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REVIEW

Emerging drugs of abuse: current perspectives on synthetic cannabinoids

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Abstract: New psychoactive drugs that have appeared over the last decade are typically dominated by cathinones and synthetic cannabinoids (SCs). SCs have been emerging as recreational drugs because they mimic the euphoria effect of cannabis while still being legal. Sprayed on natural herb mixtures, SCs have been primarily sold as "herbal smoking blends" or "herbal incense" under brand names like "Spice" or "K2". Currently, SCs pure compounds are available from websites for the combination with herbal materials or for the use in e-cigarettes. For the past 5 years, an ever increasing number of compounds, representative of different chemical classes, have been promoted and now represent a large assortment of new popular drugs of abuse, which are difficult to properly identify. Their legal status varies by country with many government institutions currently pushing for their control. The in vitro binding to CB1/CB2 receptors is usually well-known and considerable differences have been found in the CB1 versus CB2 selectivity and potency within the different SCs, with several structure-activity relations being evident. Desired effects by CB1 agonist users are relaxation/recreative, however, cardiovascular, gastrointestinal, or psychiatric/neurological side effects are commonly reported. At present there is no specific antidote existing if an overdose of designer drugs was to occur, and no curative treatment has been approved by health authorities. Management of acute toxic effects is mainly symptomatic and extrapolated from experience with cannabis.

Keywords: synthetic cannabinoids, chemistry, analysis, pharmacology, toxicology, dependence, medical care

Introduction

Synthetic cannabinoids (SCs) were originally developed in the 1970's for the research on ligands and the exploration of their pharmacological endocannabinoid pathways.[1] Just like the primary psychoactive component of cannabis, Δ^9-tetrahydrocannabinol (Δ^9-THC), and in the same manner as the main endogenous ligands, anandamide, and 2-arachydonylglycerol, SCs bind to the two subtypes of cannabinoid receptors, CB1 and CB2, with a varying degree of affinity. SCs were first reported for their use in recreational settings in December 2008 by a German firm who identified them in the smoking blends sold as herbs sprayed or mixed with one or more synthetic compounds, and were referred to as "Spice", "Yucatan", "Chill", "K2", or "Black Mamba".[2]

Over the following years SCs gained in popularity, especially among young people. Proposed as medicinal and legal products, newly synthetized cannabimimetics continue to emerge on the "legal highs" market as an alternative to phytocannabinoids. Among SCs, CB1 agonists mimic the effects of cannabis where consumers may feel happy and relaxed. However, unwanted serious adverse effects, such as neuropsychiatric disturbances or

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somatic effects of variable intensity, may occur with the use of recreational SCs.[3] Moreover, as result of the various forms of synaptic plasticity mediated by endocannabinoids, which allows the cannabinoid receptor to recognize multiple classes of compounds,[4] a large variety of distinct chemical substances are now sold over the Internet. This reinforces the public health problem linked to these new SCs that have, for the greater part, never been tested in human controlled settings. Nevertheless, as ever-increasing data on the identification or analysis methods, pharmacokinetics or pharmacodynamics, animal or human pharmacology or toxicity, and addictive potential are becoming available, this review is aimed to present updated information on SCs, useful for poisons centers, clinical toxicologists and emergency physicians.

Availability and usage demographics

SCs were first developed with the aim of exploring endogenous cannabinergic pathways and finding new therapeutics.[5] In the mid-1970s, Pfizer created CP 55,940, and in the 1980's and 1990's, other chemicals such as HU-210 and WIN 55,212 were investigated as potent pharmacotherapies.[6] The most important series of SCs appeared from the study by Huffman and Dong in 1994.[7] From this time on new classes of SCs have been developed, with numerous representatives inside every drug class.

The history on the use of SCs as drugs of abuse began approximately around 2004 when herbal mixtures, mainly known as Spice, were marketed on the Internet as a substitute to cannabis, in colorful attractive packages. Initially, these blends seemed to be made from plants traditionally used by shamans and/or other well known "phyto-chemistry" adepts. Four years later, in December 2008, the first reported case of SCs misuse appeared with the discovery of five compounds (JWH-018, CP 47,497 and its C6, C7, C8 analogs) in herbal blends produced by a German company.[2] Neither the seller nor the consumer of herbal mixtures, such as Spice, K2, or Black Mumba, can predict their content. For example, the overall range of concentrations in nine different brands investigated by Lindigkeit et al was between 3–11 mg/g of CP 47,497 C8, and 6–23 mg/g of JWH-073. One sample contained a small amount of JWH-018, ie, 2.3 mg/g, while two other samples were found to be free of SCs.[8] Similar findings were published in another study by Uchiyama et al based on 46 Spice products.[9] Concomitantly with the emergence of herbal blends, SCs quickly become available in large amounts of "pure" powder, sold especially on websites from the People's Republic of China, with the aim of adding to tobacco for smoking.

Nowadays, new SCs constantly appear on the market,[10] along with new types of consumption, which could be called a third-generation of use, such as cartridges filled with SCs solution designed for using with e-cigarettes. These are called "buddha-blue", "C-Liquid", "Herbal e-Liquid", or others and are discussed on drug-user forums.

From published data available from poisoning, toxicological, or epidemiological centers the use of SCs is common in the USA, varying from 1.4% based on Wohlfarth et al's study on USA military urine specimens (n=20,017) collected from July 2011 to June 2012,[11] up to approximately 10% found in Palamar and Acosta's study taken on high school seniors (n=11 863).[12] Similar findings were reported from studies on the USA nightlife scene (n=1740)[13] and on college students in Florida (n=852).[14] However, it has been recently shown that while lifetime prevalence has increased, the past 6 month prevalence has decreased substantially over time.[15] In Europe, a retrospective study based on serum samples collected in Germany in 2010, estimated a prevalence at approximately 2.8% (n=12/422),[16] and 4% (n=164/4080) in a youth population (18–34 year olds) from the French Health Barometer.[17] Considering the new attraction for SCs, studies or reports on driving impairment have started to be considered in USA[18,19] and in Europe.[20,21]

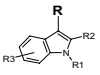
It is also important to note that SCs can be used as a therapeutic. Even if many fundamental research is conducted, only a few SCs are available for medical use, belonging to dibenzopyrane derivatives such as nabilone or dronabinol. They are mostly used for their antiemetic properties, especially in chemotherapy-induced nausea and vomiting, or for their orexigenic properties in anorexia. In addition, analgesic properties of cannabinoids are advanced in some *Cannabis sativa* plant extracts for adjunctive treatment of neuropathic pain in patients with multiple sclerosis. To date, several investigations are currently underway to find new therapeutic applications of SCs, for example, neuroprotective effects in neurodegenerative diseases such as Parkinson's disease,[22] or inflammatory cell modulation.[23]

Chemical structure and designation

SCs family is extremely large, including numerous substances belonging to various chemical groups and subgroups. New compounds which can belong to unknown chemical classes emerge constantly, making the inventory of existing products never ending. We have brought together approximately 120 SCs, which are the most recent and popular compounds, but we do not claim this list to be exhaustive (Tables 1 and 2).

We specify trade names, radicals, formula, and CAS numbers for an easy and quicker tracking. Only a few SCs are structurally related to Δ^9-THC, the others belonging to

Table 1 Chemical structure of cannabinoid 3-indole derivatives



Name	R	R′	R1	R2	R3	Formula	CAS number
Benzoyl derivatives							
AM-679		2-iodo	Pentyl	H	…	C20H20INO	335160-91-3
AM-694		2-iodo	5-fluoropentyl	H	…	C20H19FINO	335161-03-0
RCS-4 = SR 19 = E 4 = BTM 4 = OBT 199		4-methoxy	Pentyl	H	…	C21H23NO2	1345966-78-0
WIN-48,098 = pravadoline		4-methoxy		Methyl	…	C23H26N2O3	92623-83-1
AM-2233		2-iodo		H	…	C22H23IN2O	444912-75-8
RCS-8		2-methoxy		H	…	C25H29NO2	1345970-42-4
Naphthoyl derivatives							
JWH-007		…	Pentyl	Methyl	…	C25H25NO	155471-10-6
JWH-015		…	Propyl	Methyl	…	C23H21NO	155471-08-2
JWH-018		…	Pentyl	H	…	C24H23NO	209414-07-3
JWH-019		…	Hexyl	H	…	C25H25NO	209414-08-4
JWH-022		…	Pentenyl	H	…	C24H21NO	209414-16-4
JWH-071		…	Ethyl	H	…	C21H17NO	209414-05-1
JWH-073		…	Butyl	H	…	C23H21NO	208987-48-8
JWH-081		4-methoxy	Pentyl	H	…	C25H25NO2	210179-46-7
JWH-098		4-methoxy	Pentyl	Methyl	…	C26H27NO2	316189-79-9
JWH-116		…	Pentyl	Ethyl	…	C26H27NO	619294-64-3
JWH-122		4-methyl	Pentyl	H	…	C25H25NO	619294-47-2
JWH-149		4-methyl	Pentyl	Methyl	…	C26H27NO	548461-82-1
JWH-182		4-propyl	Pentyl	H	…	C27H29NO	824960-02-3
JWH-193		4-methyl		H	…	C26H26N2O2	133438-58-1
JWH-198		4-methoxy		H	…	C26H26N2O3	166599-76-4
JWH-200 = WIN 55,225		…		H	…	C25H24N2O2	103610-04-4
JWH-210		4-ethyl	Pentyl	H	…	C26H27NO	824959-81-1
JWH-387		4-bromo	Pentyl	H	…	C24H22BrNO	1366067-59-5
JWH-398		4-chloro	Pentyl	H	…	C24H22ClNO	1292765-18-4
JWH-412		4-fluoro	Pentyl	H	…	C24H22FNO	1364933-59-4
JWH-424		8-bromo	Pentyl	H	…	C24H22BrNO	1366068-04-3
AM-1220		…		H	…	C26H26N2O	137642-54-7
AM-1221		…		Methyl	NO2	C27H27N3O3	335160-53-7
AM-1235		…	5-fluoropentyl	H	NO2	C24H21FN2O3	335161-27-8
AM-2201		…	5-fluoropentyl	H	…	C24H22FNO	335161-24-5
AM-2232		…		H	…	C24H20N2O	335161-19-8
MAM-2201		4-methyl	5-fluoropentyl	H	…	C25H24FNO	1354631-24-5
EAM-2201		4-ethyl	5-fluoropentyl	H	…	C26H26FNO	1364933-60-7
Phenylacetyl derivatives							
JWH-167		…	Pentyl	H	…	C21H23NO	864445-37-4
JWH-201		4-methoxy	Pentyl	H	…	C22H25NO2	864445-47-6
JWH-203		2-chloro	Pentyl	H	…	C21H22ClNO	864445-54-5
JWH-204		2-chloro	Pentyl	Methyl	…	C22H24ClNO	864445-55-6
JWH-206		4-chloro	Pentyl	H	…	C21H22ClNO	864445-58-9
JWH-207		4-chloro	Pentyl	Methyl	…	C22H24ClNO	864445-59-0
JWH-208		4-methyl	Pentyl	H	…	C22H25NO	864445-41-0
JWH-209		4-methyl	Pentyl	Methyl	…	C23H27NO	864445-42-1
JWH-249		2-bromo	Pentyl	H	…	C21H22BrNO	864445-60-3
JWH-250		2-methoxy	Pentyl	H	…	C22H25NO2	864445-43-2
JWH-251		2-methyl	Pentyl	H	…	C22H25NO2	864445-39-6
JWH-253		3-methoxy	Pentyl	Methyl	…	C23H27NO2	864445-46-5
JWH-302		3-methoxy	Pentyl	H	…	C22H25NO2	864445-45-4
JWH-311		2-fluoro	Pentyl	H	…	C21H22FNO	864445-49-8
JWH-316		4-fluoro	Pentyl	Methyl	…	C22H24FNO	864445-53-4

(*Continued*)

Table 1 (*Continued*)

Name	R	R'	R1	R2	R3	Formula	CAS number
Alkoyl derivatives							
A-790,260				H	…	C22H30N2O2	895155-26-7
A-834,735				H	…	C22H29NO2	895155-57-4
AB-005				H	…	C23H32N2O	8951555-25-6
UR-144			Pentyl	H	…	C21H29NO	1199943-44-6
XLR-11 = 5F-UR-144			5-fluoropentyl	H	…	C21H28FNO	1364933-54-9
AB-001			Pentyl	H	…	C24H31NO	1345973-49-0
AM-1248				H	…	C26H34N2O	335160-66-2
Piperazoyl derivatives							
Mepirapim		Methyl	Pentyl	H	…	C19H27N3O	Not attributed
Carboxylate derivatives							
BB-22 = QUCHIC				H	…	C25H24N2O2	1400742-42-8
PB-22 = QUPIC			Pentyl	H	…	C23H22N2O2	1400742-17-7
5F-PB-22			5-fluoropentyl	H	…	C23H21FN2O2	1400742-41-7
FUB-PB-22				H	…	C25H17FN2O2	Not attributed
FDU-PB-22				H	…	C26H18FNO2	Not attributed
NM-2201 = CBL-2201			5-fluoropentyl	H	…	C24H22FNO2	Not attributed
Carboxamide derivatives							
ADBICA			Pentyl	H	…	C20H29N3O2	1445583-48-1
CUMYL-BICA			Butyl	H	…	C22H26N2O	Not attributed
CUMYL-PICA			Pentyl	H	…	C23H28N2O	Not attributed
CUMYL-5FPICA			5-fluoropentyl	H	…	C23H27FN2O	Not attributed
MDMB-CHMICA = MMB-CHMINACA				H	…	C23H32N2O3	832231-92-2
NNEI = MN24			Pentyl	H	…	C24H24N2O	1338925-11-3
MN-25 = UR-12				H	Methoxy	C26H37N3O3	501926-82-5
5F-NNEI = 5F-MN24			5-fluoropentyl	H	…	C24H23FN2O	1445580-60-8
SDB-001 = APICA = 2-NEI			Pentyl	H	…	C24H32N2O	1345973-50-3
STS-135			5-fluoropentyl	H	…	C24H31N2O	1354631-26-7
SDB-006			Pentyl	H	…	C21H24N2O	695213-59-3
5F-SDB-006			5-fluoropentyl	H	…	C21H23FN2O	Not attributed
SRF-30 = PX-1 = 5F-APP-PICA			5-fluoropentyl	H	…	C23H26FN3O2	Not attributed
Thiazolyl derivatives							
PTI-1			Pentyl	H	…	C21H29N3S	1400742-46-2
PTI-2			Pentyl	H	…	C23H33N3OS	Not attributed
Naphthylmethyl derivatives							
JWH175			Pentyl	H	…	C24H25N	619294-35-8

Note: "…" demonstrates that there is no substituant on the phenyl core in position R' or R3.
Abbreviation: CAS, Chemical Abstracts Service.

different and various chemical families. The major structural group is the indole group (Table 1, Figure 1) which includes several indole sub-groups (R): benzoyl, Naphthol, phenylacetyl, alkyl, piperazinyl, carboxylate, carboxamide, thiazolyl, and naphthylmethyl derivatives.

Besides these abundant indole derivatives, many other SCs groups have very different structural characteristics (Table 2). In spite of the diversity of products, some similarities should be noted: 1) a quite constant unsaturated and substituted five-membered ring incorporating at least one nitrogen (pyrrole), and merged to another aromatic cycle; and 2) within series, changes in substituent are often limited to the simple addition of a methyl or halogen group to a linear alkyl chain. Nevertheless, more marked modifications are possible, making the classification of such compounds very difficult. Some of these compounds are chiral, and can exist in two stereoisomer forms. SCs are usually referred to by usual trade names such as JWH-XXX (John W Huffmann), CP-XX, XXX (Charles Pfizer), HU-XXX (Hebrew University), AM-XXXX (Alexandros Makriyannis), and many others. Note that within a trade name family, several chemical classes may be represented. For example, JWH-XXX series includes Naphthol indoles, phenylacetyl indoles, naphthylmethyl indoles, naphthylmethyl indene, and Naphthol pyrroles.

Current and developing analytical methods for detection

Immunochemistry

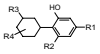
As a general rule, immunoassay screening methodologies used to detect cannabis fail to detect SCs, but some specific

Table 2 Chemical structure of other cannabinoid derivatives

Name	R	R′	R1	R2	R3	R4	Formula	CAS number
Indene derivatives								
								
Naphthylmethylindenes								
JWH-176		H	Pentyl	…			C25H24	619297-62-1
JWH-220		Methyl	Pentyl	…			C26H26	Not attributed
Pyrrole derivatives								
								
Naphthoyl pyrroles								
JWH-030		…	Pentyl	…			C20H21NO	162934-73-8
JWH-145		…	Pentyl	Phenyl			C26H25NO	914458-19-8
JWH-147		…	Hexyl	Phenyl			C27H27NO	914458-20-1
JWH-307		…	Pentyl	2-fluorophenyl			C26H24FNO	914458-26-7
JWH-368		…	Pentyl	3-fluorophenyl			C26H24FNO	914458-31-4
JWH-370		…	Pentyl	2-methylphenyl			C27H27NO	914458-22-3
Indazole derivatives								
								
Carboxamide indazole derivatives								
AB-CHMINACA				…			C20H28N4O2	1185887-21-1
AB-FUBINACA				…			C20H21FN4O2	1185282-01-2
AB-PINACA			Pentyl	…			C18H26N4O2	1445752-09-9
5F-AB-PINACA			5-fluoropentyl	…			C18H25FN4O2	Not attributed
ADB-CHMINACA = MAB-CHMINACA				…			C21H30N4O2	8322231-92-1
ADB-FUBINACA				…			C21H23FN4O2	1445583-51-6
ADB-PINACA			Pentyl	…			C19H28N4O2	1633766-73-0
5F-ADB-PINACA			5-fluoropentyl	…			C19H27FN4O2	Not attributed
5F-ADB			5-fluoropentyl	…			C20H28FN3O3	Not attributed
5F-AMB = 5F-AMP			5-fluoropentyl	…			C19H26FN3O3	Not attributed
APINACA = AKB-48			Pentyl	…			C23H31N3O	1345973-53-6
5F-APINACA = 5F-AKB-48			5-fluoropentyl	…			C23H30FN3O	1400742-13-3
FUB-APINACA = FUB-AKB-48				…			C25H26FN3O	Not attributed
5F-APP-PINACA = FU-PX = PX-2			5-fluoropentyl	…			C22H25FN4O2	Not attributed
CUMYL-PINACA			Pentyl	…			C22H27N3O	Not attributed
CUMYL-5FPINACA = SGT-25			5-fluoropentyl	…			C22H26FN3O	Not attributed
CUMYL-THPINACA				…			C23H27N3O2	Not attributed
MN-18			Pentyl	…			C23H23N3O	1391484-80-2
5F-MN-18			5-fluoropentyl	…			C23H22FN3O	1445581-91-8
Carboxylate indazole derivatives								
NPB-22			Pentyl	…			C22H21N3O2	1445579-61-2
5F-NPB-22			5-fluoropentyl	…			C22H20FN3O2	1445579-79-2
FUB-NPB-22				…			C24H16FN3O2	Not attributed
SDB-005			Pentyl	…			C23H22N2O2	Not attributed
5F-SDB-005			5-fluoropentyl	…			C23H21FN2O2	Not attributed
Benzimidazole derivatives								
								
FUBIMINA = BIM-2201		…	5-fluoropentyl				C23H21FN2O	Not attributed
Dihydroisoindole-1one derivatives								
								
JTE 7-31				Pentylamino	Methoxy		C22H28N2O3	194358-72-0

(*Continued*)

Table 2 (*Continued*)

Name	R	R'	R1	R2	R3	R4	Formula	CAS number
Azaindole derivatives								
								
5-F PCN = 5F MN-21			5-fluoropentyl	...			C24H22FN3O	152624-02-7
Cyclohexylphenol derivatives								
								
CP-47,497-C6 homologue				…	OH		C20H32O2	70435-06-2
CP-47,497				…	OH		C21H34O2	70434-82-1
CP-47,497-C8 homologue				…	OH		C22H36O2	70434-92-3
CP-47,497-C9 homologue				…	OH		C23H38O2	70435-08-4
CP-55,940				…	OH	Hydroxypropyl	C24H40O3	83002-004-4
O-1871				OH		$(methyl)_2$	C23H38O2	620964-96-7
Naphtalene derivatives								
								
CB-13 = CRA-13 = SAB-378			Pentyloxy	…			C26H24O2	432047-72-8
Dibenzopyrane derivatives = tetrahydrobenzochromene derivatives								
								
Δ9-tetrahydrocannabinol			Pentyl	Hydroxymethyl			C21H30O3	36557-05-8
HU-210				Hydroxymethyl			C25H38O3	112830-95-2
Thiazolidène derivatives								
								
A-836,339			Methoxyethyl	H			C16H26N2O2S	959746-71-1
Carbazole derivatives								
								
Naphtoyl carbazole derivatives								
EG-018		…	Pentyl				C28H25NO	Not attributed
Anandamide derivatives								
								
Anandamide	H						C22H37NO2	94421-68-8
Methanandamide = AM-356	methyl						C23H39NO2	157182-49-5
Pyrrolo 1,4-benzoxazine derivatives								
								
WIN 55212-2		…	Methyl				C27H26N2O3	131543-23-2

Notes: "…" demonstrates that there is no substituant on the aromatic core in position R' or R2. When there is no R3 or R4 in the basic structure the column was left blank. "H" has been included when the structure was not a phenyl or an aromatic core.
Abbreviation: CAS, Chemical Abstracts Service.

enzyme-linked immunosorbent assays or homogenous enzyme immunoassays have been recently designed to detect the use of common SCs in urine, such as JWH-018, JWH-250, UR-144, and others.[24–26]

Gas chromatography-mass spectrometry

Several gas liquid chromatography (LC) connected to electron-impact mass spectrometry (GC-MS) methods have been developed to rapidly identify and quantify SCs in herbal and powder materials.[27–31] In our own experience we used a DB-5 fused-silica capillary column (30 m×0.25 mm×0.25 µm). Oven temperature was increased from 100°C (hold time: 1 minute) by 8°C/min up to 280°C (26.5 minutes), with helium flow at 1 mL/min.

A standard method to screen new psychoactive substances was to have a total runtime of 60 minutes, with the retention times of SCs ranging between 21.9 and 48.0 minutes. The rank order (retention time) of ten analyzed SCs was as follows

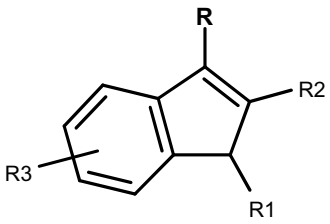


Figure 1 Chemical structure of indole derivatives.

from the lowest rank to the highest rank: UR-144; JWH-250; HU210; RCS-4; JWH-073; JWH-018; JWH-019; AM-2201; JWH-122; JWH-081; and JWH-200. The selected mass spectrometry (MS) data that we collected in the literature, and from our own data bank are summarized in Table 3, and identify several SCs, some are among the most notorious. Consistent with the large variety of chemical structures, mass spectra under electron impact conditions differ largely from one SC to another, with some discrepancies between reported spectra in terms of ion intensity. An intense molecular ion (M^+) is frequently present and fragmentations are commonly observed on both sides of the carbonyl group: for example, SCs bearing an n-pentyl moiety show an intense ion at m/z =214 corresponding to n-pentyl indoloyl,[27] and those bearing a 5-fluoropentyl moiety show an intense ion at m/z =232 (fluoropentyl indoloyl). The mass-spectral fragmentation pattern of SCs also includes formations of different immonium ions at m/z =144 (indoloyl moiety), 155 (Naphthol moiety), or 127 (Naphthol moiety).[32] GC-MS methods have been developed to determine the composition of Spice herbal mixtures but appear inadequate to measure concentrations in the user's biological specimen.

LC-MS

Different LC-MS/MS screening or semi-quantitative and quantitative methods have been published and identify and quantify SCs in various specimens – urine, serum, blood, oral fluid, or hair.[33–40] A classic or ultra-performing reverse phase C18 is typically used for the chromatographic separation prior to analysis by LC-tandem MS using electrospray positive ionization multiple reaction monitoring mode.[33–40] Multiple reaction monitoring transitions for SCs are presented in Table 4. For all substances, the dominant Q1 ions were the protonated molecular ions ($[M+H]^+$), and at least two product ions of acceptable abundance can be obtained. Ions $C11H7O^+$ (m/z =155.0) and $C10H7^+$ (m/z =127.0) can be referred to as common characteristic ions. Simultaneous determinations and quantifications of SCs metabolites have also been successfully applied to urine specimens.[37,41] In order to complete targeted MS/MS screening, ultra-high performance LC coupled with high resolution quadrupole time-of-flight MS high-sensitivity methods have also been developed to directly screen SCs in specimens such as in urine or hair.[42–45] Real time MS was employed to detect the SCs protonated molecules $[M+H]^+$ directly on herbal matrices, without extraction or sample preparation.[46] The limits of quantification for the assay of SCs in urine, using an electrospray ionization source in positive polarity, are approximately 0.1–1 µg/L, with upper limits of linearity at 50–100 µg/L.[37] Accordingly, LC-MS-MS is the only method that presents sufficient sensibility to quantify SCs in biological fluids.

Extraction procedures for quantification in herbal and biological samples

Herbal material has to be crushed and stirred or sonicated in methanol or ethanol before chromatographic analysis. Human urine is the favorite biological matrix explored to detect SCs consumption. Biological samples may be enzymatically hydrolyzed before pretreatment. Solid-phase extraction or simple precipitation is next used for oral fluid or urine samples.[33,37,47] Basic liquid-liquid extraction after deproteinization with acetonitrile followed by a concentration step is generally preferred to prepare blood samples.[34,38] Liquid-liquid extraction is preceded by an incubation with NaOH at 95°C for finely cut hair samples.

Experimental pharmacology and neuropharmacology

By acting as retrograde messengers at various synapses, endocannabinoids (anandamide and 2-arachidonoylglycerol) have a neuromodulatory role in motor activity, pain perception, feeding, emotional state, learning and memory, and reward behaviors.[48,49] They also influence cardiovascular and immune systems and control progenitor cell proliferation.[48] Endocannabinoids bind to CB1 receptors mainly located at the terminals of central and peripheral neurons and to CB2 receptors principally expressed in immune and hematopoietic cells both within and outside the central nervous system. CB1 receptors are often localized presynaptically where their stimulation usually inhibits neurotransmitter release and accounts for most of the neurobehavioral effects, while CB2 receptors are mainly implicated in the immunomodulatory effects. Yet, CB1 receptors are also present at much lower concentrations in peripheral tissues and CB2 in neurons and microglia.

In vitro

The complex molecular architecture of the cannabinoid receptors allow for a single receptor to recognize multiple

Table 3 Gas chromatography mass spectrometry (GC-MS) identification of synthetic cannabinoids

Chemical class	Name	Molecular weight	GC-MS identification (electronic impact)		Reference
			Base peak	Other peaks	
Benzoyl indoles	AM-694	435,27	232	435, 220, 380	30
			232	435, 220, 360	28
	RCS-4	321,41	312	284, 214, 135	30
			321	135, 264, 214,	27
			321	265, 135, 214	Personal data
	RCS-4-(N-Me)	265,31	158	265, 77, 264, 266	27
	WIN-48,098	378,46	100	135, 378	28
Naphthoyl indoles	JWH-018	341,45	341	284, 214, 127, 324	30
			341	284, 214, 127, 324	28
			341	325, 285, 215	Personal data
	JWH-019	355,47	355	284, 228, 127, 338	30
			355	338, 284, 228	Personal data
	JWH-073	327,42	327	200, 284, 127, 310	30
			327	200, 284, 310, 127	28
			327	310, 284, 200	Personal data
	JWH-081	371,47	371	354, 314, 214,185	30
			371	354, 370, 314, 214, 185	27
			371	354, 314, 214	Personal data
	JWH-122	355,47	355	338, 298, 215	30
			355	298, 214, 338	Personal data
	JWH-122-pentenyl	353,45	353	351, 335, 127, 284	31
	JWH-200	384,47	100	384, 339, 155, 127	Personal data
	JWH-210	369,50	369	352, 312, 214, 340	30
			369	352, 312, 214, 368, 340	27
	JWH-412	359,44	359	302, 145, 173, 214	29
	AM-1220	382,21	98	70, 127, 254, 284	31
			98	70, 127, 155, 254	32
	AM-1220- azepane	382,21	382	84, 127, 184, 57	31
			127	84, 57, 382, 98	32
	AM-2201	359,44	359	284, 232, 342, 358, 127	31
			359	127, 284, 232, 342	29
			359	127, 284, 232, 342	28
			359	284, 232, 342, 358	27
			359	284, 232, 127, 342	30
			355	338, 284, 228	Personal data
	AM-2201-pMe	373,46	373	298, 232, 356, 372	31
			373	298, 232, 356, 372	27
	AM-2232	352,43	352	351, 335, 225, 127	31
Phenylacetyl indoles	JWH-203	339,86	214	144, 116, 339	30
	JWH-250	335,44	214	144, 116, 335	30
			214	144, 335, 116	28
			214	144, 215, 335	Personal data
Alkoyl indoles	UR-144	311,2	214	144, 296, 215, 311	31
			215	296, 144, 311	Personal data
	XLR-11	329,2	232	144, 233, 329, 41	31
Carboxylate indoles	MN-27	396	109	252, 396	128
	NM-2201	375,16	232	144, 115	128
Carboxamide indoles	STS-135	382,2	232	382, 307, 144, 383	31
Naphtoyl pyrroles	JWH-147		381	155,127, 310, 296	30
	FUB-NPB-22	397,4	109	253, 397	128
Carboxylate indazoles	5-fluoro-NPB-22	377,4	233	145, 377	128
	5-fluoro-SDB-005	376	233	145, 213, 376	128
Dibenzopyranes	HU-210	386,57	303	387, 331, 285, 270	Personal data

Table 4 Liquid chromatography – tandem mass spectrometry identification of synthetic cannabinoids

Name	Molecular weight	Precursor ion	Product ions	Reference
Positive mode				
AM-251	555.2	555.0	454.0; 472.0	39
AM-694	435.3	435.9	231,0; 309,2; 203,2	39
AM-2201	359.4	360.1	155.1; 127.2	11,34,37,40
AM-1220	382.5	383,2	112,0; 98,1; 286,2	34,36
AM-1241	503.3	504.1	98.0; 275.0	39
AM-2201	359.4	360.2	155.0; 232.0	39
AM-2233	458.3	459.1	112.1; 98.1; 230.0	33,39
HU-210	386.6	387,2	243,2; 261,3; 85,0	36,39
JWH-007	355.5	356.2	155.2; 127.2	33,38,39
JWH-011	383.5	384.2	155.0; 286.0	39
JWH-015	327.4	328.1	155.1; 200.1; 127.0	34,36,38
JWH-018	341.4	342.1	155.1; 214.2; 127.1	36–38,40
JWH-019	355.5	356.2	155.1; 126.9; 228.1	34,36,37
JWH-020	369.5	370.4	155.1; 242.1; 127.1	33,36
JWH-022	339.4	340.2	155.0; 212.0	39
JWH-030	291.4	292.2	155.0; 168.0	39
JWH-073	327.4	328.1	155,0; 200,0; 127,0	34,36–38,40
JWH-081	371.5	372.2	185.1; 157.1; 127.0	34,36,37
JWH-098	385.5	386.2	185.0; 198.0; 228.0	39
JWH-122	355.5	356.1	169.1; 214.2; 141.0	34,36–38,40
JWH-182	383.5	384.2	197.0; 214.0; 144	38,39
JWH-200	384.5	385.2	155.1; 114.0; 127.0	34,36,37
JWH-201	335.4	336.2	121.0; 135.0; 214.0	39
JWH-203	339.9	340,1	124.9; 188.1; 89.0	33,36
JWH-210	369.5	370.1	183.1; 214.1; 153.1	36–38
JWH-249	384.3	385	144	38
JWH-250	335.4	336.1	121.2; 91.1; 200.3	34,36–38
JWH-251	319.4	320,1	104,9; 214,1; 144,2	33,34,36,37
JWH-302	335.4	336	144; 121	38
JWH-307	385.5	386,2	155,0; 127,1; 77,1	33,34,36
JWH-398	375.9	376.1	189; 161.1; 126.1	33,36,37
JWH-412	359.4	360.4	173.2; 145.1	33
JWH-424	420.3	422	144	38
MAM-2201	373.5	374.1	169.0; 115.0	37,40
RCS-4	321.4	322,2	135,0; 77,0; 92,0	36,37
RCS-8	375.5	376,2	121,0; 90,9; 143,9	36,37
WIN-48,098	378.5	379,1	134,9; 114,0; 77,1	36
WIN 55,212-2	426.5	427,3	155,1; 127,0; 100,0	33,36,38
XRL-11	329.5	330.1	125.1; 232.0	37
Negative mode				
CP-47,497-C7	318.5	317.1	245.1; 159.1	37
CP-47,497-C8	332.5	331.1	259.1; 159.0	37
HU-210	386.6	385.6	301.3; 281.1	37

classes of compounds.[50] SCs which present a large variety of chemical structures like that previously shown in Table 1 and 2, bind to the two types of cannabinoid receptors with a varying degree of affinity. These CB1 and CB2 receptor affinities of SCs have been determined in displacement assays using tritiated cannabinoid receptor ligands and membranes obtained from brain (CB1-rich), spleen (CB2-rich), or using culture cells transfected with CB1 or CB2 receptors.[51] Ki values of SCs collected from literature are grouped in Table 5.[7,52–64] The majority of compounds used as drug of abuse have Ki in the range 1 to 10 nM or 10 to 100 nM for both CB1 and CB2 receptors. Some synthetic compounds bind more strongly to CB1 receptor than Δ^9-THC. JWH-210 from the Naphthoylindole family, acts as a potent cannabinoid agonist with both the CB1 and CB2 receptors, with Ki values of 0.46 nM at CB1 and 0.69 nM at CB2.[52] At the opposite end, JWH-071 binds with the central CB1 receptor (Ki =1,340 nM) and the peripheral CB2 receptor

Table 5 Affinities of much of synthetic cannabinoids

	CB1				
	Ki < 1 nM	**1 nM < Ki < 10 nM**	**10 nM < Ki < 100 nM**	**100 nM < Ki < 1000 nM**	**Ki > 1000 nM**
CB2					
Ki < 1 nM	JWH-210[52*]	JWH-149;[52] AB-005;[56] A-834,735;[56] O-1871[64]	AM-1221[54]	A-836,339[57]	
1 nM < Ki < 10 nM	AM-694;[54] JWH-122;[53] JWH-182;[52] AM-2232[54]	AM-2233;[58] JWH-007;[7,52] JWH-018;[53] JWH-019;[53] JWH-098;[53] JWH-387;[59] JWH-398;[59] JWH-412;[59] AM-220;[57] JWH-203;[55] JWH-250;[55] NM-2201;[54] JWH-307;[52] JWH-370;[52]	JWH-424;[61] UR-144;[56] JWH-145;[52] JWH-147;[52] JWH-368[52]	A-796,260[56]	
10 nM < Ki < 100 nM		JWH-073;[53] JWH-081;[53] AM-1235;[54] JWH-249[55]	AM-679;[54] **Δ9-THC**;[52] JWH-204;[55] JWH-253;[55] JWH-302;[55] JWH-311;[55] JWH-176;[63] JWH-220[63]	JWH-015;[53] JWH-251;[55] MN-25[62]	
100 nM < Ki < 1000 nM			JWH-167;[55] methanandamide[60]	JWH-206;[55] JWH-208[55]	JWH-201;[55] JWH-316[55]
Ki > 1000 nM				JWH-209[55]	JWH-071;[53] JWH-207[55]

Notes: *The number in exponent is the reference in the literature giving the Ki. The bold text represents the lead natural cannabinoid of *Cannabis sativa*.

(Ki =2,940 nM) at a micromolar level.[53] The majority of SCs are unspecific CB1/CB2 ligands (Table 5), with only a few are CB2 selective such as AM-1221 (Ki =0.28 nM at CB2 vs 52.3 nM at the CB1)[54] and A-836,339 (Ki =0.64 nM at CB2 vs 270 nM at CB1).[57]

CB1 and CB2 receptors are G protein-coupled receptors. Two in vitro assays using cell membranes or cultured cells that express CB1 or CB2 receptors are commonly employed to determine the SCs agonist property; the [^{35}S] GTPγS assay that measures cannabinoid receptor agonist-stimulated binding to G proteins, and the cyclic adenosine monophosphate assay that quantitatively determine the drug-induced production of this important second messenger.[51]

As a general rule, the agonists show little selectivity between the CB1 and CB2 receptors, while the antagonist compounds are highly selective.[65]

In vivo

SCs that target CB1 and/or CB2 receptors may be classified in CB1/CB2 agonists, CB2 selective agonists, peripherally restricted CB1/CB2 agonists, CB1/CB2 antagonists, and inverse agonists.[66] Additionally, chiral centers can exist in many SCs and stereoisomer forms may differ in their pharmacological potencies.[67] All may have an interest as recreational or medicinal drugs. In vivo in mice, activation of CB1 receptors produces a "tetrad" of dose-dependent effects, including suppression of locomotor activity, hypothermia, immobility in the ring test, and antinociception in the tail-flick or hot-plate test.[66] This cannabinoid tetrad is extremely useful in the characterization of the biological activity of SCs but the development of CB1, CB2, or CB1/CB2 knockout mice provided additional methods to test the SCs specificities. In addition, agonistic binding to CB1 receptors resulted in behavioral effects including euphoria, elevation or anxiety, or alteration of memory.[68] In agreement with in vitro studies, in vivo studies show SCs pharmacological effects commonly more potent than Δ^9-THC. Similarly, SCs perfectly substituted for Δ^9-THC in discrimination studies.[3] Activation of CB2 receptors results in release of immunomodulating agents and reduction of inflammatory induced pain. Accordingly, our purpose primarily focused on specific or unspecific CB1 agonists.

Many studies in mice suggest a major regulatory role of cannabinoid signaling in pregnancy with multiple sites and stages of pregnancy potential targets of SCs, including preimplantation embryo development, oviductal embryo transport, implantation, placentation, and parturition.[69]

Studies on animals have proved that cannabinoids have an addictive potential, involving reward system and CB1 receptors. Δ^9-THC activates the brain reward circuit by stimulating the mesolimbic dopamine system.[70,71] It has been previously demonstrated that high doses of natural and SCs produced conditioned place aversion,[72,73] whereas lower doses induced conditioned place preference.[74,75] Furthermore, microinjections in the ventral tegmental area and nucleus

accumbens produced conditioned place preference, an effect that was blocked by SR141716A (ie, rimonabant), a CB1 antagonist. Recently, Cha et al evaluated the psychological dependency potential of JWH-073, JWH-081, and JWH-210 using conditioned place preference, with significant dose-dependent increases for the SCs administered groups.[76] It must be noticed that SCs show a positive self-administration effect when the catheter was inserted directly into the ventral tegmental area,[77] but failed to induce any effect by the venous route.[57] Drug discrimination tests can establish a potential of abuse by comparing a substance to a well-known head file drug for its abuse potential. In such studies, CP47,497 generalizes for Δ^9-THC in the rat,[78] JWH-018 and JWH-073 in the monkey,[79] and JWH-200, JWH-203, JWH-250, AM-2201, and CP 47,497-C8-homologue in mice, with interesting differences in the duration of the effect.[80] HU-210 generalizes for BAY 59-3074, a partial CB1/CB2 agonist in rat, and shows no effect when the CB1-antagonist is administrated.[81]

Human use of SCs

Modalities of administration

The herbal mixtures that are sprayed with SCs and are proposed as legal alternatives to marijuana are often smoked by users.[2] Apart from herbal smoking blends, some consumers prefer homemade mixtures, using some "purified" powders of SCs sold on websites, solved in alcohol and spayed on herbals. With the recent development of electronic nicotine delivery system (e-cigarettes) as a new alternative for tobacco withdrawal, e-liquids containing SCs have recently appeared as a new trend and also as a more discreet way of consumption.

Ingestion of SCs is not often reported. One study detailed the cardiovascular effects on a man who had drunk SCs that was mixed with alcohol.[82] A case series, including eleven users that ingested brownies laced with SCs, in the manner of the well-known "space-cake" consumption of cannabis, has been recently published.[83] Other marginal routes of administration have been reported or have been discussed on user forum's such as nasal insufflation, either vaporized or not. MAM-2201 was recently quantified in the serum of a 20-year-old subject that snorted a powder sold as "Synthacaine".[84] Administration by injection could theoretically produce the typical effects of SCs, but experimental data on mice suggest that differences can exist between inhalation and injection, especially in catalepsy and perhaps discriminative effects.[85] Nevertheless, the injection route does not seem to be user's preference, partly due to the low water solubility of a number of SCs, leading to use some adjuvants.[86]

Dose used varied a lot between products, reported in experimental findings on SCs CB1 affinity. They fluctuate from several mg for the lead JWH-018, to several µg for the more potent HU-210. JWH-018 and JWH-073 were measured in a herbal incense product at concentrations of 17 mg/g and 22 mg/g respectively.[87]

Recreational effects

In humans, the recreational use of SCs generates psychoactive effects similar to cannabis, such as relaxation, calmness, euphoria, hilarity, lowering of inhibitions, disorientation, and an altered perception. Effects begin after only a few minutes from inhalation, and generally disappear after approximately 2–6 hours.[2] SCs reportedly had both a shorter duration of action and a quicker time to peak onset of effect.[88]

Acute and chronic, physical and psychological adverse/toxic effects

After the use of SCs, it is essentially neurological and cardiovascular effects that essentially occur, with a prevalence of 61.9% and 43.5% respectively, reported from 464 cases at Texas poisoning centers over 2010.[89] For the 305 adolescents, the medical outcome was known or suspected to be serious in 61% of these cases. In this young population, the most frequently reported adverse clinical effects were tachycardia (41.6%), drowsiness/lethargy (24.3%), agitation/irritability (18.5%), vomiting/nausea (21.6%), and hallucinations/delusions (10.8%). Nausea, confusion, hypertension, chest pain, and dizziness/vertigo were observed in $<$10% of the cases.[90] It is important to note that seizures were observed in 3.8% of the SCs intoxication cases, whereas they are not typically seen with marijuana use.[91] Most of these effects lasted for $<$8 hours (78.4%) and 92.9% of these cases did not have a life threatening clinical effect.[92] Meanwhile, some evaluations on emergency medical treatments suggest that SCs potentially pose a greater risk to users' health than natural cannabinoids.[93]

In addition to acute SCs-induced psychosis disorders that include disorientation and hallucinations and can have life-threatening outcome, long-term effects also are to be feared. Although the long-term consequences of SC use are unclear, in patients with psychiatric disorders, new psychiatric phenomena could appear. Celofiga et al observed a marked worsening of mood and anxiety, without exacerbation of the pre-existing known psychotic symptoms.[94] In 2015, Van Amsterdam et al showed that psychosis-inducing risk is higher with SCs than with natural cannabis.[95] Hence, the psychosis outcomes associated with SCs provide additional data to the ongoing debate on cannabinoids and psychosis.[96]

In terms of physical damage there have been several recently reported cases; a severe pulmonary syndrome in an otherwise healthy young man which was related to habitual SCs smoking;[97] a case of a cardiac arrest following K2 abuse; and a case of acute cerebral infarction in a 33 year old man, all close-temporally linked with the inhalation of XLR-11.[98,99]

Little is known on pregnancy/fertility impairment effects induced by SCs in humans due to limited studies, but regular cannabis consumption throughout pregnancy is statistically associated with decreases in birth weight.[100] This data suggests that using SCs is a potential risk factor that could impact several stages of pregnancy.[69]

Addictive potential

In humans, tolerance to SCs has been reported in literature.[101] The most common symptoms observed after an acute withdrawal are agitation, tachycardia, irritability, anxiety, and mood swings. In Auckland (New Zealand), patients withdrawing from SCs required intensive support, including medication and admission to an inpatient detoxification service. Between May 2013 and May 2014, SCs users represented the third largest group of patients admitted to this unit. Due to the stronger potency of some SCs, withdrawal signs appeared more severe but did not seem to be improved by Δ^9-THC.[102,103] Furthermore, concurrently to a craving experienced by a 23 year old man, a user of "Spice gold", substantial but reversible short-term alterations of dopamine D2/3 receptor availability were shown in a PET Scan.[104]

Pharmacokinetics

Concentrations in biological samples

The JWH-018 and JWH-073 concentrations determined in postmortem whole blood samples varied from 0.1 to 199 μg/L and 0.1 to 68.3 μg/L respectively.[105] Obtained in a patient who had smoked an herbal incense containing these two SCs, the concentrations fall from 4.8 and 4.2 μg/L (measured = 19 minutes after dose administration) to 0.6 and 0.3 μg/L (measured = 107 minutes after dose administration) for JWH-018 and JWH-073 respectively.[87] The concentration of UR-144 in a blood sample collected on admission of a patient who was unconscious on arrival was 6.1 μg/L. The parent compound was not found in urine but metabolites were identified.[106] SCs quantitated in twelve SCs serum users ranged from 0.21 to 2.94 μg/L for JWH-0250, and 0.35 to 73.05 μg/L for JWH-0122.[16] In users driving under the influence of SCs, a very large difference was seen between the lowest (0.07, 0.08, and 0.24 μg/L, respectively) and the highest (4, 9.9, and 24.5 μg/L) blood concentrations of AM-2201, JWH-08, and APINACA.[107]

Wide variations were also observed for the quantitative results in 23 hair samples of SCs abuse suspects: 0.4 to 38.9 pg/mg for JWH-018, 0.1 to 0.8 pg/mg for JWH-073, 1.7 to 739.01 pg/mg for AM-2201, 0.1 to 402.0 pg/mg for JWH-122, and 0.2 to 276.0 pg/mg for MAM-2201.[40] In two volunteers who smoked a joint prepared from different herbal incense products, the concentrations of measured SCs in neat oral fluid 5 hours later fluctuated between 0.1 and 1 μg/L for JWH-018 and JWH-210, but it was lower than 0.1 μg/L for JWH-200.[33]

Metabolism

Several recent publications characterized the metabolism pathways of SCs in vitro or identified degradant products in animal or human blood/urine samples. They all showed that SCs are extensively metabolized. SCs parent compounds are mainly hydroxylated, dealkylated, carboxylated, glucuronate. Furthermore, hydroxylation's take place on the aliphatic chain, the indole, the naphthalene, or the substituted aromatic rings that can be secondarily metabolized to carboxylic acids then conjugated to glucuronic acid.[108,109] CYP3A4 has been recently demonstrated to be the major CYP enzyme responsible for the oxidative metabolism of AKB-48.[110] Ashino et al suggested that SCs, especially naphthoylindole derivatives, are capable of inhibiting CYP1A enzymatic activity as do the major metabolites present in marijuana, cannabinol and cannabidiol.[111]

Elimination rate

The half-live of JWH-018 and JWH-073 calculated from the concentration data measured by Kacinko et al in a patient who had smoked an herbal incense containing these SCs, were 41 and 44 minutes respectively.[87] Similar results were found after an incense JWH-018 smoking experiment performed on two healthy subjects, with the calculated half-live at 43 and 34 minutes.[112] These data confirm the rapid decline of JWH-018 as early as the first puncture time at 5 minutes.

In another study an adult male volunteer orally ingested a 5 mg dose of pure AM-2201, and the AM-2201 serum concentrations was reported to decreased from 1.4 μg/L at approximately 1 hour to 0.7 μg/L at 5 hours after ingestion. AM-2201 was still detectable in serum 25 hours after administration. The half-life of AM-2201 was estimated to be approximately 4 hours.[33]

After two volunteers smoked a mixture of SCs, JWH-018, JWH-019, JWH-210, JWH-251, and JWH-307 were

still detectable for approximately 26 hours in oral fluid; and JWH-251, JWH-210, and JWH-307 could be detected at 37, 47, and 55 hours, respectively.[33]

Clinical management of acute and chronic adverse effects and addiction

As for all other new psychoactive substances, there are limited reliable data to guide clinicians managing patients with toxicity due to SCs. As a consequence, management of SCs users with acute toxic effects is mainly extrapolated from experience with longer established cannabis effects.

Diagnostic tests

Routine laboratory tests in the work-up of a potentially SCs toxic patient include 1) a basic metabolic panel with blood glucose levels, serum electrolyte concentrations, liver and kidney function tests; 2) a complete blood cell count with coagulation studies; 3) cardiac markers; and 4) total creatinine kinase. The typically available urine toxicology screen will not detect SCs but could be useful to detect other possible substances ingested. If the patient presents signs and symptoms consistent with cannabis and concurrent with a natural cannabinoid screen negative, clinicians should suspect SCs use. More specific and sensitive chromatographic methods associated to MS would successful identify SCs. Electrocardiograms might be useful especially if the patient is profoundly tachycardic, and electroencephalogram might be indicated if a seizure is suspected or observed.

Clinical exam

In addition to the above mentioned laboratory tests, detailed physical and neurological exams are imperative.

The SCs which are high-affinity and high-efficacy agonists of the CB1 receptor mimic the "tetrad" of effects induced by cannabis in rodents.[113] The common signs of SCs use are hallucinations, agitation, irritability,[114] and psychotropic disturbances and paranoia have been also described.[115] Myoclonia, seizure, nausea, vomiting, and hypokalemia may worsen the clinical status.[115] Furthermore, cardiovascular effects such tachycardia/palpitation, hypertension, chest pain, and myocardial infarction, may occur.[116] However, it is necessary to consider other well-known risk factors before formally linking SCs consumption to myocardial troubles.[117]

Due to the great variability of chemical classes that could be taken while using K2, Spice, or other mixes containing SCs, unexpected toxic effects could also appear. For example, a case series of kidney injuries was collected in 2012 and was often linked, when identified, to XLR-11 and/or UR-144.[118] Another unexpected clinical event, more potential than observed to our knowledge, due to the monoamine oxidase inhibitor activity of SCs demonstrated as real but weak in vitro, is serotoninergic syndrome that could be observed in patients, especially when high doses of SCs are taken by users.[119] More recently, new physiopathological hypotheses could explain some of the undesired effects of SCs. For example, Irie et al observed that MAM-2201 is likely to suppress neurotransmitter release in CB1 receptor expressing neurons in mouse cerebellum purkinje cells, contributing to some of the symptoms of SCs intoxication including impairments in cerebellum-dependent motor coordination and motor learning.[120] This kind of study is only the beginning step but it reinforces the need for vigilance to detect new toxicological syndromes in cases of suspicious SCs consumption. Faced with an unexplained clinical outcome, physicians have to be attentive in taking a proper history of the patient, with toxicological analysis (identification and quantification of the active substances in patient biological fluids as well as in taken drug), even if it is sometimes difficult to obtain. Also, physicians should always keep in mind that the combination of various SCs, which may be present in available products, and the taking of other illegal substances or alcohol could lead to unforeseen toxidromes.

Treatment

Considering that absorbed compounds are rarely identified and that clinical signs may be unspecific, no directive on the management of such patients has been formally promulgated by public health agencies. In fact, appropriate supportive care, targeting manifesting signs and symptoms and addressing any complications, is the primary treatment for the acutely intoxicated patient.[121] Initial management should also include monitoring telemetry for arrhythmia, myocardial ischemia, serum electrolytes, and ensuring a secure airway.[122] No specific antidote exists for SCs exposure and no curative treatment is approved by health authorities. The most common therapeutic intervention is hydration with intravenous fluids.[92] Observation until the patient demonstrates clinical improvement is recommended and chemical dependency counseling or social service involvement should be considered before discharge.[123]

The course of treatment for SCs withdrawal is not well described in the literature. In Auckland, patients appearing at a detoxification service for support with SCs withdrawal and presenting withdrawal symptoms, are managed with benzodiazepine (diazepam) and antipsychotics (quetiapine).[102] Based on a preclinical studies demonstrating a

bidirectional modulatory relationship between opioid and cannabinoid systems, naloxone was tested to manage the SCs cravings in a 39 year old woman seeking detoxification for SC addiction, and could appear to be a potential option.[124,125]

Legal status

SCs have a different legal status around the world. Many states globally still schedule them "substance-by-substance" as new ones appear on the market, in an endless race against the resellers.[10,126] On the other hand, some countries, UK being the first, have adopted a generic control status that has the great advantage of eluding the "cat and mouse game" problem. However, in the specific case of cannabimimetics that cover a large number of diversified chemical classes, it postpones the problem at one level but without solving it completely. Furthermore, generic control can pose the problem of unintended status for some substances that 1) are not CB1 agonist, and 2) show a medical interest, with an obstacle in the clinical development, as it has been seen in the UK.[127]

Conclusion

New psychoactive drugs that have appeared over the last decennia are typically dominated by cathinones and SCs. Commercialized as synthetic cannabis, SCs are sprayed onto various herbal smoking blends and traded under brand names like Spice or K2. More recently, SCs are also sold as pure substances ready to use with herbal mixtures or liquids for e-cigarettes. New compounds belonging to new chemical series are continuously emerging which generates a phenomenon that is very difficult to check. SCs pharmacologically act by binding to CB1 and/or CB2 receptors with CB1 agonists accountable for the recreational effects of SCs. The in vitro binding characteristics of SCs have been repeatedly determined, but the pharmacological properties are infrequently explored before human use. Along with unpleasant central nervous system effects, there are several physical adverse effects including kidney damage, pulmonary, gastrointestinal, and cardiovascular effects that can make consumption unsafe. Even if most of the SCs mimic marijuana effects, some SCs bind much more strongly to CB1 receptors than natural cannabinoids, which can lead to more potent, unpredictable, or dangerous effects. Because of the multitude of compounds, a complete toxicological profile of SCs is far from being drawn and understood. In addition, these SCs are often taken in conjunction with other recreational drugs or alcohol, which makes observed effects difficult to attribute to a specific product. Despite their status being illegal in some countries, SCs continue to be prevalent drugs of abuse with collateral damage such as increased road traffic risks. Accordingly, clinicians should be aware of this developing trend as an explanation for patients presenting unexpected toxidromes. Standard routine toxicology screens, particularly targeted for cannabis detection, may not detect the presence of these compounds. More specific methods may be required for identification and quantification in biological samples, with the ever-increasing diversity of new products making the updates unrealizable for the most part of toxicological laboratories. Meanwhile, clinicians should remain attentive for the risk of increasing morbidity and mortality associated to these products, continue to collect and publish new trends about these highs, and help promote awareness in their communities.

Disclosure

The authors report no conflicts of interest in this work.

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