Uses, effects and toxicity of synthetic cannabinoids from the perspective of people with lived experiences

Sulaf Assi[1]*, Danielle Marshall[2], Francesco Saverio Bersani[3], and Ornella Corazza[4]

[1] Pharmacy and Bimolecular Science, Liverpool John Moores University, Liverpool, United Kingdom

[2] Faculty of Science and Technology, Bournemouth University, Poole, United Kingdom

[3] Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy

[4] School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom

Correspondence author details:

Dr Sulaf Assi

Senior lecturer in Analytical Chemistry

Pharmacy and Bimolecular Sciences

Liverpool John Moores University, Liverpool

L3 3AF, UK

Email: s.assi@ljmu.ac.uk

ABSTRACT

Introduction: Synthetic cannabinoids (SCs) are a class of synthetic chemicals with cannabis-like properties, and little is known about their pharmacological and toxicological effects. This objective of this study was to explore the effects of SCs and the underlying motivations of use among subjects with lived experiences. **Methods:** Content analysis of experiences of people using SCs was carried out based on online discussions. A total of 1660 posts from 50 threads between 2004 and 2016 were examined. **Results:** Relevant information was recorded on characteristics of users as well as on characteristics of SCs, the modality of their use, and the SC-related experienced effects and toxicity. **Conclusions:** Users exchanged online significant information on SCs consumption. While a growing amount of attention has been given to the chemical and pharmacological profile of SCs, very little is known about the subjective components of such use. It remains fundamental to study the lived experiences of people who used novel psychoactive substances (NPSs) to implement prevention and treatment, and to guide future research in the field.

Keywords: Synthetic Cannabinoids; Internet Fora; Toxicity; Addiction; Novel Psychoactive Substances.

1. INTRODUCTION

Synthetic cannabinoids (SCs) are a class of novel psychoactive substances (NPSs) that have similar effects to cannabis despite having a different structure from Δ^9-tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis (Elsohly et al. 2014; Schifano et al. 2019; Tung, Chiang & Lam 2012). SCs are often available as single or multiple synthetic substances sprayed onto herbal material or plants (Wells & Ott 2011). The drugs are usually marketed under various names relating to 'herbal incense' or 'plant food' (Gunderson et al. 2012; Winstock & Barratt 2013). Reasons for taking SCs include curiosity, relaxation, change in perception, mood and cognition, the possibility to avoid drug tests, and their legal status (Castellanos et al. 2011; Vandrey et al. 2012; Winstock & Barratt 2013).

Whereas THC is a partial CB1 receptor agonist, most SCs are full agonists of the CB1 receptor, and their effects are not limited by the dose response relationship (Papanti et al. 2013; Schifano et al. 2019). Subsequently, the increased affinity for CB1 receptors results in higher potency and greater adverse effects, including anxiety, agitation, drowsiness, hallucinations, hypertension, tachycardia, paranoia, poor coordination, respiratory depression and seizures (Adamowicz et al. 2017; Auwarter et al. 2009; Castaneto et al. 2014; Castellanos et al. 2011; Cooper 2016; Hermanns-Clausen et al. 2013; Papanti et al. 2013; Schneir, Cullen & Ly 2011; Zawilska & Wojcieszak 2014). SCs are associated with more adverse effects and increased emergency department admission than many other NPSs (Gummin et al. 2018; Spaderna, Addy & D'Souza 2013), and can have a negative impact on the treatment course for substance-related withdrawal and craving symptoms (Prilutskaya et al. 2017).

Despite the above concerns, there are limited studies regarding the effects and toxicity associated with SCs based on the perspective of people with lived experiences. Moreover, most of the information available regarding the effects of SCs arises from admissions to emergency departments or treatment centres, likely resulting in incomplete data. Therefore, this work aims to explore the effects and toxicity of SCs from the perspective of users.

2. METHODS

A qualitative study of online discussion fora was conducted to explore users' knowledge and experience of the effects and toxicity of SCs. Data were retrieved from five key discussion fora that had been previously identified by the Psychonaut Web Mapping Project (Deluca et al. 2012). After inspecting each discussion forum thoroughly, 128,000 threads were retrieved of which 50 threads (1660 posts) were found relevant to the objectives of the study. Hence, a thread was made of multiple posts whereas each post comprised a single entry in a thread. All of the included threads were in English.

The study was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethical approval was obtained from the Bournemouth University Internal Ethics Committee (ID 20840). Although the information collected in this study was already available in the public domain, anonymity was ensured in all online discussion by giving each thread a number and removing any users' data that could hint identities/nicknames. No posts or contribution to the discussion fora were made, and no data were shared outside the remits of the study.

Threads were saved as PDFs and subjected to conventional content analysis (Bilgrei 2016; Kassai et al. 2017; Soussan & Kjellgren 2014). Data in threads were initially coded independently by two investigators to minimise bias. The threads were then read carefully, line-by-line, and subthemes/themes reflecting key concepts were identified. After the threads were coded, investigators met to discuss any discrepancies among codes, to cluster codes into themes, and to discuss potential relationships among the constituted categories. Five broad themes were obtained: characteristics of users, characteristics of SCs, use of SCs, wanted effects related to SCs, and toxicity/adverse effects related to SCs. The inter-rater reliability of the themes was appraised by postulating the threads to a third researcher. Threads and codes were provided to the researcher without the themes. The inter-rater reliability for the final themes was 95%, which

suggested the validity of the coding methodology. To evaluate the quality of the threads a checklist made up of a series of questions was adapted from (Robinson 2001) (Appendix A). In addition, the information from the threads was validated by matching the interpretations with findings from clinical reviews regarding SCs (Forrester et al. 2012; Hoyte et al. 2012) that authenticated the truthfulness and accuracy of the findings.

3. RESULTS

As mentioned above, the analysis of online discussion fora related to SCs yielded 50 relevant threads with 1660 posts. These threads were combined into five main themes: characteristics of users, characteristics of SCs, use of SCs, wanted effects related to SCs, and toxicity/adverse effects related to SCs (Table 1).

3.1 Characteristics of users

Analysis of the threads identified 540 people with lived experiences of SCs from 36 different countries, with the majority of posts coming from the United States (n=296), the United Kingdom (n=88), Australia (n=58) and Canada (n=34). Only 68 of them reported their age, of which 65 were adult (between 18- and 64-years-old), and three were minors (n=2) or elderly (n=1). One-hundred-eleven (111) users reported their gender (97 males and 14 females).

The major reason for which users took SCs were: passing a drug test (n=51), unavailability of cannabis (n=20), cheaper price compared to cannabis (n=11), no legal consequences from taking SCs (n=6), and stronger effects of SCs with shorter half-life (n=3).

3.2 Characteristics of synthetic cannabinoids

A total of 81 different derivatives were reported from 1053 posts (Table 2). The reported derivatives belonged to seven different subclasses, among which indole and indazole-based SCs were the most common. Indole-based derivatives were the most frequently mentioned, with 46 derivatives reported 716 times. The main indole-based derivatives encountered were AM2201 (n=125), JWH018 (n=107) and UR144 (n=66). Also, 22 different indazole-based derivatives were reported 220 times. The most commonly mentioned indazole-based derivatives were 5F-AKB48 (n=63), AB-FUBINACA (n=42) and THJ018 (n=35). The frequency of the reports on the SC derivatives was not related to the time they have been on the market but was rather attributable to the unique subjective effects associated with the SC (Table 3).

Four-hundred-seventy-five users reported using 148 different blends of SCs. The most commonly mentioned blends were Spice, K2, Mr Kosh and Kronic (Table 4). Spice was the most prevalent blend and was used by 80 users; Spice was labelled as a mixture containing varying SCs, among which AM2201, CP47497, HU210, JWH derivatives, JWH018, JWH019, JWH073 and JWH122. K2 was used by 45 users; derivatives of JWH (including JWH018 and JWH073) were defined by some users as the main ingredients in K2. Mr Kosh and Kronic were used by 33 and 32 users respectively; the SC derivatives in Mr Kosh were not reported, while Kronic was stated to contain JWH or AM derivatives with JWH018 being the main ingredient. All the remaining blends were used by 10 users or less.

One-hundred-fifty-seven users reported the source they had purchased the drug from. The main sources were the Internet and street headshops, that were mentioned by 65 and 62 users respectively. Other sources for SCs were gas stations (n=10), off-license shops (n=6), adult shops (n=4), bookshops (n=2) and street markets (n=1).

3.3 Use of synthetic cannabinoids

Two main subthemes emerged in relation to SCs use: route of administration and polydrug use. The most widely used route of administration of SCs was smoking (n=540), followed by oral administration

(n=99). Additional routes encountered were sublingual (n=7), nasal insufflation (n=5), intravenous (n=3) and rectal (n=2). Details are given in Table 5.

Users experienced the combination of SCs with other drugs: antipsychotics, opioid analgesics, hallucinogens, stimulants and depressants. These combinations ranged from two to five substances; yet, the exact doses and effects of such combinations were note provided in detail. Users sought caffeine (n=2), tobacco (n=13), cannabis (n=4), unspecified NPSs (n=2) or other SCs (n=40) in order to intensify the psychedelic effects, increase the duration of effects or resist the urgency to re-dose. Only one antipsychotic combination was reported and involved mixing a SC (ABFUBINACA) with aripiprazole and chlorprothixene. Four users reported mixing SCs with opioids: one user did not specify the opioid and three reported codeine (with dextromethorphan in two cases). In addition to dextromethorphan, four other users combined SCs with psychedelics: 4-acetoxy-N,N-dimethyltryptamine, ketamine, methoxetamine and an unspecified psychedelic. Additional combinations of SCs included alcohol (n=17) or benzodiazepines (n=5), mainly in order to mask the SC effects, to counteract SC-induced panic attacks, and to increase depressant effects.

3.4 Wanted effects

Users mainly sought SCs to improve mood, escape reality or relax. The major psychological effects reported by users were psychedelic effects (n=93). The JWH series was considered the 'strongest for tripping', alongside 5FPB22, 5FABPINACA, ABPINACA, AM2201 and UR144. The choice of SCs was also influenced by the dose, route of administration and modality of intake of the drug (e.g. certain users recommended a dose above 5 mg to start the visual hallucinations, while other users recommended the combination of several SCs, among which 5AKB48 and STS135, in a smoking mixture to have a more intense tripping effect). The tripping effect was reported as equivalent to that induced by ketamine and phencyclidine derivatives.

Users were also interested in the relaxation (n=82) and sedative (n=23) effects induced by SCs. SCs were found to be more calming, healing and relaxing than natural cannabis. SC-related euphoria (n=38) was described as ‘extreme’, ‘pleasant’ and ‘surreal’. The duration of the euphoric effect varied markedly between 20 min and up to 6 h. Euaphoria was associated with uncontrollable intense laughter, which was reportedly associated with elevated mood (n=10), mental clarity (n=7) and music appreciation (n=10). Such effects on euphoria were reported to be more intense than those of cannabis.

SCs were considered by users as mood stabilisers, mood enhancers, antidepressants and/or as substances able to fill the room with happiness. SCs were reported to increase users’ alertness, creativity, insight and sociability. The duration of the effects varied between person but was generally described as short (3 min to 3 h). Most users experienced rapid effects, with an onset within 5 min; yet, some users did not see onset until 7 h.

3.5 Toxicity and adverse effects

Toxicity and adverse effects reported by users involved the nervous, cardiovascular, respiratory, gastrointestinal, hepatic and renal systems.

Nervous system adverse effects: SCs reportedly induced alteration in perception (n=82) and in behaviour (n=24), anxiety (n=147), paranoia (n=83), psychosis (n=22), depression (n=19), and addiction (n=92). This included dissociation, auditory, zooptic and visual hallucinations, tachyphagia, aggression, hyperactive thoughts, irritability, social withdrawal, and antisocial behaviour. In rare cases, users experienced psychopathological episodes related to schizophrenia and bipolar disorder after using SCs. When compared to cannabis, effects of SCs were described as shorter acting but more addictive. In extreme cases, loss of consciousness and passing out was seen among users. Users reported having frequent panic attacks and blackouts related to the use of SCs: some of them reportedly suffered convulsion prior to

blackouts, fell on the floor, tried to crawl, then eventually passed out and woke up with ‘face down in vomit’.

Cardiovascular adverse effects: The main cardiovascular adverse effects experienced by users were tachycardia (n=53), hypertension (n=5) and palpitations (n=6). Less reported cardiovascular adverse effects included cardiac irregularities, cardiac damage and cardiac arrest.

Respiratory adverse effects: Respiratory adverse effects included bronchitis (n=3; it was described as severe and comparable to lung cancer), chest pain (n=17; it included difficulty in breathing and it was associated with anxiety, shortness of breath, numbness and coughs), coughing (n=12; some users reported ‘bad coughs’ described as extreme and horrid, yielding black/dark mucus on many occasions.), dyspnoea (n=27) and respiratory irritation (n=15; it was described as chemical burns to lungs associated with throat burns and, in some instances, it was compared to a mustard attack).

Gastrointestinal adverse effects: Gastrointestinal adverse effects experienced by users included general gastrointestinal irritations, with abdominal pain, abdominal cramps, nausea, vomiting and diarrhoea. Gastrointestinal adverse effects were described as intense, strong and of long duration (up to seven days after smoking).

Hepatic and renal adverse effects: Users experienced hepatic and renal adverse effects that included liver damage (n=10; it was described as direct, extreme and painful), increased urination (n=3), and kidney damage (n=11; this was sometimes associated with pain lasted more than one week) that occasionally exacerbated to kidney failure (n=2) that could be lethal.

SCs-drug interactions: When SCs were mixed with other SCs, users experienced more intense tripping, anxiety, depression, psychosis and tachycardia. Effects encountered when SCs were mixed with opioids included tremors, tachycardia, respiratory disturbances and liver damage. One user warned against mixing SC with codeine and dextromethorphan as it resulted in drug-induced psychosis. Depressants were reported to counteract the panic attacks of SCs, yet users experienced negative effects after using depressants with SCs including nausea, vomiting, sweating and severely depressed breathing. Moreover,

mixing stimulants and depressants caused “couch lock”, “munchies” and dry mouth. Mixing SCs with psychedelics resulted in more intense effects, tripping, seizures and loss of consciousness.

Overdose: Overdose related to SCs use was reported by 63 users and involved multiple organ toxicity. The doses of individual SCs were not always specified but were stated to range between 1 and 300 mg. Main reactions included anxiety, difficulty in breathing, palpitations, paranoia, tachycardia, tremors and loss of motor control. Other symptoms seen as a result of overdose were tachycardia, palpitations, hypotension, vomiting and difficulty in breathing.

Withdrawal symptoms: Withdrawal symptoms experienced after stopping SCs included anxiety, sweating, insomnia, nausea, vomiting and diarrhoea.

4. DISCUSSION

Previous studies related to SCs have mainly relied on quantitative data from emergency department admission, psychiatric clinics or questionnaire surveys (Adamowicz et al. 2017; Gummin et al. 2018; Hermanns-Clausen et al. 2013; Higgins et al. 2019; Le Boisselier et al. 2017; Loeffler, Delaney & Hann 2016; Vandrey et al. 2012). There are only two qualitative studies that have explored the toxicity and harm reduction of such NPSs using online discussion fora (Kronstrand et al. 2013; Thayer & Ray 2006), which were limited to discussion fora of a single country (Sweden and Norway). Hence, the present study contributes to the literature through directly exploring the users’ experience and knowledge regarding the use, effects and toxicity of SCs via content analysis of online discussions among individuals from several different countries.

The specific results of the study are summarized in Tables 1-5. Several findings are consistent with previous evidence. The users of online discussion fora were mainly males, with a self-reported median age of 29-years-old. This was also found in observational studies conducted in psychiatric hospitals (Heltsley et al. 2012; Loeffler, Delaney & Hann 2016; Vandrey et al. 2012), and could be related to the fact that (i)

males have been described as more likely to use illicit drugs than females (Center for Behavioral Health Statistics and Quality 2017; European Monitoring Centre for Drugs and Drug Addiction 2019; Kikura-Hanajiri et al. 2013) and more prone to share their drug experience or seek treatment (European Monitoring Centre for Drugs and Drug Addiction 2005), and (ii) Internet use is higher among young adults than among middle-aged and older adults (Kikura-Hanajiri et al. 2013). The main motivation to take SCs for the online users was the possibility to get high while passing a drug test; such motivation for SC use was found to be relevant also in several previous reports, summarized by Loeffler et al (Loeffler, Delaney & Hann 2016). The most popular SCs among users were AM2201 and JWH018, which have been identified in previous reports as popular derivatives due to their psychedelic effects (Gunderson et al. 2012; McQuade et al. 2013).

The most commonly reported blends were Spice and K2, as also observed in other studies on the topic (Corazza et al. 2014; Kjellgren, Henningsson & Soussan 2013; Schneir, Cullen & Ly 2011). Consistently with previous research (Ashton et al. 2008; Pertwee 2006), the most common wanted effects experienced with SCs reported by users were euphoria, relaxation and psychedelic effects; these effects are mainly caused by activation of the CB1 receptors, which can result in increased or decreased release of monoamines (Auwarter et al. 2009; Banerjee, Snyder & Mechoulam 1975; Kendall & Yudowski 2016; Steffens & Feuerstein 2004; Szabo & Schlicker 2005). Analgesia was reported by several users after consuming the drug, and many clinical studies have focused on the use of SCs as analgesic agents (Ashton et al. 2008; Every-Palmer 2011; Fattore & Fratta 2011).

Users reported adverse effects associated with SCs in relation to multiple systems, including the psychiatric, cardiovascular, respiratory and gastrointestinal systems. Psychiatric effects included anxiety, paranoia, sedation, addiction, psychosis, aggression and depression. Psychotic relapses resulting from the use of SCs were identified in previous studies(Schifano et al. 2019); notably, Papanti et al. have coined the term “spiceophrenia” in order to highlight how SCs can trigger the onset of acute psychosis in vulnerable individuals and/or the exacerbation of psychotic episodes in those with a previous psychiatric history with

increased impact compared to natural cannabis (Papanti et al. 2013). The respiratory toxicity reported by users was characterised as difficulty breathing, chest pain and coughing, which is in line with previous findings (Cooper 2016; Küçük et al. 2016); surprisingly, in the present study users experienced respiratory adverse effects even after oral use of SCs, this possibly being related with redistribution of SCs to the lungs.

The present study has several limitations, among which: (i) as the research was retrospective, it was not always possible to attain all the desired information regarding drugs used, uses, doses and duration of action of SCs, and therefore the reported identity of derivatives was not confirmed my any other means; (ii) missing information from threads could influence the results; (iii) there was no method to verify the subjective experience of users; (iv) no biological validation (such as hair testing) was conducted. However, the use of Internet as a source of information can also be considered a strength, as Web monitoring represents a unique opportunity for understanding users' point of view about the effects of drugs: writing in a Web forum allows the user to hide his/her identity and to comment without any hesitation. This is particularly useful in the case of SCs, where there has been only a limited number of animal and human studies focused on adverse effects after the failure of clinical trials in the 1950s. The use of the Internet has been performed extensively in the research on addiction over the last decade (Corazza et al. 2013; Davey et al. 2012), and the present study provides data (summarized in Tables 1-5) based on users' personal experiences that contribute to increase our understanding of different aspects of the phenomenon of SC use.

It is difficult to evaluate whether the results of the study are representative to SC users in general or specific to those considered as "e-psychonauts", i.e. individuals highly connected to Web sources with high levels of general and pharmacological knowledge of substances (Davey et al. 2012). However, the present study provides information on SCs arising from individuals who experienced them, with this contributing to increase our understanding of the SC-use phenomenon. Lived experiences are important for the development of clinical guidance as well as for our research, and should be taken into consideration when addressing research, clinical and political interventions (e.g. harm reduction interventions) on substance-related issues. Future studies are encouraged which include analyses of SC-related effects correlating lived

experiences with other sources (such as data from toxicology and poison centres) in order to obtain a more detailed and reliable knowledge of the substances.

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Conflict of interest

None declared.

Table 1. Main themes and subthemes emerging from the study

Theme	Subtheme	Quotation
Characteristics of users	Passing a drug test	Many of “us” are subject to harsh and random drug testing, that doesn’t test for synthetics, as a condition of our employment.
	Unavailability of cannabis	I tried a few times with a friend from high school when we couldn't get a decent dealer for weed

	Price	Availability and Price would be the main two reasons for me
	No legal consequences of taking SCs	One of the other advantages was you didn't have to associate them (synthetic cannabinoids) with criminal element.
Characteristics of SCs	Derivatives	The most traditional was AM2201. AM2233 was good to me
	Blends	Spice was a mixture containing CP47,497, JWH019 and HU210
	Sources	Plenty of sites sell it online, a simple google search will help you find it
Use of SCs	Route of administration	In the past, I would mix 1 gram of JWH-122 into 1L of Vegetable oil and make some pretty awesome brownies . . . around 10 mg/brownie of 122 would do the trick
	Polydrug use	I also found both this combination and oral 5FAKB48 more psychedelic than smoked or oral AKB48. The combination of smoking 5FAKB48 and STS135 even though more potent, also gives me more of an uncomfortable feeling and more of a, for me, unwanted buzz.
SCs: wanted effects	Psychedelic	Much more psychedelic than natural cannabinoids
	Relaxing	But I do like the 'relaxing plateau' you get for an hour or so afterwards
	Sedative	I really enjoyed that heavy sedating/physical effects
	Euphoric	Experience with pure JWH018 got me to a headspace I had never been able to get to in 18 years of using natural cannabis.
SCs: toxicity and adverse effects	Alteration in perception	Time felt extremely slow; I'd say about 3-times slower than normal… as if space and time were altered, so a definite disconnect going on in perception.
	Alteration in behaviour	You will become antisocial, violent, won't give a s*** about others
	Anxiety	Too much anxiety is felt at higher doses
	Paranoia	Because they are so much strongerm the JWHxxx compounds can produce a more intense version of weed paranoia
	Psychosis	Taking syn noid resulted in me experiencing an acute psychotic reaction first time I ever heard voices inside my head
	Depression	I feel depressed and anxious afterwards several days.
	Addiction	Shorter acting, more intense hence more addictive… I got withdrawals now after smoking approximately 300 mg daily of various synth 'noids…Synth 'noids are certainly very addictive, and can cause bad withdrawals after a heavy binge.
	Tachycardia	I was sure that my heart was going to just rip out of my chest it was beating so hard and so fast
	Bronchitis	The effects…sounded like I had lung cancer and coughed up big chunks of grey/black/green/yellow s***, which my doctor called chronic bronchitis.
	Chest pain	Comes with chest pain, feeling short on breath
	Cough	I got such a terrible cough when I was smoking them
	Dyspnoea	Also, I've experienced severly depressed breathing
	Liver damage	I've got the start of a cyst on my liver from smoking them
	SCs-drug interactions	
	Overdose	Overdoses on synthetic cannabinoids are a terrible feeling. I've had six or seven, and I always end up in the foetal position with uncontrollable tremors
	Withdrawal symptoms	Withdrawal after smoking a half g for months was worse than benzos or opiates

Table 2. SC derivatives reported by users

Derivative	Synonyms	Chemical Name	Chemical Formula	Mwt.	N
Indole					
AM-2201	FUBIMINA, JWH2201	1-[(5-Fluoropentyl)-1H-indol-3-yl] -(naphthalen-1-yl) methanone	C24H22FNO	359.44	125
JWH-018	AM-678, JWH 018	Naphthalen-1-yl-(1-pentylindol-3-yl)methanone	C24H23NO	341.45	107
UR-144	KM-X1, MN001,TMCP-018, YX-17	(1-pentylindol-3-yl) -(2,2,3,3-tetramethylcyclopropyl) methanone	C21H29NO	311.461	66
JWH-073	Spice	Naphthalen-1-yl-(1-butylindol-3-yl) methanone	C23H21NO	327.42	38
JWH-250	No information	2-(2-methoxyphenyl)-1-(1-pentylindol-3-yl) ethanone	C22H25NO2	335.439	37
JWH-122	No information	(4-methyl-1-naphthyl) -(1-pentylindol-3-yl)methanone	C25H25NO	355.472	32
JWH-210	No information	4-ethylnaphthalen-1-yl-(1-pentylindol-3-yl)methanone	C26H27NO	369.498	32
MAM-2201	5F-JWH-122, AM2201 4-methylnaphthyl analogue	(1-(5-fluoropentyl)-1H -indol-3-yl) (4-methyl-1- naphthalenyl)-methanone	C25H24FNO	373.462	30
XLR-11	5F-UR-144	(1-(5-fluoropentyl)-1H-indol-3-yl) (2,2,3,3-tetramethylcyclopropyl)methanone	C21H28FNO	329.46	29
5F-PB-22	5F-QUPIC, 5-fluoro-PB-22, QCBL-2201, MN-25F, QUPIC N-(5-fluoropentyl) analogue	1-pentyfluoro-1H-indole-3-carboxylic acid 8- quinolinyl ester	C23H21FN2O2	376.42	24
MMB-Chminaca	MDMB-CHMICA	Methyl (2S)-2-{[1-(cyclohexylmethyl)-1H-indol-3-yl] formamido}-3,3-dimethylbutanoate	C23H32N2O3	384.52	20
STS-135	5F-Apica	N-(adamantan-1-yl)-1-(5-fluoropentyl)-1H-indole-3-carboxamide	C24H31FN2O	382.51	19
2NE1	SDB-001, APICA	N-(1-adamantyl)-1-pentyl-1H-indole-3-carboxamide	C24H32N2O	364.522	16
AM-2233	No information	1-[(N-methylpiperidin-2-yl) methyl]-3-(2-iodobenzoyl) indole	C22H23IN2O	458.334	16
BB-22	QUCHIC	1-(cyclohexyl methyl)-1H-indole-3-carboxylic acid 8-quinolinyl ester	C25H24N2O2	384.47	13
JWH-081	No information	4-methoxynaphthalen-1-yl- (1-pentylindol- 3-yl)methanone	C25H25NO2	371.47	13

PB-22	QUPIC	1-Pentyl-1H-indole-3-carboxylic acid 8-quinolinyl ester	C23H22N2O2	358.43	10
EAM-2201	4'-ethyl-AM-2201, 5"-fluoro-JWH-2201	(4-ethyl-1-naphthalenyl) [1-(5-fluoropentyl)-1H-indol-3-yl] -methanone	C26H26FNO	387.488	8
JWH-200	WIN 55,225	(1-(2-Morpholin-4-ylethyl) indol-3-yl)-naphthalen-1-ylmethanone	C25H24N2O2	384.469	7
JWH-203	No information	2-(2-chlorophenyl)-1-(1-pentylindol-3-yl) ethanone	C21H22ClNO	339.858	7
NM-2201	CBL-2201	naphthalen-1-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate	C24H22FNO2	375.4	7
AM-694	No information	1-[(5-fluoropentyl)-1H-indol-3-yl] -(2-iodophenyl) methanone	C20H19FINO	435.273	6
FUB-PB-22	No information	quinolin-8-yl 1-[(4-fluorophenyl) methyl]-1H-indole-3- carboxylate	C25H17FN2O2	396.41	6
JWH-019	No information	1-hexyl-3-(naphthalen-1-oyl) indole	C25H25NO	355.471	6
AB-001	No information	1-pentyl-3-(1-adamantoyl) indole	C24H31NO	349.508	5
JWH-251	2-(2-methylphenyl)-1-(1-pentyl-1H-indol-3-yl) ethanone	1-pentyl-3-(2-methylphenylacetyl) indole	C22H25NO	319.44	4
AM-1220	No information	(R)-(1-((1-methylpiperidin-2-yl) methyl)-1H-indol-3-yl) (naphthalen-1-yl) methanone	C26H26N2O	382.497	3
JTE-907	No information	N-(benzo [1,3] dioxol-5-ylmethyl)-7-methoxy-2-oxo-8-pentyloxy-1,2-dihydroquinoline-3-carboxamide	C24H26N2O6	438.472	3
JWH-182	No information	(1-pentyl-1H-indol-3-yl) (4-propyl-1-naphthalenyl)-methanone	C27H29NO	383.5	3
WIN-55,212-2	No information	(11R)-2-methyl-11-[(morpholin-4-yl) methyl]-3- (naphthalene-1-carbonyl)-9-oxa-1-azatricyclo [6.3.1.0] dodeca-2,4(12),5,7-tetraene	C27H26N2O3	426.52	3
AB-FUBICA	No information	N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-1-[(4- fluorophenyl) methyl]-1H-indole-3-carboxamide	C21H22FN3O2	367.42	2
ADBICA	ADB-PICA	N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indole-3-carboxamide	C20H29N3O2	343.46	2
FDU-PB-22	No information	naphthalen-1-yl 1-[(4-fluorophenyl) methyl]-1H-indole-3-carboxylate	C26H18FNO2	395.42	2
RCS-4	SR-19, BTM-4, Eric-4, E-4, OBT-199	2-(4-methoxyphenyl)-1-(1-pentyl-indol-3-yl)methanone	C21H23NO2	321.413	2

RCS-8	SR-18, BTM8	2-(2-methoxyphenyl)-1-[1-(2-cyclohexylethyl) indol-3- yl] ethanone	C25H29NO2	375.503	2
5F-JWH-018	5F-AB-001, 5-fluoro JWH 018 adamantyl analog, AM2201 adamantyl analogue	[1-(5-fluoropentyl)-1H-indol-3-yl] tricyclo [3.3.1.13,7]-dec-1-yl-methanone	C24H30FNO	367.5	1
5F-MN-24	5F-NNE1, 5F-NNEI	1-(5-Fluoropentyl)-N-(naphthalen-1-yl)-1H-indole-3-carboxamide	C24H23FN2O	374.45	1
A-796,260	LTI-258	[1-[2-(4-morpholinyl) ethyl]-1H-indol-3-yl] (2,2,3,3-tetramethylcyclopropyl)-methanone	C22H30N2O2	354.5	1
A-834,735	No information	[1-[(tetrahydro-2H-pyran-4-yl) methyl]-1H-indol-3-yl] (2,2,3,3-tetramethylcyclopropyl)-methanone	C22H29NO2	339.5	1
AB-005	No information	[1-[(1-methyl-2-piperidinyl) methyl]-1H-indol-3-yl] (2,2,3,3-tetramethylcyclopropyl)-methanone	C23H32N2O	352.51	1
AB-BICA	No information	N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-1- (phenylmethyl)-1H-indole-3-carboxamide	C21H23N3O2	349.4	1
ADB-Fubica	No information	(S)-N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4- fluorobenzyl)-1H-indole-3-carboxamide	C22H24FN3O2	381.45	1
AM-1248	No information	1-[(N-methylpiperidin-2-yl) methyl]-3-(adamant-1-oyl) indole	C26H34N2O	390.561	1
JWH-180	No information	(1-propyl-1H-indol-3-yl) (4-propyl-1-naphthalenyl)-methanone	C25H25NO	355.5	1
JWH-201	No information	2-(4-methoxyphenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone	C22H25NO2	335.4	1
WIN-48,098	Pravadoline	(4-methoxyphenyl) [2-methyl]-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl] -methanone	C23H26N2O3	378.5	1
Indazole					
5F-AKB48	5F-APINACA	N-(adamantan-1-yl)-1-(5-fluoropentyl)-1H-Indazole-3-carboxamide	C23H30FN3O	383.5	63
AB-Fubinaca	Ab-fubi	N-[(2S)-1-amino-3-methyl-1-oxobutan-2-yl]-1-[(4- fluorophenyl) methyl] indazole-3-carboxamide	C20H21FN4O2	368.4	42
THJ-018	JWH018 indazole analogue	1-naphthalenyl(1-pentyl-1H-indazol-3-yl)-methanone	C23H22N2O	342.4	35

AKB48	APINACA	N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide	C23H31N3O	365.51	19
AB-Chminaca	No information	N-[(2S)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl) indazole-3-carboxamide	C20H28N4O2	356.46	17
THJ-2201	No information	[1-(5-Fluoropentyl)-1H-indazol-3-yl] (1-naphthyl) methanone	C23H21FN2O	360.42	14
AB-PINACA	No information	N-[(1S)-1-(aminocarbonyl) -2-methylpropyl]-1-pentyl-1H-indazole-3-carboxamide	C18H26N4O2	330.43	9
AFUBINACA	AKB48 N-(4-fluorobenzyl) analogue, AFB-48, FUB- AKB48, FUB-APINACA	N-((3s,5s,7s)-adamantan-1-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide	C25H26FN3O	403.5	3
5F-SDB-005	No information	naphthalen-1-yl 1-(5-fluoropentyl)-1H-indazole-3-carboxylate	C23H21FN2O2	376.4	2
5F-THJ-018	No information	1-(5-fluoropentyl)-N-(quinolin-8-yl)-1H-indazole-3-carboxamide	C22H21FN4O	376.4	2
MAB-CHMINACA	ADB-CHMINACA	N-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide	C21H30N4O2	370.5	2
MN-18	No information	N-(naphthalen-1-yl)-1-pentyl-1H-indazole-3-carboxamide	C23H23N3O	357.5	2
5F-ADB	5F-MDMB-PINACA	Methyl (S)-2-[1-(5-fluoropentyl)-1H-indazole-3-carboxamido]-3,3-dimethylbutanoate	C20H28FN3O3	377.46	1
5F-ADB-PINACA	No information	N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(5- fluoropentyl)-1H-indazole-3-carboxamide	C19H27FN4O2	362.5	1
5F-AMB	5F-MMB-PINACA, 5F-AMB-PINACA	Methyl (2S)-2-{[1-(5-fluoropentyl)-1H-indazol-3-yl]formamido}-3-methylbutanoate	C19H26FN3O3	363.43	1
5F-Cumyl-Pinaca	SGT-25, CUMYL 5F PINACA	1-(5-Fluoropentyl)-N-(2-phenylpropan-2-yl)-1H- indazole-3-carboxamide	C22H26FN3O	367.5	1
ADB-Binaca	No information	N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-benzyl-1H-indazole-3-carboxamide	C21H24N4O2	364.4	1
ADB-Fubinaca	No information	N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl) -1-(4- fluorobenzyl)-1H-indazole-3-carboxamide	C21H23FN4O2	382.43	1

ADSB-FUB-187	No information	7-chloro-N-[(2S)-1-[2-(cyclopropylsulfonylamino) ethylamino]-3,3-dimethyl-1-oxobutan-2-yl]-1-[(4- fluorophenyl) methyl] indazole-3-carboxamide	C26H31ClFN5O4S	564.07	1
APP-Fubinaca	No information	N-[(1S)-2-amino-2-oxo-1-(phenylmethyl) ethyl]-1-[(4-fluorophenyl) methyl]-1H-indazole-3-carboxamide	C24H21FN4O2	416.5	1
FUB-AMB	AMB-FUBINACA, MMB-FUBINACA	methyl (1-(4-fluorobenzyl) -1H-indazole-3-carbonyl)-L-valinate	C21H22FN3O3	383.4	1
PX-3	APP-CHMINACA	N-[(2S)-1-amino-1-oxo-3-phenylpropan-2-yl]-1-(cyclohexylmethyl) indazole-3-carboxamide	C24H28N4O2	404.5	1
Cyclohexylphenol					
HU-210	1,1-Dimethylheptyl-11-hydroxy-tetrahydrocannabinol, (–)-1,1-dimethylheptyl analog of 11-hydroxy- Δ8-tetrahydrocannabinol	(6aR,10aR)-9-(hydroxymethyl)-6,6-dimethyl-3-(2- methyloctan-2-yl)-6H,6aH,7H,10H,10aH- benzo[c] isochromen-1-ol	C25H38O3	386.567	5
AM-906	No information	(6aR,9R,10aR)-3-[(Z)-hept-1-enyl]-9-(hydroxymethyl)-6,6-dimethyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-ol	C23H34O3	358.513	1
JWH-051	No information	((6aR,10aR)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrobenzo[c] chromen-9-yl)methanol	C25H38O2	370.567	1
JWH-133	No information	(6aR,10aR)-3-(1,1-Dimethylbutyl)-6a,7,10,10a-tetrahydro -6,6,9-trimethyl-6H-dibenzo [b, d] pyran	C22H32O	312.489	1
O-2545	No information	6a,7,10,10a-tetrahydro-3-[5-(1H-imidazol-1-yl)-1,1-dimethylpentyl]-6,6,9-trimethyl-6H-dibenzo [b, d] pyran-1-ol,monohydrochloride	C26H36N2O2 •	445	1
Cannabicyclohexanol					
Cannabicyclohexanol	CP 47497 dimethyloctyl homologue, (C8)-CP47497, CAY10596	rel-2-[(1S,3R)-3-hydroxycyclohexyl]-5-(2- methylnonan-2-yl) phenol	C22H36O2	332.5	3
CP 47,497	(C7)-CP 47,479	rel-5-(1,1-dimethyl heptyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol	C21H34O2	318.5	3
CP-55,940	No information	2-[(1R,2R,5R)-5-hydroxy-2-(3-hydroxypropyl) cyclohexyl]-5-(2-methyloctan-2-yl) phenol	C24H40O3	376.573	3
Naphtoylpyrrole					

JWH-307	No information	(5-(2-fluorophenyl)-1-pentylpyrrol-3-yl)-naphthalen-1-ylmethanone	C26H24FNO	385.472	1
Naphthylmethylindene					
CB-13	CRA13, SAB-378	naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone	C26H24O2	368.467	3
Indane					
BAY-38-7271	KN 38-7271	(−) -(R)-3-(2-Hydroxymethylindanyl-4-oxy) phenyl-4,4,4-trifluorobutyl-1-sulfonate	C20H21F3O5S	430.437	1
FAAH inhibitor					
URB-597	KDS-4103	(3'-(aminocarbonyl) [1,1'-biphenyl]-3-yl)-cyclohexyl carbamate	C20H22N2O3	338.4	1
Diarylpyrazole					
SR-141716	Rimonabant, Acomplia, Zimulti	5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-1-piperidinyl-1H-pyrazole-3-carboxamide	C22H21Cl3N4O	463.8	1

Mwt: Molecular weight, N: Number of threads reporting each derivative.

Table 3. Reports of SC derivatives per year

SC	N	2004	2009	2010	2011	2012	2013	2014	2015	2016
AM2201	125									
JWH018	107									
UR-144	63									
5FAKB48	59									
AB-Fubinaca	42									
JWH073	38									
JWH250	37									
JWH122	32									
JWH210	32									
MAM2201	30									
THJ018	30									
5F-UR-144	29									

SC: synthetic cannabinoid, N: total number of reports.

Table 4. SC-related blends reported by more than 10 users

Blend	Synonyms	Derivatives included	N
Spice	Spice Gold, Spice Silver	AM2201, CP47497, HU210, JWH derivatives, JWH018, JWH019, JWH073 and JWH122	80
K2	K2 Space Cadet, K2 Summit, K2 Blonde, K2 Bubble Gum Flavour and Strong K2.	JWH derivatives, JWH018, JWH073	45
Kosh	Mr Kosh Apple, Mr Kosh Blueberry, Mr Kosh Double Blueberry, Mr Kosh Grape, Mr Kosh Potpourri, Mr Kosh Raspberry, Mr Kosh Strawberry and Mr Kosh Watermelon.	NR	33
Kronic	Kronic Purple Haze, Kronic Black Label	JWH derivatives, JWH018, AM derivatives	32

N: Number of threads reporting each derivative

Table 5. Routes of administration of SCs

Route	Derivatives	Blends	Modality of intake	Doses range (mg)	Onset (min)	Duration (min)	N
Smoking	5FAKB48, AM2201, JWH019	Spice, K2 , Kronic	Smoking SC/mixtures in bongs, pipes, rolling a drug into a joint, blunt or spliff, Smoking a cigarette dipped in SC powder.	0.5 -500	0.5 - 40	2 – 270	540
Oral	AB-FUBINACA, AM2201, JWH018, JWH122	Spice, Clockwork orange	Swallowing powder, capsule, pellet, pill. Drinking powder dissolved in alcohol or other liquid. Eating Food with SC sprinkled onto it or baked with the food.	0.1 - 400	10 - 210	20 – 960	99
Sublingual	AM-2201, AB-Chminaca, AB-Fubinaca, JWH-073, JWH-210, MAM-2201, UR-144	NR	Placing the SC powder or SC entrapped in a paper under the tongue	5 - 50	60	150 – 300	7
Nasal insufflation	CP-47,497, JWH-018, WIN-55,212-2, XLR-11	NR	Snorting SC powder	2 - 60	NR	NR	5
Intraveous	2NE1, HU210, STS135	NR	Injecting solution of SC derivative	NR	NR	NR	3
Rectal	JWH073, UR144	NR	Plugging SC derivative rectally in powder form	3.5 mg	NR	NR	2

N: Number of threads reporting each derivative, NR: Not reported

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