKJG. Synthetic cannabinoid WIN55, 212-2 inhibits generation of inflammatory mediators by IL-1β-stimulated human astrocytes. 2005;49(2):211-9.