

**Citation for published version:**

Giovanni Martinotti, Rita Santacroce, Duccio Papanti, Yasmine Elgharably, Mariya Prilutskaya, Ornella Corazza, 'Synthetic Cannabinoids: Psychopharmacology, Clinical Aspects, and Psychotic Onset', *CNS & Neurological Disorders – Drug Targets*, Vol. 16, 2017.

**DOI:**

<https://doi.org/10.2174/1871527316666170413101839>

**Document Version:**

This is the Accepted Manuscript version.

The version in the University of Hertfordshire Research Archive may differ from the final published version.

**Copyright and Reuse:**

This manuscript version is made available under the terms of the Creative Commons Attribution-NonCommercial CC BY-NC 3.0 licence <https://creativecommons.org/licenses/by-nc/3.0/>

**Enquiries**

If you believe this document infringes copyright, please contact the Research & Scholarly Communications Team at [rsc@herts.ac.uk](mailto:rsc@herts.ac.uk)

# Synthetic Cannabinoids: psychopharmacology, clinical aspects, and psychotic onset

Giovanni Martinotti<sup>1,2</sup>, Rita Santacroce<sup>1</sup>, Duccio Papanti<sup>3</sup>, Yasmine Elgharably<sup>2</sup>, Mariya Prilutskaya<sup>2</sup>, Ornella Corazza<sup>2</sup>

<sup>1</sup>Department of Neuroscience, Imaging and Clinical Sciences, University "G.d'Annunzio", Chieti, Italy

<sup>2</sup>Department of Pharmacy, Pharmacology, Clinical Science, University of Hertfordshire, Herts, UK

<sup>3</sup>Department of Medical, Surgical, and Health Sciences, University of Trieste, Italy

**Corresponding author:** Rita Santacroce, Department of Neuroscience, Imaging and Clinical Sciences, University "G.d'Annunzio", Via dei Vestini 31, 66100, Chieti, Italy.

Email: [rita.santacroce82@gmail.com](mailto:rita.santacroce82@gmail.com)

## *Abstract*

Synthetic Cannabinoids (SC) are the widest and most diffuse class of Novel Psychoactive Substances. SC are chemically heterogeneous and structurally dissimilar from delta-9-tetrahydrocannabinol (THC), being full agonists of the endocannabinoid system receptors CB1 and CB2. Desired effects include euphoria, talkativeness, feelings of joy and laughter, relaxation. With respect to cannabis, SC intake may also be associated with quicker arise of the effects, shorter duration of action, and larger levels of hangover. SC are more psychoactive than cannabis: symptoms may include a wide range of clinically relevant positive, negative and cognitive psychopathological symptoms that mimic symptoms of schizophrenia. The risk of two widespread symptoms of SC intoxication, namely agitation and cardiotoxicity, exceeds this of traditional cannabis of 3.8 and 9.2 times respectively. A number of deaths have been related to SC ingestion, either on their own or in combination with other recreational drugs. Prompt and reliable information available for health professionals, more specific analytic techniques, and designed preventive strategies are all required to face this unprecedented challenge.

## *Introduction*

Novel psychoactive substances (NPS) are defined as substances, either in pure form or in preparation, that have not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs or the 1971 United Nations Convention on Psychotropic Substances, but which may pose a public health threat comparable to the substances there listed [1]. The use of NPS, peculiarly by adolescents and young adults, is emerging as a new trend worldwide [2], shaping an unprecedented and dangerous global phenomenon in the field of substance misuse. The short- and long- term health risks associated with the consumption of novel psychoactive substances are, in fact, often unknown to both users and health professionals [3]. Among NPS, synthetic cannabinoids (SC) are the largest and most prevalent group [4]. SC are chemically heterogeneous and structurally dissimilar from delta-9-tetrahydrocannabinol (THC), but they all share a

common mechanism of action, being agonists of the endocannabinoid system receptors CB1 and CB2 [5]. SC are usually sold as “legal” alternatives to natural cannabis, and they gained popularity in the early 2000s with the appearance on the market of the *Spice* brand [6], which is the reason they are still often referred to as *Spice drugs*. As many other NPS, most SC are neither recently patented, nor originally synthesised as recreational drugs: one of the widest series of SC was developed in the 1990s by John William Huffman [7], who was an organic chemistry professor at Clemson University researching on cannabinoid compounds as possible therapeutic options for multiple sclerosis and HIV. SC are easy to be purchased, not only from smart shops, but also online: the number of web pages offering SC for sale to European customers has been constantly growing since 2010 [8]. Potential consumers may be attracted by marketing strategies such as cheap prices, colourful and apparently “harmless” names and packaging, and the often false believe to be buying something legal, and therefore safe [9, 10]. SC are produced in clandestine laboratories, located mostly in India and China, either as pure powder, sold as a research chemical, or vaporised and sprayed on dried plants material, advertised as “herbal incenses” [11]. All products containing SC are labelled “not for human consumption”; nevertheless, SC are primarily smoked or inhaled by users to obtain a quick “high”. SC prevalence presents significant differences between Europe and US: according to the most recent American data, the use of SC may be declining among young adults (5.8% in 2014, in comparison with 7.9% in 2013 and 11.3% in 2012), while European surveys highlight increasing trends [12]. A growing interest in the field is also registered by scientific literature: a PubMed and Scopus search performed on November 8th, 2016 for the following terms “synthetic cannabinoid\*”, “synthetic cannabimimetic\*”, “synthetic cannabis”, “synthetic marijuana” and “Spice AND cannabinoid\*” yielded a total of 162 relevant results, mainly published in the past two years (exclusion criteria: papers not in English; mini reviews, letters, book chapters, case reports erratum; papers related to SC as therapeutic options). Most results (93) emerged for the keyword “synthetic cannabinoid\*”, followed by the combination “Spice\* AND “cannabinoid\*” (42), accounting respectively for 57% and 26% of the total. Only about 9% of the results were case report or case series: most papers were epidemiological, forensic, toxicologic, or analytical. 3% of the studies were on animal models. Aim of the present paper is to provide a synthesis of the most recent and relevant insights on the pharmacology, clinical and psychopathological aspects of SC.

## ***Pharmacology***

Whilst THC, the main active component of natural cannabis, is a partial agonist at cannabinoid receptors CB1 and CB2, SC can be full, or even super agonists [13, 14], hence possessing high levels of receptors’ affinity whilst eliciting maximal activity on cannabinoid receptors [5]. CB1 and CB2 agonism of SC is also potentiated by a slow rate of dissociation from cannabinoid receptors [15]. The effects of SC are also achieved through reversible indirect dopamine stimulation [16-17] and activation of G-protein-coupled receptors [18]. Consecutive stimulation of the neurotransmitters is associated with enhanced metabolic activity throughout the brain, especially in rewarding and reinforcing centres, i.e. nucleus accumbens, amygdala, cingulate cortex, prefrontal cortex, ventral pallidum, caudate putamen, ventral tegmental area, and lateral hypothalamus [19-20]. Additionally, exogenous CB1 activation with SC reveals sensorimotor and motor alteration accompanied by significant modifications of the activity in visual and auditory cortices [21-22]. Each “new generation” within the class of SC demonstrates greater potency on CB receptors compared to earlier ones [23-24-25-26]. In contrast, THC and “old generation” SC show a more significant inhibitor ability on hippocampal and cerebellum glutamate transmission [27-28]. The

potency and duration of the pharmacological effects may be partially explained by the retention of CB1 agonism in the process of their metabolism. For instance, hydroxylated compounds demonstrate equal or greater efficacy with respect to THC [29-30]. Additionally, SC metabolites reveal CB2 receptors affinity, distributing immune reactions and modulating addictive properties [31]. The grade of SC toxicity can be also determined and associated with polymorphic alleles of the metabolising enzyme P450 [32]. The pharmacological properties of SC go beyond neurotransmission, and include cytotoxicity and genetic effects. SC can cause cell damaging through affecting lipid metabolism and inflammatory signalling [33]. Chronic systemic exposure can modify the structure of cortical and sub-cortical neurons [34], with effects on nuclei and nucleus membranes [35] and suppression of neuronal activity in the hippocampus [36-37]. Metabolites of SC also demonstrate neurotoxic effects decreasing cellular viability, apoptosis and necrosis [38-39] as well as DNA damaging and micronuclei aberration of chromosomes [40-41]. The genotoxicity of SC also refers to hepatocytes, lymphocytes and cells of cardiovascular system. In these cases, acute and chronic exposure to SC may induce genes significantly associated with dysfunction of oxidation and inflammation in liver, cardio-vascular and blood systems [42-43]. Taking into consideration the endocannabinoid regulation properties on reproductive system, SC showed a damaging effect on gonads. In series of experiments with human cell lines and primary cells, SC represented hormonal antiestrogenic activity [44]. In turn, long-term use of SC can have adverse effects on both spermatogenesis and sperm function acting on spermal endocannabinoid system [45].

Chronic exposure to SC associates with abuse liability, and determines behavioural activity in form of modulation of discriminative stimulus effects [46-47]. Furthermore, repeated SC administration can lead to modulation, internalisation and desensitisation of CB receptors, linked to tolerance and withdrawal symptoms [48-49].

Furthermore, THC effects are mitigated by the presence of other compounds identified in cannabis, e.g. terpenoids, cannabidiol and tetrahydrocannabivarin [50], while none of these 'modulating' compounds are detected in SC, a number of SC molecules incorporates indole-derived moieties as components of the structure or as substituents [51], typically identified in indoleamine hallucinogens such as dimethyltryptamine [52]. Moving from this point of view, it could be argued that the intake of indole SC compounds may be associated with significant levels of 5-HT receptors' activation [53,54]. SC demonstrates also interactions with other transmission systems, namely  $\mu$ -opioid [55], glutamate and GABA [56]. Meanwhile, for some SC agents abuse potential contributes also to alteration in neurobiological function, cognitive potency or behaviour without significant influence on rewarding or reinforcing systems [57-58]. Overall, SC activity at non-cannabinoid receptors may well contribute to the complex clinical effects observed [5].

As SC-containing preparations are almost always produced mixing multiple SC in a single product [59], there is a strong potential for between-drug interactions [60]. Furthermore, some SC metabolites retain levels of both affinity and activity for CB1 receptors, hence delaying/intensifying receptors' activation and contributing to the toxicity of the products [61]. The recent trend of SC fluorination, commonly applied in medicinal chemistry, may increase the compounds' lipophilicity, promoting the absorption through biological membranes/blood brain barrier [62, 63], possibly enhancing CB receptor affinity [64] the overall toxicity [61]. Other factors potentially contributing to SC toxic effects may include: the pharmacological activity of SC pyrolysis by-products [65, 66]; the presence of contaminants, side-products, and solvents in the package [59]; the lack of any quality control of the final product, leading to significant differences in concentration ('hot-spots') of SC present in herbal incenses [50, 67]; and the increased vulnerability to some SC adverse effects due to either pre-existing conditions of drug users, or concurrent intake of other [61, 68].

## *Clinical aspects*

Desired effects arise quickly after the consumption of SC products, and include euphoria, talkativeness, feelings of joy and laughter, relaxation [69]. In terms of psychoactive effects, there are similarities between low doses of SC and THC intake [70], as delusional and hallucinatory symptoms most commonly occur for higher SC doses. Nevertheless, it has to be considered that determining the exact dosage of a single SC in a preparations is usually extremely difficult, if not impossible, for the user [10]. SC-related perceptual disturbances may include ‘fractals/ geometric patterns’, ‘trails’, and ‘flashes of colour’, together with relaxation and increased creativity levels [71]. With respect to cannabis, SC intake may also be associated with quicker arise of the effects, shorter duration of action, and larger levels of hangover [72]. High SC dosages may induce increasing levels of anxiety [73], together with a range of unpleasant experiences (e.g. ‘bad trips’). Bad trips are characterised by a range of symptoms such as: suspiciousness/paranoid feelings, altered experience of one’s self, and sensations of living in different/parallel realities [74-76].

SC psychoactive effects may be more intense in individuals with any/minimal levels of previous exposure to cannabis [77]. Adverse SC-related side effects may be severe; indeed, SC intake is associated with a 30-fold higher risk of seeking emergency room as compared with traditional cannabis [78]. The risk of two widespread symptoms of SC intoxication, namely agitation and cardiotoxicity, exceeds this of traditional cannabis of 3.8 and 9.2 times respectively [79]. Acute SC intoxication may sometimes resemble the clinical picture associated with the use of stimulant/sympathomimetic recreational drugs [80,82,83]. On other occasions, a short-standing, potentially life threatening, serotonin-like syndrome may be observed, with reported signs/symptoms of elevated heart rate/blood pressure levels; mydriasis; agitation/anxiety; hyperglycaemia; dyspnoea/tachypnoea; nausea/vomiting; diaphoresis, hot flushes and seizures, hyperthermia [5, 77, 82-84]. Other SC-related acute adverse effects include: somnolence, self-injurious/aggressive behaviour; hyperemesis; nystagmus; stroke; chest pain, myocardial infarction; rhabdomyolysis, risk of cardiovascular diseases including alteration in ECG parameters, limb twisting, muscle tremors, respiratory failure, catatonia, losses of consciousness and acute kidneys injuries, , elevation of creatine kinase, cerebral ischaemia, metabolic derangements (hypokaliemia, insulin resistance, metabolic acydosis) [85-99]. Metabolic decompensation initiated by SC may contribute to and exaggerate neurotoxic effects that anecdotal report on adrenoleukodystrophy suggests [100]. Neurotoxic effects of SC are clinically confirmed by morphometric assays in form of reduction of thalamus and cerebellum, grey matter and white matter of left temporal lobe, subcortical structures and brain-stream [101-102]. Conditions of agitated/excited delirium have recently been associated with SC intoxication [103-106]. Patients may be very aggressive, hallucinating, combative, suicidal and tachycardic for up to several days [71, 107-108]. Overall, so far most clinicians are not well trained in terms of treatment/management issues relating to SC misuse and intoxication [109]. A number of deaths have been related to SC ingestion, either on their own or in combination with other recreational drugs/prescription drugs [110-115]. Conversely, there are no reports of fatal cannabis overdoses in the epidemiological literature [116].

Both tolerance and symptoms of withdrawal have been described for SC, suggesting that they may have a relatively high abuse and dependence liability [71, 117-118]. SC withdrawal syndrome is characterised by drug craving, tachycardia, tremor, profuse sweating, nightmares/insomnia, headache, anxiety/irritability, and feelings of emptiness/depressive symptoms, cenestopathic sensations and somatic complaints

(chest pain, dyspnoea, nausea /vomiting, diarrhoea, diaphoresis, palpitation [119-122] Severe symptoms of SC withdrawal include reoccurring seizures and cardiovascular arrest [123].

### ***Synthetic Cannabinoids and Psychosis***

SC are more psychoactive than cannabis, helping to achieve the desire of feeling “high”, easily available as “legal” product, and undetectable in routine examinations: these factors may increase their popularity among different populations, such as high school seniors [124], young people and adolescents [125], with men being more consumers than women [126]. SC do not contain any cannabidiol (or other modulating compounds) that may counteract the psychoactive properties, and their intrinsic activity on CB1 receptors, spread over CNS, is maximal [5, 66]. Psychotic disorders associated with SC intake can be conceptualised as: toxic acute psychotic episodes [77, 127-132]; ‘ex novo’, long-standing/persistent, psychotic disorders [68,133-134]; and relapse/worsening of a pre-existing psychosis [77, 135-137]. The exact mechanism of association is not well understood and still debated. Family history, childhood trauma, age of exposure and genetics are thought to be the mediators and moderators of the association between SC and psychosis effects [138,139]. Acute psychotic reactions in healthy individuals can occur following either a single or repeated use of SC, and may include a wide range of clinically relevant positive, negative and cognitive psychopathological symptoms that mimic symptoms of schizophrenia, among which: perceptual alterations, depersonalisation, dissociation, illusions, auditory and visual hallucinations, paranoid delusions, bizarre/disorganised behaviour and speech, catatonia, agitation/aggression, and suicidal ideation/behaviour. Negative symptoms including blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity, and reduced rapport are less frequently seen in studied SC users than in schizophrenic patients [140]. SC may exacerbate symptoms in patients already diagnosed with psychotic illness [138-140]. Acute psychosis outlasting the period of intoxication, and persistent disorders are still under study. So far, no longitudinal studies to evaluate the impact of long-term effects of SC consumption have been carried out in humans. However, a cross sectional study on 81 male patients diagnosed with psychotic disorders induced by at least 4 months of SC use was performed to identify the clinical psychotic characteristics induced by SC in relation to schizophrenia [141]. Results revealed that SC-induced psychosis shows remarkable states of suicidal ideation, as well as schizomimetic psychotic features. Younger age at onset is related to poor frontal lobe functioning domains, specifically affected by SC [141]. Occurrence of hallucinations/delusions is less likely with cannabis than with SC; the phenomenon has been observed in 2% and 11.2% of misusers, respectively [125]. Furthermore, in comparison to cannabis, SC-related psychotic episodes are associated with more frequent and higher levels of agitation/behavioural dyscontrol [142]. Overall, comparative studies of SC vs cannabis users admitted to psychiatric units show that SC users are generally younger, and presenting with: higher rates of compulsory admissions; higher severity of disease; more frequent levels of aggression; and longer length of admission [143, 144]. Finally, a number of complete suicides following SC intake has been described [110,145-147]. No extensive literature available on this topic and further studies needed to reveal the truth about the link between SC use and psychosis.

### ***SC fatalities***

A number of deaths have been related to SC ingestion, either on their own or in combination with other recreational drugs/prescription drugs [110-115]. Conversely, there are no reports of fatal cannabis overdoses in the epidemiological scientific literature [116]. Based on the fact that SC have no available antidote, unlike opiates, and cannot be detected in the routine urine and blood examination, often unpredictable adverse effects may become fatal if not treated [106]. Deaths among SC users in USA ranged from 13 to 56 years of age in a study correlating reported severe illnesses and deaths to SC use between 2012 and 2015 [148]. Table 1 illustrates death cases reported following SC use with or without pathological findings at the autopsy, as well as detection of variable SC metabolites in the blood [149-155]. Medical examiners certified most cases as accident death along with SC intoxication. ELISA and GC-MS drug screen were negative in all cases reported. Autopsies revealed different pathological findings; acute kidney injury, fulminant liver failure, pulmonary oedema were the most common. Diabetic ketoacidosis with persistent hypokalaemia was an unpredictable presentation associated with use of SC [154]. Mortality data are mainly based on case reports and data available from emergency rooms and poison centres. Case reports often do not explain whether or not the deaths were due to SC use, whilst the potential association of SC intoxication and death should be clarified. Up to date, all the metabolites detected in case reports previously illustrated belong to Schedule I controlled substance Act by Drug Enforcement Administration, with the exception of 5F-AMB, which has not been added yet despite being similar in structure to AB-PINACA [151,156]. This latter compound, together with AB-CHMINACA, has been responsible of a number of fatalities in the past two years [157-159].

*Table 1: Case histories, pathology and toxicology findings, and death cause for 15 SC-related fatalities*

Ref.	Age /sex	Witnessed symptoms	Pathology on autopsy	Hx of significant disease	SC detected	History of drug abuse	Medical examiner certificate
149	29 F	Signs of intoxication & agitation	unremarkable	N/A	XLR-11	Herbal incense/potpourri. Black Dragon packages	Accident death with SC toxicity
149	32 F	Chest pain, nausea, agitation	Pulmonary oedema/ anthracosis, acute visceral congestion		XLR-11	Methamphetamine, Heroin, SC	Accident death with SC intoxication

150	41 F	Violent, aggressive with her family	pulmonary oedema, vascular congestion, occlusion of LAD coronary artery with ischemia of the anterior left ventricular	N/A	ADB-FU-BINACA	SC "Mojo"	Coronary artery occlusion with SC intoxication
151	34 M	Rigor mortis, nasal frothy purge substance	N/A	unremarkable	5F-AMB	Ethanol abuse SC "Apollo bag was found in his pocket"	Accident death with SC toxicity
110	57 M	Unresponsive	Enlarged heart	N/A	JWH-018	Herbal incense, spice, white powdery substance. Prescription drugs held with him.	N/A
110	52 M	Nude and unresponsive	N/A	N/A	JWH-018 JWH-073	Herbal incense. "K2" package was found	N/A
110	29 M	Committed suicide	N/A		JWH-018 JWH-073	"K2" herbal blend	N/A
152	17 M	Gasped the air and fell down.	unremarkable		5F-PB-22	Alcohol & SC	Accident death with SC toxicity
152	27 M	Ill & diaphoretic	fulminant liver failure	N/A	THCCOOH 5F-PB-22	Marijuana	Accident death with SC toxicity



152	18 M	Unresponsive & cool to touch	bilateral pulmonary and abdominal organs congestion	N/A	5F-PB-22	K2 & spice	Accident death with SC toxicity
152	19 M	Unconscious with drinking	bilateral pulmonary oedema, necrotizing granulomatous inflammation with histoplasma microorganisms and congestion of viscera.	N/A	5F-PB-22	N/A	Accident death with SC toxicity
153	34 M	Dead in bedroom	Asphyxia due to aspiration of gastric contents		5F-AMB AB-CHMINACA	Herbal blend 3 herbal packages were found with him	Accident death with SC toxicity
154	25 M	Found dead in his kitchen	Brain & pulmonary oedema with subepicardial petechial haemorrhage	Insulin dependent diabetes mellitus	AB-CHMINACA, AB-FUBINACA, 5F-APINACA, 5F-AMB, STS-135, THJ2201, AM2201, EAM-2201, JWH-122 and MAM2201	SC self-made bong & cannabis mill were found in his room"	Diabetic ketoacidosis with SC intoxication

154	25 M	Un responsive. All reflexes lost	Multiple organ failure		MDMB-CHMICA	SC "Mocarz, combing comb , Baka" ethanol	Multiple organ failure with SC intoxication
-----	---------	-------------------------------------	------------------------	--	-------------	--	---

## **Conclusions**

SC are the widest and most diffuse class of NPS. The use of these substances is apparently growing especially among youth in the European Union, and together with it there are increasing health risks that should be more carefully monitored and addressed. Prompt and reliable information available for health professionals, more specific analytic techniques, designed preventive strategies for at-risks categories and a commune strategy for law enforcement are all required to face this unprecedented challenge.

## **References**

- [1] Council of the European Union. Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk-assessment and control of new psychoactive substances. Available at: <http://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX:32005D0387>
- [2] Martinotti, G, Lupi, M, Carlucci, L, Cinosi, E, Santacroce, R, Acciavatti, et al. Novel psychoactive substances: use and knowledge among adolescents and young adults in urban and rural areas. *Hum. Psychopharmacol Clin Exp.* 2015;30, 295–301.
- [3] Simonato P, Corazza O, Santonastaso P, Corkery J, Deluca P, Davey Z, et al. Novel psychoactive substances as a novel challenge for health professionals: Results from an Italian survey. *Hum Psychopharmacol.* 2013;28(4).
- [4] EMCDDA. European Drug Report 2015. Lisbon, Portugal, 2015.
- [5] Schifano F, Orsolini L, Duccio Papanti G, Corkery JM. Novel psychoactive substances of interest for psychiatry. *World Psychiatry.* 2015;14(1):15–26.
- [6] Corazza O, Valeriani G, Bersani FS, Corkery J, Martinotti G, Bersani G, et al. "Spice," "Kryptonite," "Black Mamba": An Overview of Brand Names and Marketing Strategies of Novel Psychoactive Substances on the Web. *J Psychoactive Drugs.* 2014;46(4).

- [7] Huffman JW, Dai D. Design, synthesis and pharmacology of cannabimimetic indoles. *Bioorg. Med. Chem. Lett.* 1994;4:563–566.
- [8] EMCDDA. European Drug Report 2013: trends and developments. Lisbon, Portugal, 2013.
- [9] Corazza O, Demetrovics Z, van den Brink W, Schifano F. “Legal highs” an inappropriate term for “Novel Psychoactive Drugs” in drug prevention and scientific debate. *Int J Drug Policy.* 2013;24(1).
- [10] Corazza O, Assi S, Simonato P, Corkery J, Bersani FS, Demetrovics Z, et al. Promoting innovation and excellence to face the rapid diffusion of novel Psychoactive substances in the EU: The outcomes of the reDNet project. *Hum Psychopharmacol.* 2013;28(4).
- [11] United Nations Office on Drugs and Crime. Synthetic Cannabinoids in Herbal Products. 2011. Available at: [http://www.unodc.org/unodc/en/scientists/synthetic-cannabinoids-in-herbal-products\\_new.html](http://www.unodc.org/unodc/en/scientists/synthetic-cannabinoids-in-herbal-products_new.html)
- [12] EMCDDA. Synthetic cannabinoids in Europe. *Perspect Drugs* [Internet]. 2015; Available from: <http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids>
- [13] De Luca MA, Castelli MP, Loi B, Porcu A, Martorelli M, Miliano C, et al. Native CB1 receptor affinity, intrinsic activity and accumbens shell dopamine stimulant properties of third generation SPICE/K2 cannabinoids: BB-22, 5F-PB-22, 5F-AKB-48 and STS-135. *Neuropharmacology.* 2015 Dec 11;105:630–8.
- [14] Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol.* 2008 Jan;153(2):199–215.
- [15] Hrubá L, McMahon LR. The cannabinoid agonist HU-210: pseudo-irreversible discriminative stimulus effects in rhesus monkeys. *European journal of pharmacology.* 2014 Mar 15;727:35-42.
- [16] De Luca MA, Bimpisidis Z, Melis M, Marti M, Caboni P, Valentini V, Margiani G, Pintori N, Polis I, Marsicano G, Parsons LH. Stimulation of in vivo dopamine transmission and intravenous self-administration in rats and mice by JWH-018, a Spice cannabinoid. *Neuropharmacology.* 2015 Dec 31;99:705-14.
- [17] Rominger A, Cumming P, Xiong G, Koller G, Förster S, Zwergal A, Karamatskos E, Bartenstein P, La Fougère C, Pogarell O. Effects of acute detoxification of the herbal blend ‘Spice Gold’ on dopamine D 2/3 receptor availability: A [18 F] fallypride PET study. *European Neuropsychopharmacology.* 2013 Nov 30;23(11):1606-10.
- [18] De Petrocellis L, Di Marzo V. Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: focus on G-protein-coupled receptors and transient receptor potential channels. *Journal of Neuroimmune Pharmacology.* 2010 Mar 1;5(1):103-21.

- [19] Miliano C, Serpelloni G, Rimondo C, Mereu M, Marti M, De Luca MA. Neuropharmacology of New Psychoactive Substances (NPS): Focus on the Rewarding and Reinforcing Properties of Cannabimimetics and Amphetamine-Like Stimulants. *Front Neurosci.* 2016 Apr 19;10:153.
- [20] Glass M, Faull RL, Dragunow M. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience.* 1997 Feb 21;77(2):299-318.
- [21] Ossato A, Canazza I, Trapella C, Vincenzi F, De Luca MA, Rimondo C, Varani K, Borea PA, Serpelloni G, Marti M. Effect of JWH-250, JWH-073 and their interaction on "tetrad", sensorimotor, neurological and neurochemical responses in mice. *Progress in Neuro-Psychopharmacology and Biological Psychiatry.* 2016 Jun 3;67:31-50.
- [22] Ossato A, Vigolo A, Trapella C, Seri C, Rimondo C, Serpelloni G, Marti M. JWH-018 impairs sensorimotor functions in mice. *Neuroscience.* 2015 Aug 6;300:174-88.
- [23] Banister SD, Longworth M, Kevin R, Sachdev S, Santiago M, Stuart J, Mack JB, Glass M, McGregor IS, Connor M, Kassiou M. Pharmacology of Valinate and tert-Leucinate Synthetic Cannabinoids 5F-AMBICA, 5F-AMB, 5F-ADB, AMB-FUBINACA, MDMB-FUBINACA, MDMB-CHMICA, and Their Analogues. *ACS Chem Neurosci.* 2016 Sep 21;7(9):1241-54.
- [24] Banister SD, Moir M, Stuart J1, Kevin RC, Wood KE, Longworth M, Wilkinson SM, Beinat C, Buchanan AS, Glass M, Connor M1, McGregor IS, Kassiou M. Pharmacology of Indole and Indazole Synthetic Cannabinoid Designer Drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. *ACS Chem Neurosci.* 2015 Sep 16;6(9):1546-59.
- [25] Banister SD, Stuart J, Kevin RC, Edington A, Longworth M, Wilkinson SM, Beinat C, Buchanan AS, Hibbs DE, Glass M, Connor M, McGregor IS, Kassiou M. Effects of bioisosteric fluorine in synthetic cannabinoid designer drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. *ACS Chem Neurosci.* 2015 Aug 19;6(8):1445-58.
- [26] Cha HJ, Lee KW, Song MJ, Hyeon YJ, Hwang JY, Jang CG, Ahn JI, Jeon SH, Kim, HU, Kim YH, Seong WK, Kang H, Yoo HS, Jeong HS. Dependence Potential of the Synthetic Cannabinoids JWH-073, JWH-081, and JWH-210: In Vivo and In Vitro Approaches. *Biomol Ther (Seoul).* 2014 Jul;22(4):363-9.
- [27] Hoffman AF, Lycas MD, Kaczmarzyk JR, Spivak CE, Baumann MH, Lupica CR. Disruption of hippocampal synaptic transmission and long-term potentiation by psychoactive synthetic cannabinoid 'Spice' compounds: comparison with  $\Delta(9)$ -tetrahydrocannabinol. *Addict Biol.* 2016 Jan 5.
- [28] Irie T, Kikura-Hanajiri R, Usami M, Uchiyama N, Goda Y, Sekino Y. MAM-2201, a synthetic cannabinoid drug of abuse, suppresses the synaptic input to cerebellar Purkinje cells via activation of presynaptic CB1 receptors. *Neuropharmacology.* 2015 Aug;95:479-91.

- [29] Brents LK, Reichard EE, Zimmerman SM, Moran JH, Fantegrossi WE, Prather PL. Phase I hydroxylated metabolites of the K2 synthetic cannabinoid JWH-018 retain in vitro and in vivo cannabinoid 1 receptor affinity and activity. *PLoS One*. 2011;6(7):e21917.
- [30] Chimalakonda KC, Seely KA, Bratton SM, Brents LK, Moran CL, Endres GW, James LP, Hollenberg PF, Prather PL, Radominska-Pandya A, Moran JH. Cytochrome P450-mediated oxidative metabolism of abused synthetic cannabinoids found in K2/Spice: identification of novel cannabinoid receptor ligands. *Drug Metab Dispos*. 2012 Nov;40(11):2174-84.
- [31] Rajasekaran M, Brents LK, Franks LN, Moran JH, Prather PL. Human metabolites of synthetic cannabinoids JWH-018 and JWH-073 bind with high affinity and act as potent agonists at cannabinoid type-2 receptors. *Toxicol Appl Pharmacol*. 2013 Jun 1;269(2):100-8.
- [32] Chimalakonda KC, James LP, Radominska-Pandya A, Moran JH. Sulfaphenazole and  $\alpha$ -naphthoflavone attenuate the metabolism of the synthetic cannabinoids JWH-018 and AM2201 found in K2/spice. *Drug Metab Lett*. 2013 Mar;7(1):34-8.
- [33] Bileck A, Ferik F, Al-Serori H, Koller VJ, Muqaku B, Haslberger A, Auwärter V, Gerner C, Knasmüller S. Impact of a synthetic cannabinoid (CP-47,497-C8) on protein expression in human cells: evidence for induction of inflammation and DNA damage. *Arch Toxicol*. 2016 Jun;90(6):1369-82.
- [34] Carvalho AF, Reyes BA, Ramalhosa F, Sousa N, Van Bockstaele EJ. Repeated administration of a synthetic cannabinoid receptor agonist differentially affects cortical and accumbal neuronal morphology in adolescent and adult rats. *Brain Struct Funct*. 2016 Jan;221(1):407-19.
- [35] Cha HJ, Seong YH, Song MJ, Jeong HS, Shin J, Yun J, Han K, Kim YH, Kang H, Kim HS. Neurotoxicity of Synthetic Cannabinoids JWH-081 and JWH-210. *Biomol Ther (Seoul)*. 2015 Nov;23(6):597-603. doi: 10.4062/biomolther.2015.057.
- [36] Costain WJ, Tauskela JS, Rasquinha I, Comas T, Hewitt M, Marleau V, Soo EC. Pharmacological characterization of emerging synthetic cannabinoids in HEK293T cells and hippocampal neurons. *Eur J Pharmacol*. 2016 Sep 5;786:234-45.
- [37] Tauskela JS, Comas T, Hewitt M, Aylsworth A, Zhao X, Martina M, Costain WJ. Effect of synthetic cannabinoids on spontaneous neuronal activity: Evaluation using Ca(2+) spiking and multi-electrode arrays. *Eur J Pharmacol*. 2016 Sep 5;786:148-60.
- [38] Couceiro J, Bandarra S, Sultan H, Bell S, Constantino S, Quintas A. Toxicological impact of JWH-018 and its phase I metabolite N-(3-hydroxypentyl) on human cell lines. *Forensic Sci Int*. 2016 Jul;264:100-5.
- [39] Tomiyama K, Funada M. Cytotoxicity of synthetic cannabinoids on primary neuronal cells of the forebrain: the involvement of cannabinoid CB1 receptors and apoptotic cell death. *Toxicol Appl Pharmacol*. 2014 Jan 1;274(1):17-23.

- [40] Ferk F, Gminski R, Al-Serori H, Mišík M, Nersesyan A, Koller VJ, Angerer V, Auwärter V, Tang T, Arif AT, Knasmüller S. Genotoxic properties of XLR-11, a widely consumed synthetic cannabinoid, and of the benzoyl indole RCS-4. *Arch Toxicol.* 2016 Feb 8.
- [41] Koller VJ, Auwärter V, Grummt T, Moosmann B, Mišík M, Knasmüller S. Investigation of the in vitro toxicological properties of the synthetic cannabimimetic drug CP-47,497-C8. *Toxicol Appl Pharmacol.* 2014 Jun 1;277(2):164-71.
- [42] Hsin-Hung Chen M, Dip A, Ahmed M, Tan ML, Walterscheid JP, Sun H, Teng BB, Mozayani A. Detection and Characterization of the Effect of AB-FUBINACA and Its Metabolites in a Rat Model. *J Cell Biochem.* 2016 Apr;117(4):1033-43.
- [43] Koller VJ, Ferk F, Al-Serori H, Mišík M, Nersesyan A, Auwärter V, Grummt T, Knasmüller S. Genotoxic properties of representatives of alkylindazoles and aminoalkyl-indoles which are consumed as synthetic cannabinoids. *Food Chem Toxicol.* 2015 Jun;80:130-6.
- [44] Koller VJ, Zlabinger GJ, Auwärter V, Fuchs S, Knasmueller S. Toxicological profiles of selected synthetic cannabinoids showing high binding affinities to the cannabinoid receptor subtype CB<sub>1</sub>. *Arch Toxicol.* 2013 Jul;87(7):1287-97.
- [45] Lewis SE, Paro R, Borriello L, Simon L, Robinson L, Dincer Z, Riedel G, Battista N, Maccarrone M. Long-term use of HU210 adversely affects spermatogenesis in rats by modulating the endocannabinoid system. *Int J Androl.* 2012 Oct;35(5):731-40.
- [46] Gatch MB, Forster MJ. Δ9-Tetrahydrocannabinol-like discriminative stimulus effects of compounds commonly found in K2/Spice. *Behav Pharmacol.* 2014 Dec;25(8):750-7.
- [47] Grim TW, Wiebelhaus JM, Morales AJ, Negus SS2, Lichtman AH. Effects of acute and repeated dosing of the synthetic cannabinoid CP55,940 on intracranial self-stimulation in mice. *Drug Alcohol Depend.* 2015 May 1;150:31-7.
- [48] Cha HJ, Lee K-W, Song M-J, et al. Dependence Potential of the Synthetic Cannabinoids JWH-073, JWH-081, and JWH-210: In Vivo and In Vitro Approaches. *Biomolecules & Therapeutics.* 2014;22(4):363-369.
- [49] Tai S, Hyatt WS, Gu C, Franks LN, Vasiljevik T, Brents LK, Prather PL, Fantegrossi WE. Repeated administration of phytocannabinoid Δ(9)-THC or synthetic cannabinoids JWH-018 and JWH-073 induces tolerance to hypothermia but not locomotor suppression in mice, and reduces CB<sub>1</sub> receptor expression and function in a brain region-specific manner. *Pharmacol Res.* 2015 Dec;102:22-32.
- [50] Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol.* 2011 Aug;163(7):1344-64.
- [51] Lewin AH, Seltzman HH, Carroll FI, Mascarella SW, Reddy PA. Emergence and properties of spice and bath salts: a medicinal chemistry perspective. *Life Sci.* 2014 Feb 27;97(1):9-19.

- [52] Halberstadt AL, Geyer MA. Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens. *Neuropharmacology*. 2011 Sep;61(3):364–81.
- [53] Yip L, Dart RC. Is there something more about synthetic cannabinoids? *Forensic Toxicol*. 2014 Jan 28;32(2):340–1.
- [54] Wells DL, Ott CA. The ‘new’ marijuana. *Ann Pharmacother*. SAGE Publications; 2011 Mar 1;45(3):414–7.
- [55] Maguire DR, France CP. Interactions between cannabinoid receptor agonists and mu opioid receptor agonists in rhesus monkeys discriminating fentanyl. *Eur J Pharmacol*. 2016;784:199-206.
- [56] Barbieri M, Ossato A, Canazza I, Trapella C, Borelli AC, Beggiato S, Rimondo C, Serpelloni G, Ferraro L, Marti M. Synthetic cannabinoid JWH-018 and its halogenated derivatives JWH-018-Cl and JWH-018-Br impair Novel Object Recognition in mice: Behavioral, electrophysiological and neurochemical evidence. *Neuropharmacology*. 2016 Oct;109:254-69.
- [57] Botanas CJ, de la Peña JB, Dela Pena IJ, Tampus R, Kim HJ, Yoon SS, Seo J, Jeong EJ, Cheong JH. Evaluation of the abuse potential of AM281, a new synthetic cannabinoid CB1 receptor antagonist. *Eur J Pharmacol*. 2015 Nov 5;766:135-41.
- [58] Cannizzaro C, Malta G, Argo A, Brancato A, Roda G, Casagni E, Fumagalli L Valoti E, Froidi R, Procaccianti P, Gambaro V. Behavioural and pharmacological characterization of a novel cannabinomimetic adamantane-derived indole, APICA, and considerations on the possible misuse as a psychotropic spice abuse, in C57bl/6J mice. *Forensic Sci Int*. 2016 Aug;265:6-12.
- [59] Abdulrahim D, Bowden-Jones O. Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances. 2015. 335 p.
- [60] Brents LK, Zimmerman SM, Saffell AR, Prather PL, Fantegrossi WE. Differential drug-drug interactions of the synthetic Cannabinoids JWH-018 and JWH-073: implications for drug abuse liability and pain therapy. *J Pharmacol Exp Ther*. 2013 Sep;346(3):350-61.
- [61] Fantegrossi WE, Moran JH, Radominska-Pandya A, Prather PL. Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to  $\Delta(9)$ -THC: mechanism underlying greater toxicity? *Life Sci*. 2014 Feb 27;97(1):45–54.
- [62] Ismail FMD. Important fluorinated drugs in experimental and clinical use. *J Fluor Chem*. 2002 Dec;118(1–2):27–33.
- [63] Wilkinson SM, Banister SD, Kassiou M. Bioisosteric Fluorine in the Clandestine Design of Synthetic Cannabinoids. *Aust J Chem*. 2015;68(1):4–8.
- [64] Canazza I, Ossato A, Trapella C, Fantinati A, De Luca MA, Margiani G, Vincenzi F, Rimondo C, Di Rosa F, Gregori A, Varani K, Borea PA, Serpelloni G, Marti M. Effect of the novel synthetic cannabinoids AKB48 and 5F-AKB48 on tetrad, sensorimotor, neurological and neurochemical responses in mice. In vitro and in vivo pharmacological studies. *Psychopharmacology (Berl)*. 2016 Oct;233(21-22):3685-3709.

- [65] Bell S, Nida C. Pyrolysis of drugs of abuse: A comprehensive review. *Drug Test Anal.* 2015;(November 2014).
- [66] Fattore L. Synthetic cannabinoids – further evidence supporting the relationship between cannabinoids and psychosis. *Biol Psychiatry.* Elsevier; 2016.
- [67] Baggaley K. Corrupt chemists tweak compounds faster than law enforcement can call them illegal. *Sci News.* 2015;187(10):22–5.
- [68] Papanti D, Schifano F, Botteon G, Bertossi F, Mannix J, Vidoni D, et al. ‘Spiceophrenia’: a systematic overview of ‘spice’-related psychopathological issues and a case report. *Hum Psychopharmacol.* 2013 Jul;28(4):379–89.
- [69] Santacroce R, Corazza O, Martinotti G, Bersani FS, Valeriani G, Di Giannantonio M. Psyclones: a roller coaster of life? Hidden synthetic cannabinoids and stimulants in apparently harmless products. *Hum Psychopharmacol Clin Exp.* 2015;30(4):265–71.
- [70] Bassir Nia A, Medrano B, Perkel C, Galynker I, Hurd YL. Psychiatric comorbidity associated with synthetic cannabinoid use compared to cannabis. *J Psychopharmacol.* 2016 Jul 26.
- [71] Spaderna M, Addy PH, D’Souza DC. Spicing things up: Synthetic cannabinoids. *Psychopharmacology (Berl).* 2013;228(4):525–40.
- [72] Winstock AR, Barratt MJ. Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample. *Drug Alcohol Depend.* 2013 Jul 1;131(1–2):106–11.
- [73] Wessinger WD, Moran JH, Seely KA. Synthetic Cannabinoid Effects on Behavior and Motivation. In: Campolongo P, Fattore L, editors. *Cannabinoid Modulation of Emotion, Memory, and Motivation.* New York: Springer; 2015. p. 205–24.
- [74] Soussan C, Kjellgren A. The flip side of ‘Spice’: The adverse effects of synthetic cannabinoids as discussed on a Swedish Internet forum. *NAD Nord Stud Alcohol Drugs.* 2014;31(2):207–19.
- [75] Kjellgren A, Henningsson H, Soussan C. Fascination and Social Togetherness—Discussions about Spice Smoking on a Swedish Internet Forum. *Substance Abuse Res Treat.* 2013;7:191–8.
- [76] Bilgredi OR. From ‘herbal highs’ to the ‘heroin of cannabis’: Exploring the evolving discourse on synthetic cannabinoid use in a Norwegian Internet drug forum. *Int J Drug Policy.* Elsevier B.V.; 2016.
- [77] Hermanns-Clausen M, Kneisel S, Szabo B, Auwärter V. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. *Addiction.* 2013 Mar;108(3):534–44.



- [78] Winstock A, Lynskey M, Borschmann R, Waldron J. Risk of emergency medical treatment following consumption of cannabis or synthetic cannabinoids in a large global sample. *J Psychopharmacol*. 2015;29(6):698–703.
- [79] Zaurova M, Hoffman RS, Vlahov D, Manini AF. Clinical Effects of Synthetic Cannabinoid Receptor Agonists Compared with Marijuana in Emergency Department Patients with Acute Drug Overdose. *J Med Toxicol*. 2016 Jun 2.
- [80] Schifano F, Deluca P, Agosti L, Martinotti G, Corkery JM, Alex B, Caterina B, Heikki B, Raffaella B, Anna C, Lucia DF, Dorte DR, Magi F, Susana F, Irene F, Claude G, Lisbet H, Lene SJ, Mauro L, Christopher L, Aino M, Teuvo P, Milena P, Salman R, Damien R, Angela RM, Francesco R, Norbert S, Holger S, Josep T, Marta T, Francesco Z; Psychonaut 2002 Research Group.. New trends in the cyber and street market of recreational drugs? The case of 2C-T-7 ('Blue Mystic'). *J Psychopharmacol*. 2005 Nov;19(6):675-9.
- [81] Wood DM, Dargan PI. Novel psychoactive substances: how to understand the acute toxicity associated with the use of these substances. *Ther Drug Monit*. 2012;34(4):363–7.
- [82] Naviglio S, Papanti D, Moressa V, Ventura A. An adolescent with an altered state of mind. *BMJ*. 2015;350(jan21\_1):h299.
- [83] Waugh J, Najafi J, Hawkins L, Hill SL, Eddleston M, Vale JA, Thompson JP, Thomas SH. Epidemiology and clinical features of toxicity following recreational use of synthetic cannabinoid receptor agonists: a report from the United Kingdom National Poisons Information Service. *Clin Toxicol (Phila)*. 2016 Jul;54(6):512-8.
- [84] Katz, K. D., Leonetti, A. L., Bailey, B. C., Surmaitis, R. M., Eustice, E. R., Kacinko, S., & Wheatley, S. M. (2016). Case series of synthetic cannabinoid intoxication from one toxicology center. *Western Journal of Emergency Medicine*, 17(3), 290-294.
- [85] Louh IK, Freeman WD. A 'spicy' encephalopathy: synthetic cannabinoids as cause of encephalopathy and seizure. *Crit Care*. 2014 Jan;18(5):553.
- [86] Freeman MJ, Rose DZ, Myers MA, Gooch CL, Bozeman AC, Burgin WS. Ischemic stroke after use of the synthetic marijuana 'spice'. *Neurology*. 2013 Dec 10;81(24):2090–3.
- [87] Rose DZ, Guerrero WR, Mokin M V, Gooch CL, Bozeman AC, Pearson JM, et al. Hemorrhagic stroke following use of the synthetic marijuana 'spice'. *Neurology*. 2015 Sep 29;85(13):1177–9.
- [88] Hopkins CY, Gilchrist BL. A case of cannabinoid hyperemesis syndrome caused by synthetic cannabinoids. *J Emerg Med*. 2013 Oct;45(4):544–6.
- [89] Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. *Pediatrics*. 2011 Dec;128(6):e1622-7.
- [90] Centers for Disease Control and Prevention (CDC). Acute kidney injury associated with synthetic cannabinoid use--multiple states, 2012. *MMWR Morb Mortal Wkly Rep*. 2013 Feb

15;62(6):93–8.

- [91] Aydin Sunbul E, Sunbul M, Terzi A, Calli S, Koca E, Bilici R, Citak S. The Effect of Synthetic Cannabinoids on P-Wave Dispersion: An Observational Study. *Med Princ Pract*. 2016;25(5):483-7.
- [92] Hermanns -Clausen M, Kneisel S., Szabo B, Auwärter V Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. *Addiction*, 2013 Mar; 108 (3):534-44
- [93] Takematsu M, Hoffman RS, Nelson LS, Schechter JM, Moran JH, Wiener SW A case of acute cerebral ischemia following inhalation of synthetic cannabinoid *Clin Toxicol (Phila)* 2014 Nov; 52(9):973-5
- [94] Ergül, D. F., Ekemen, S., & Yelken, B. B. (2015). Synthetic cannabinoid 'bonzai' intoxication: Six case series. *Turk Anesteziyoloji Ve Reanimasyon Dernegi Dergisi*, 43(5), 347-351.
- [95] Epub 2016 Jun 10., Durand D, Delgado LL, de la Parra-Pellot DM, Nichols-Vinueza D Psychosis and severe rhabdomyolysis associated with synthetic cannabinoid use: a case report. *Clin Schizophr Relat Psychoses* 2015 Jan; 8(4):205-8
- [96] Kazory A, Aiyer R. Synthetic marijuana and acute kidney injury: an unforeseen association. *Clin Kidney J*. 2013 Jun;6(3):330-3.
- [97] Khan, M., Pace, L., Truong, A., Gordon, M., & Moukaddam, N. (2016). Catatonia secondary to synthetic cannabinoid use in two patients with no previous psychosis. *American Journal on Addictions*, 25(1), 25-27. doi:10.1111/ajad.12318
- [98] McQuade D, Hudson S, Dargan PI, Wood DM. First European case of convulsions related to analytically confirmed use of the synthetic cannabinoid receptor agonist AM-2201. *Eur J Clin Pharmacol*. 2013 Mar;69(3):373-6.
- [99] Sherpa D, Paudel BM, Subedi BH, Chow RD. Synthetic cannabinoids: the multi-organ failure and metabolic derangements associated with getting high. *J Community Hosp Intern Med Perspect*. 2015 Sep 1;5(4):27540.
- [100] Fellner A, Benninger F, Djaldetti R. Synthetic cannabinoids revealing adrenoleukodystrophy. *J Clin Neurosci*. 2016 Feb;24:155-6.
- [101] Nurmedov S, Metin B, Ekmen S, Noyan O, Yilmaz O, Darcin A, Dilbaz N. Thalamic and Cerebellar Gray Matter Volume Reduction in Synthetic Cannabinoids Users. *Eur Addict Res*. 2015;21(6):315-20.
- [102] Zorlu N, Angelique Di Biase M, Kalayci 33, Zalesky A, Bagci B, Oguz N, Gelal F, Besiroglu L, Gölseren S, Sarizizek A, Bora E, Pantelis C. Abnormal white matter integrity in synthetic cannabinoid users. *Eur Neuropsychopharmacol*. 2016 Sep 8. pii: S0924-977X(16)30178-X.

- [103] Berry-Caban CS, Ee J, Ingram V, Berry CE, Kim EH. Synthetic cannabinoid overdose in a 20-year-old male US soldier. *Subst Abus.* 2013;34(1):70–2.
- [104] Trecki J, Gerona RR, Schwartz MD. Synthetic Cannabinoid–Related Illnesses and Deaths. *N Engl J Med.* 2015 Jul 9;373(2):103–7.
- [105] Kasper AM, Ridpath AD, Arnold JK, Chatham-Stephens K, Morrison M, Olayinka O, et al. Severe Illness Associated with Reported Use of Synthetic Cannabinoids - Mississippi, April 2015. *MMWR Morb Mortal Wkly Rep.* 2015;64(39):1121–2.
- [106] Tyndall JA, Gerona R, De Portu G, Trecki J, Elie MC, Lucas J, Slish J, Rand K, Bazydlo L, Holder M, Ryan MF, Myers P, Iovine N, Plourde M, Weeks E, Hanley JR, Endres G, St Germaine D, Dobrowolski PJ, Schwartz M. An outbreak of acute delirium from exposure to the synthetic cannabinoid AB-CHMINACA. *Clin Toxicol (Phila).* 2015;53(10):950–6.
- [107] Schwartz MD, Trecki J, Edison LA, Steck AR, Arnold JK, Gerona RR. A Common Source Outbreak of Severe Delirium Associated with Exposure to the Novel Synthetic Cannabinoid ADB-PINACA. *J Emerg Med.* 2015 May;48(5):573–80.
- [108] Vilke GM, Debard ML, Chan TC, Ho JD, Dawes DM, Hall C, et al. Excited delirium syndrome (ExDS): Defining based on a review of the Literature. *J Emerg Med.* Elsevier Ltd; 2012;43(5):897–905.
- [109] Lank PM, Pines E, Mycyk MB. Emergency Physicians' Knowledge of Cannabinoid Designer Drugs. *West J Emerg Med.* 2013;14(5):467–70.
- [110] Shanks KG, Dahn T, Terrell AR. Detection of JWH-018 and JWH-073 by UPLC-MS-MS in post-mortem whole blood casework. *J Anal Toxicol.* 2012 Apr 1;36(3):145–52.
- [111] Saito T, Namera A, Miura N, Ohta S, Miyazaki S, Osawa M, et al. A fatal case of MAM-2201 poisoning. *Forensic Toxicol.* 2013 May 5;31(2):333–7.
- [112] Kronstrand R, Roman M, Andersson M, Eklund A. Toxicological findings of synthetic cannabinoids in recreational users. *J Anal Toxicol.* 2013 Oct;37(8):534–41.
- [113] Schaefer N, Peters B, Bregel D, Kneisel S, Schmidt PH, Ewald AH. A fatal case involving several synthetic cannabinoids. *Toxichem Krimtech.* 2013;80:248–51.
- [114] Corkery J, Claridge H, Loi B, Goodair C, Schifano F, Deaths SA. Drug-related deaths in the UK : 2012 Annual Report 2013 National Programme on Substance Abuse Deaths Annual Report 2013 on deaths between. 2013.
- [115] Wikström M, Thelander G, Dahlgren M, Kronstrand R. An accidental fatal intoxication with methoxetamine. *J Anal Toxicol.* 2013 Jan 1;37(1):43–6.
- [116] Calabria B, Degenhardt L, Hall W, Lynskey M. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug Alcohol Rev.* 2010 May;29(3):318–30.

- [117] Gunderson EW, Haughey HM, Ait-Daoud N, Joshi AS, Hart CL. 'Spice' and 'k2' herbal highs: A case series and systematic review of the clinical effects and biopsychosocial implications of synthetic cannabinoid use in humans. *Am J Addict*. 2012;21(4):320–6.
- [118] Vandrey R, Dunn KE, Fry JA, Girling ER. A survey study to characterize use of Spice products (synthetic cannabinoids). *Drug Alcohol Depend*. Elsevier; 2012 Jan 1;120(1–3):238–41.
- [119] Nacca N, Vatti D, Sullivan R, Sud P, Su M, Marraffa J. The synthetic cannabinoid withdrawal syndrome. *J Addict Med*. Jan;7(4):296–8.
- [120] Zimmermann US, Winkelmann PR, Pilhatsch M, Nees JA, Spanagel R, Schulz K. Withdrawal phenomena and dependence syndrome after the consumption of 'spice gold'. *Dtsch Ärzteblatt Int*. 2009 Jul;106(27):464–7.
- [121] Rominger A, Cumming P, Xiong G, Koller G, Förster S, Zwergal A, et al. Effects of acute detoxification of the herbal blend 'Spice Gold' on dopamine D2/3 receptor availability: a [<sup>18</sup>F]fallypride PET study. *Eur Neuropsychopharmacol*. Elsevier; 2013 Nov 1;23(11):1606–10.
- [122] Macfarlane V, Christie G. Synthetic cannabinoid withdrawal: a new demand on detoxification services. *Drug Alcohol Rev*. 2015 Mar;34(2):147–53.
- [123] Sampson CB, Bedy SM, Carlisle T Withdrawal seizures seen in the settings of synthetic cannabinoid abuse. *Am J Emerg Med*. 2015 Nov; 33(11);1712. e3].
- [124] Palamar JJ, Acosta P. Synthetic cannabinoid use in a nationally representative sample of US high school seniors. *Drug and alcohol dependence*. 2015 Apr 1;149:194-202.
- [125] Forrester MB, Kleinschmidt K, Schwarz E, Young A. Synthetic cannabinoid and marijuana exposures reported to poison centers. *Hum Exp Toxicol*. 2012 Oct;31(10):1006–11.
- [126] Besli GE, Ikiz MA, Yildirim S, Saltik S. Synthetic cannabinoid abuse in adolescents: a case series. *The Journal of emergency medicine*. 2015 Nov 30;49(5):644-50.
- [127] Martinotti G, Di Nicola M, Quattrone D, Santacroce R, Schifano F, Murray R, Di Giannantonio M. Novel psychoactive substances and induced phenomena in psychopathology: the lysergic psychoma. *Journal of Psychopathology* 2015;21:400-405
- [128] Martinotti G, Ferro F. The exogenous model of induced psychotic experience in addiction. *Research and Advances in Psychiatry* 2015 Vol. 2 (N. 2) April-June
- 
- [129] Vearrier D, Osterhoudt KC. A teenager with agitation: higher than she should have climbed. *Pediatr Emerg Care*. 2010;26(6):462–5.
- [130] Hurst D, Loeffler G, McLay R. Psychosis associated with synthetic cannabinoid agonists: A case series. *Am J Psychiatry*. 2011;168(10):1119.

- [131] Bebarta VS, Ramirez S, Varney SM. Spice: A New ' Legal ' Herbal Mixture Abused by Young Active Duty Military Personnel. *Subst Abus.* 2012;33(July 2013):191-4.
- [132] Peglow S, Buchner J, Briscoe G. Synthetic cannabinoid induced psychosis in a previously nonpsychotic patient. *Am J Addict.* 2012;21(3):287-8.
- [133] Benford DM, Caplan JP. Psychiatric sequelae of Spice, K2, and synthetic cannabinoid receptor agonists. *Psychosomatics.* Jan;52(3):295.
- [134] Van Der Veer N, Friday J. Persistent psychosis following the use of Spice. *Schizophr Res.* Elsevier B.V.; 2011;130(1-3):285-6.
- [135] Müller H, Sperling W, Köhrmann M, Huttner HB, Kornhuber J, Maler JM. The synthetic cannabinoid Spice as a trigger for an acute exacerbation of cannabis induced recurrent psychotic episodes. *Schizophr Res.* 2010;118(1-3):309-10.
- [136] Every-Palmer S. Synthetic cannabinoid JWH-018 and psychosis: An explorative study. *Drug Alcohol Depend.* Elsevier Ireland Ltd; 2011;117(2-3):152-7.
- [137] Tung CK, Chiang TP, Lam M. Acute mental disturbance caused by synthetic cannabinoid: A potential emerging substance of abuse in Hong Kong. *East Asian Arch Psychiatry.* 2012;22(1):31-3.
- [138] Radhakrishnan R, Addy PH, Sewell RA, Skosnik PD, Ranganathan M, D'Souza DC. Cannabis, cannabinoids, and the association with psychosis. In *The Effects of Drug Abuse on the Human Nervous System* 2013 Nov 15. Academic Press, New York.
- [139] Wilkinson ST, Radhakrishnan R, D'Souza DC. Impact of cannabis use on the development of psychotic disorders. *Current addiction reports.* 2014 Jun 1;1(2):115-28.
- [140] Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to pot—a review of the association between cannabis and psychosis. *Clearing the smokescreen: The current evidence on cannabis use.* 2015 May 8:40.
- [141] Altintas M, Inanc L, Oruc GA, Arpacioğlu S, Gulec H. Clinical characteristics of synthetic cannabinoid-induced psychosis in relation to schizophrenia: a single-center cross-sectional analysis of concurrently hospitalized patients. *Neuropsychiatric Disease and Treatment.* 2016;12:1893.
- [142] Brakoulias V. Products containing synthetic cannabinoids and psychosis. *Aust N Z J Psychiatry.* 2012 Mar;46(3):281-2.
- [143] Shoval G. CLINICAL CHARACTERISTICS OF HOSPITALIZED SYNTHETIC CANNABINOID USERS. IV International Congress of Dual Disorders. 2015. p. 38.
- [144] Glue P, Al-Shaqsi S, Hancock D, Gale C, Strong B, Schep L. Hospitalisation associated with use of the synthetic cannabinoid K2. *N Z Med J.* 2013 Jun 28;126(1377):18-23.

- [145] Rosenbaum CD, Carreiro SP, Babu KM. Here today, gone tomorrow...and back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), kratom, *Salvia divinorum*, methoxetamine, and piperazines. *J Med Toxicol*. 2012 Mar;8(1):15–32.
- [146] Patton AL, Chimalakonda KC, Moran CL, McCain KR, Radomska-Pandya A, James LP, et al. K2 toxicity: fatal case of psychiatric complications following AM2201 exposure. *J Forensic Sci*. 2013 Nov;58(6):1676–80.
- [147] Lászik A, Törő K, Vannai M, Sára-Klausz G, Kócs T, Farkas R, et al. Self inflicted fatal injuries in association with synthetic cannabinoid abuse. 24th International Meeting on Forensic Medicine Alpe-Adria-Pannonia. 2015. p. 27.
- [148] Trecki J, Gerona RR, Schwartz MD. Synthetic cannabinoid-related illnesses and deaths. *N Engl J Med*. 2015 Jul 9;373(2):103-7.
- [149] Shanks KG, Winston D, Heidingsfelder J, Behonick G. Case reports of synthetic cannabinoid XLR-11 associated fatalities. *Forensic science international*. 2015 Jul 31;252:e6-9.
- [150] Shanks KG, Clark W, Behonick G. Death associated with the use of the synthetic cannabinoid ADB-FUBINACA. *Journal of analytical toxicology*. 2016 Jan 10:bkv142.
- [151] Shanks KG, Behonick GS. Death after use of the synthetic cannabinoid 5F-AMB. *Forensic science international*. 2016 May 31;262:e21-4.
- [152] Behonick G, Shanks KG, Firchau DJ, Mathur G, Lynch CF, Nashelsky M, Jaskierny DJ, Meroueh C. Four postmortem case reports with quantitative detection of the synthetic cannabinoid, 5F-PB-22. *Journal of analytical toxicology*. 2014 May 29:bku048.
- [153] Hasegawa K, Wurita A, Minakata K, Gonmori K, Nozawa H, Yamagishi I, Watanabe K, Suzuki O. Postmortem distribution of MAB-CHMINACA in body fluids and solid tissues of a human cadaver. *Forensic toxicology*. 2015 Jul 1;33(2):380-7.
- [154] Hess C, Stockhausen S, Kernbach-Wighton G, Madea B. Death due to diabetic ketoacidosis: Induction by the consumption of synthetic cannabinoids?. *Forensic Science International*. 2015 Dec 31;257:e6-11.
- [155] Adamowicz P. Fatal intoxication with synthetic cannabinoid MDMB-CHMICA. *Forensic science international*. 2016 Apr 30;261:e5-10.
- [156] Drug Enforcement Administration. Schedules of controlled substances: temporary placement of three synthetic cannabinoids into Schedule I. Final order. *Federal Register*, 80 (2015), pp. 5042–5047
- [157] Lemos NP. Driving Under the Influence of Synthetic Cannabinoid Receptor Agonist XLR-11. *Journal of forensic sciences*. 2014 Nov 1;59(6):1679-83.

- [158] Peterson BL, Couper FJ. Concentrations of AB-CHMINACA and AB-PINACA and driving behavior in suspected impaired driving cases. *Journal of analytical toxicology*. 2015 Oct 1;39(8):642-7.
- [159] Thornton SL, Akpunonu P, Glauner K, Hoehn KS, Gerona R. Unintentional pediatric exposure to a synthetic cannabinoid (AB-PINACA) resulting in coma and intubation. *Annals of emergency medicine*. 2015 Sep 1;66(3):343-4.