Synthetic Cannabinoids: psychopharmacology, clinical aspects, and psychotic onset

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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 tetrahydocannabivarin [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 μ-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 brainstream [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-FUBINACA	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 wih 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.

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