Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs

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ABSTRACT: Synthetic cannabinoid drugs have become an established part of the recreational drug landscape in the United States and internationally. These drugs are manufactured in clandestine laboratories internationally and distributed in the United States in smoking mixtures, use of which produces effects very similar to use of marijuana. The adverse-effect profile of the drugs has not been studied in humans and infrequently in animal models, so much of the information about their toxicity comes from emergency department and treatment reports and forensic case studies. This review considers the discovery and characterization of the endocannabinoid system, approaches to receptor-binding studies of various synthetic cannabinoids from the first wave of naphthoylindoles (e.g., JWH-018) to the emerging adamantoylindole drugs (e.g., AKB-48), and their analogs, to evaluate the potential activity of drugs in this class. Currently employed approaches to assessing functional activity of the drugs using in vitro and in vivo models is also described, and comparisons made to the effects of THC. The physiological effects of activation of the endocannabinoid system in humans are reviewed, and the physiological effects of cannabinoid use are described. Case reports of adverse events including emergency department admissions, mental health admissions, and clinical and forensic case reports are presented in detail and discussed to summarize the current state of knowledge of adverse effects, both clinical and forensic in humans, including effects on driving ability, and tissue injury and death. The greatest weight is accorded to those reports that include toxicological confirmation of use. Finally, we discuss the current status of attempts to schedule and control the distribution of synthetic cannabinoids and the relevance of receptor binding and functional activity in this context. There is growing toxicological and pharmacological evidence of impairment, psychosis, tissue injury, and isolated deaths attributable to this emerging class of drugs.

KEY WORDS: Designer drugs, drug toxicity, synthetic cannabinoids, synthetic drug scheduling.

INTRODUCTION

After alcohol, marijuana ranks as the most pervasive recreational drug in the United States [49], although its legal status and patterns of use are rapidly changing. Currently 18 states and the District of Columbia have laws permitting and regulating the possession of marijuana for medical purposes [64]. Six additional states have legislation pending to legalize the medical use of marijuana. Two states, Washington [108] and Colorado [110], have additionally legalized recreational use of marijuana through ballot initiatives. Marijuana is still controlled under federal law, and possession, distribution, and use of marijuana continue to be offenses in federal jurisdictions. The illegal status of marijuana has motivated drug distributers and entrepreneurs to devise various classes of synthetic compounds[a] with cannabinoid-like effects that could be manufactured, distributed, displayed and marketed to the recreational marijuana-using population and prospective new users as a legal alternative to marijuana but with the desired effects, including mood elevation, euphoria, relaxation, creative thinking, and increased sensory awareness.

Cannabinoid receptor agonists produce neutral, possibly therapeutic effects such as appetite stimulation and nausea suppression, but also negative effects. Delta-9-tetrahydrocannabinol (THC) is the most studied drug in this class, and adverse and paradoxical effects reported by some THC users include difficulties with short-term memory, agitation, feeling tense, anxiety, dizziness or lightheadedness, confusion, and loss of coordination [55]. These effects can have significant consequences in the performance of some motor tasks and activities requiring high levels of attention, coordination, and mental acuity, most notably driving. While some of the similarities in effects between plant-derived cannabinoids and synthetic cannabinoids are assumed based on their receptor binding, no systematic dosing study has been possible in humans as a result of the unknown side-effect profile of the drugs.

Harm-reduction efforts are receiving a lot of attention in public health and policy forums with respect to management of drug abuse, especially where the adverse effects are of low severity and marijuana represents relatively little risk of toxicity beyond its intoxicating effects [92]. To adequately educate and inform users about the risks of the adverse consequences of synthetic cannabinoid drugs, it is essential

[a]Each new class contains many chemically related members which are referred to in places in this manuscript as "analogs". We use the term in its chemical sense, meaning having some chemical structural similarity, without implying any assessment as to whether they meet the various technical legal definitions for drug analogs used in statutory construction.

to understand their adverse-effect risk profile. This review focuses on the pharmacology and toxicology of synthetic drugs with cannabinoid-like effects, and describes and summarizes data from basic drug research, cannabinoid pharmacology, adverse event reports, emergency room data, case studies, and short case series to evaluate the overall adverse-effect profile and toxicology of the class of synthetic cannabinoid drugs.

Development and Proliferation of Synthetic Cannabinoids

As has been described in an earlier review in this series [78] the synthetic cannabinoids belong to a continually growing and evolving series of chemical families, with successive structural modifications being introduced to keep them in an ambiguous legal status, but retaining the desired effects of the prototypical drug, THC.

The cannabinoid CB_1 and CB_2 receptors were discovered and characterized in the late 1980s [61,86]. The endocannabinoid system was recognized to have effects in regulating appetite, nausea, mood, pain, and inflammation. Following this discovery, research groups in both industry and academia began work on identifying classes of synthetic cannabinoid agonists and antagonists for possible therapeutic applications including appetite control, pain management, and antiinflammation. These are described in various publications and patents issued in the ensuing years [41,42,59].

Other families of compounds were developed and investigated and these have been reviewed elsewhere [78]. One cannabinoid CB_1 receptor antagonist, Rimonabant (Sanofi Aventis) did reach the market but was subsequently withdrawn due to concerns about its side-effect profile [19].

The synthetic cannabinoid agonist nabilone has been successfully used as an antiemetic in cancer patients undergoing chemotherapy; however, unpredictable side effects including drowsiness, postural dizziness, and lightheadedness were reported as well as euphoria or feeling "high" [1]. Nabilone is also used as an adjunct analgesic for neuropathic pain [30].

Synthetic cannabinoids that are subject to abuse or recreational use are often included in the class of New Psychoactive Substances (NPS). NPS are synthetic chemicals manufactured with the general intent of producing effects, particularly psychotropic, hallucinatory, or stimulant, similar to the compounds whose receptors they activate, e.g., the NPS mephedrone stimulates the same receptors as amphetamine and results in a stimulant effect. Sometimes known as designer drugs, emerging drugs, research chemicals, etc., the term NPS has come to be adopted by the drugs-of-abuse monitoring community as a catch-all term over some objection that many of the substances are not novel, having been discovered over the last 50 years [44]. However, their widespread popularity is new, justifying the use of that term. These chemicals are marketed to a largely young audience with the allure of being "legal highs", and being generally undetectable in routine pre-employment, military, or probation/parole drug tests [3].

The prevalence of synthetic cannabinoid use is difficult to gauge in the United States or elsewhere [23]. Many of the tools used to monitor patterns of its use have been in place for only a few years, and data are frequently released many months later, which in terms of the life cycle of the drugs involved in this market, is a long time. In addition, many of the clinical reports of adverse events are frequently unconfirmed by chemical or toxicological tests, raising questions about the actual identity of the agent causing the effect. Nevertheless, the Monitoring the Future study [49] has reported rates of last-year use of synthetic cannabinoids of 8.8% and 11.3% for 15–16-year-olds and 17–18-year-olds, respectively. European surveys suggest much lower rates of prevalence of synthetic cannabinoid use among similar populations [23].

I. CANNABINOID PHARMACOLOGY AND TOXICOLOGY

A. Cannabinoid Receptors

In 1988, researchers identified the existence of cannabinoid receptors in rat brain and characterized them. Two years later another group mapped the location of cannabinoid receptors in human brain (CB_1), and in 1993 the peripheral cannabinoid receptors (CB_2) were cloned [6]. In the succeeding 25 years, there has been a significant increase in the understanding of the cannabinoid receptor system and its complex role in modulating pain, appetite, and mood.

CB_1 and CB_2 are members of the p-glycoprotein family of receptors. Signal transduction pathways include inhibition of cyclic adenosine monophosphate (cAMP) production, modulation of ion channels, and promotion of mitogen-activated protein kinase (MAPK) activation. Detailed explanation of the variety of signaling pathways initiated by the cannabinoids is beyond the scope of this paper; however, there are several reviews of the current state of knowledge on this topic [4,39,77,80,100].

In general, the CB_1 receptor is responsible for the psychotropic effects of cannabis, and therefore the ability of a ligand to bind to and act as an agonist at the CB_1 receptor may indicate its potential as an alternative to marijuana for recreational use. The role of the CB_2 receptors is largely as immune modulators and the target for potential therapeutic agents.

B. Receptor Binding Studies

A variety of techniques have been used to measure the binding affinity of a ligand for a specific receptor. Most published studies of synthetic cannabinoid binding affinity are based on the competitive binding assay described by Compton et al. [15]. The procedure involves incubation of isolated CB1 and/or CB2 receptors with a predetermined concentration of radiolabeled CP 55,490. Different compounds are then added at increasing concentrations and allowed to compete with the radioligand for binding. As the concentration of unlabeled ligand is increased, the amount of radioligand that binds to the receptor decreases. IC_{50} (inhibitory concentration) is the concentration of unlabeled ligand necessary to displace 50% of the radiolabeled CP 55,490. Once IC_{50} is determined for a specific drug, its binding affinity (K_i) can be calculated. K_i is calculated using the Chen-Prousoff equation:

$$K_i = \frac{IC_{50}}{1 + \frac{[L]}{K_d}}$$

where [L] is the concentration of radioactive ligand used in the experiment and K_d is the dissociation constant for the ligand [12]. **Table 1** summarizes the published binding affinities for a selection of synthetic cannabinoid drugs of current interest or concern. A compound with a lower K_i binds more tughtly to the receptor.

Although binding affinity provides an important indicator for evaluating the abuse potential of a synthetic cannabinoid, it is also necessary to evaluate the efficacy and potency at the CB_1 receptor. Efficacy is the maximum biological effect a drug can have based on its receptor binding, and potency is a measure of the amount of drug needed to achieve a predefined biological effect. Functional assays designed to measure the efficacy and potency of a receptor ligand are used to determine if the substance is an agonist or antagonist and are a means of evaluating the likelihood a compound will be used for its pharmacological effect. The main functional assays used are described below.

C. Functional Assays

Howlett et al. provide a thorough review of in vitro and in vivo bioassays that have been used to evaluate the ability of compounds to elicit response by binding to the CB_1 and/or CB_2 receptors [39]. These assays can be used to evaluate the structure-activity relationship (SAR) of synthetic cannabinoids. The effects of small changes in the molecular structure can thus be assessed and quantified. The majority of SAR studies have been performed on compounds with a high affinity for the CB_2 receptor because the primary goal of many researchers was to identify compounds with therapeutic potential. However, since the rise in popularity of synthetic cannabinoids as abused substances, more studies are being performed on compounds that bind preferentially to CB_1. The most common approach used to determine if a specific analyte is an agonist for the CB_1 receptor is to assess its binding affinity, evaluate guanosine 5'-O-[gamma-thio] triphosphate (GTPγS) binding as an indicator of signal transduction, and then to perform a panel known as the mouse tetrad assay to determine physiological effects in an animal model.

1. In Vitro Functional Assay

Agonists of CB_1 receptors cause a conformational change that results in the G-protein-mediated release of guanosine diphosphate (GDP) and binding of guanosine triphosphate (GTP). Use of GTPγS, a radiolabelled GTP analog, allows for the measurement of activation of the receptor. The application of the GTPγS binding assay to WIN 55212-2, a full CB_1 receptor agonist, was first described by Seeley et al. in 1995 [83] and was later optimized by Griffin et al. [32]. Once the optimal conditions for WIN 55212-2-stimulated GTPγS binding were identified, they were employed to investigate a variety of structurally diverse compounds for cannabinoid-like activity. The ability of a variety of compounds with high CB_1 selectivity to stimulate GTPγS binding is summarized in **Table 2**. Stimulation is measured by determining the EC_{50}, i.e., the concentration of the candidate compound at which the response is 50% of the response of the normalization compound. Frequently E_{max}, the maximum response that can be achieved by the compound being tested, is also determined in this way. CB_2 receptor activity is evaluated in a similar fashion using CP 55,940 as the normalization compound.

2. In Vivo Functional Assay

The in vivo functional assay is based on the mouse tetrad assay, which consists of four tests, namely: spontaneous activity, tail-flick latency, core temperature (hypothermia), and catalepsy [54]. Spontaneous activity is measured by placing a mouse in an activity cage and recording the number of times the mouse intercepts a photocell beam during a 10-min period. Tail-flick latency is a measure of analgesia; the mouse's tail is placed in a hot water bath (52 ^{o}C) and the time it takes for the mouse to remove its tail from the water is recorded. Core temperature is taken by rectal probe and catalepsy is determined by placing the mouse on a bar and measuring how long it remains immobile. A summary of reported mouse tetrad test results for synthetic cannabinoid drugs is presented in **Table 3**.

Table 1. Binding affinities of synthetic cannabinoids determined by displacement of radioactive CP 55,940 (unless otherwise marked)

Compound	CB_1 K_i (nM)[a]	CB_2 K_i (nM)[a]	CB_2 K_i/ CB_1 K_i[b]	Ref.	Compound	CB_1 K_i (nM)[a]	CB_2 K_i (nM)[a]	CB_2 K_i/ CB_1 K_i[b]	Ref.
HU-210	0.061±0.007	0.52±0.04	8.52	[27]	XLR-11	24±(4.6)	2.1±(0.6)	0.09	[112]
AM-694	0.08	1.44	18.00	[60]	JWH-306	25±1	82±11	3.28	[43]
ADB-FUBINACA	0.36	—	—	[10]	JWH-251	29±3	146±36	0.20	[43]
JWH-210	0.46±0.03	0.69±0.01	1.50	[43]	UR-144	29±(0.9)	4.5±(1.7)	0.01	[112]
CP 55,940	0.58±0.07	0.69±0.02	1.19	[87]	JWH-251	29±3	146±36	5.03	[43]
JWH-122	0.69±0.5	1.2±1.2	1.74	[41]	JWH-237	38±10	106±2	2.79	[43]
AM-2201	1	2.6	2.60	[59]	Delta9-THC	41±2	36±10	0.88	[15,87]
JWH-081	1.20±0.03	12.4±2.23	10.33	[5]	JWH-200	42±5	—	—	[5]
WIN 55212-2	1.9±0.09	0.28±0.16	0.15	[52,87]	JWH-211	70±0.8	12±0.8	0.17	[41]
CP 47,497	2.20±0.47	—	—	[89]	JWH-312	72±7	91±20	1.26	[43]
AM-411	6.9	52	7.50	[59]	JWH-167	90±17	159±14	1.77	[43]
JWH-203	8.0±0.9	7.0±1.3	0.88	[43]	JWH-303	117±10	138±12	1.18	[43]
JWH-249	8.4±1.8	20±2	2.38	[43]	JWH-205	124±23	180±9	1.45	[43]
JWH-073	8.9±1.8	38±24	4.27	[5]	JWH-208	179±7	570±127	3.18	[43]
JWH-018	9.0±5.0	2.9±2.6	0.32	[5]	JWH-206	389±25	498±37	1.28v	[43]
JWH-019	9.80±2.00	5.55±2.00	0.57	[5]	JWH-313	422±19	365±92	0.86	[43]
JWH-250	11±2	33±2	3.00	[43]	JWH-209	746±49	1353±270	1.81	[43]
JWH-204	13±1	25±1	1.92	[43]	JWH-248	1028±39	657±19	0.64	[43]
JWH-305	15±1.8	29±5	1.93	[43]	JWH-201	1064±21	444±14	0.42	[43]
JWH-302	17±2	89±15	5.24	[43]	JWH-207	1598±134	3723±10	2.33	[43]
JWH-311	23±2	39±3	1.70	[43]	JWH-202	1678±63	645±6	0.38	[42]

[a] Results are reported as mean plus/minus standard deviation or mean plus/minus (standard error of the mean). Compounds with a lower K_i bind more tightly to the receptor.
[b] The CB_2 K_i to CB_1 K_i is an indicator of potential for recreational use. A high ratio indicates preference for the CB_1 receptor.

Table 2. GTP binding assay

Compound	EC_{50} (nM)	CB_1 E_{max} (%)	CB_2 EC_{50} (nM)	E_{max} (%)	Ref.
JWH-251	29.0±5.5	97.6±1.5	8.3±0.8	47.0±2.4	[43]
JWH-302	29.3±0.8	91.5±2.9	24.4±6.9	33.5±2.9	
UR-144	95±(20)		334±170		[112]
XLR-11	159±(38)		145±74		
JWH-210	20.4	148			[69,
AM-2201	24.4	119			70]
JWH-122	32.9	129			
JWH-018	36	111			
AM-694	52.8	63			
JWH-019	98.9	89			
RCS-4	199	72			

D. Halogen-Substituted Synthetic Cannabinoids

Halogenation, especially fluorination, of the aliphatic side chain of established cannabinoid agonists is a popular approach to synthesizing novel active drugs and attempting to increase their potency. The halogenated drugs frequently appear on the market alongside their nonhalogenated precursors; for example, AM-2201 is 5-fluoro-JWH-018, and XLR-11 is 5-fluoro UR-144. Recent drugs to appear on the market such as APINACA (AKB-48), and ADB-PINACA are in our experience encountered in mixtures alongside their 5-fluoropentyl analogs [16,46,56,69,70]. Work by researchers in drug development have demonstrated that this side-chain halogenation of synthetic cannabinoids of the naphthoylindole and benzoylindole classes can lead to an increase in both CB_1 and CB_2 binding [41,43,59,112]. CB_1 and CB_2 receptor binding affinities (K_i) for many synthetic cannabinoids and their halogenated homologs are listed in **Table 4**.

These results demonstrate that a single-atom substitution of fluorine on the terminal position of the pentyl chain increased the compound's ability to bind at the CB_1 receptor. For example, AM-2201 has approximately 10-fold stronger binding than its nonfluorinated analog JWH-018, and AM-694 has approximately 1,709-fold stronger binding than its nonfluorinated analog AM-679. The size of the halogen (with respect to atomic radii and possible steric hindrances) that substitutes the hydrogen appears to be significant in this respect. In the case of AM-698, the iodo-substituted analog of AM-679 had 10-fold weaker binding at CB_1.

Table 3. Mouse Tetrad Test: reported are either the ED_{50} (95% confidence interval) or percent inhibition of the level of activity (SA) or maximal antinoceptive effect achieved (dose in μg/kg)[a]

Compound	Spontaneous activity	%MPE	Rectal temp. change (°C)	Ring immobility	Average potency	Ref.
Delta 9-THC	0.92	2.7	2.5	Not tested	2.0	[111]
WIN 55,212-2	0.19	1.4	1.5	Not tested	1.0	
JWH-018	0.44	0.09	1.7	3.9	0.7	
JWH-073	0.34	1.3	3.3	Not tested	1.6	
JWH-019	0.96	0.73	1.5	Not tested	1.0	
JWH-167	1.6 (0.9–2.6)	1.3 (0.7–2.3)	13 (7–23)	Not tested	5.3	[113,
JWH-205	19 (9–34)	13 (9–19)	13 (9–16)	Not tested	15	114]
JWH-251	0.9 (0.6–1.6)	0.9 (0.6–1.3)	6 (3–9)	Not tested	2.6	
JWH-208	2.8 (0.9–9)	16 (9–25)	38 (22–63)	Not tested	18.9	
JWH-209	39 (21–75)	57 (33–99)	81 (42–153)	Not tested	59	
JWH-306	87% (2.9)	1.1 (0.9–1.4)	1.1 (0.9–1.7)	Not tested	1.1	
JWH-302	0.6 (0.3–1.2)	0.9 (0.6–1.2)	3 (2.1–4.2)	Not tested	1.5	
JWH-201	84% (90)	35% (90)	−2.3 (90)	Not tested	–	
JWH-202	26 (11–51)	51 (29–97)	−2.5 (86)	Not tested	38.5	
JWH-203	0.1 (0.09–0.2)	0.3 (0.2–0.6)	6 (5–6)	Not tested	2.1	
JWH-204	0.8 (0.3–1.7)	0.6 (0.6–0.8)	2 (1.4–2.5)	Not tested	1.1	
JWH-237	1.5 (0.9–3)	3 (3–6)	3 (2.6–6)	Not tested	2.5	
JWH-303	90% (85)	100% (85)	−4 (85)	Not tested	–	
JWH-206	76% (29)	Inactive (29)	Inactive (29)	Not tested	–	
JWH-207	Inactive (28)	Inactive (28)	Inactive (28)	Not tested	–	
JWH-249	1 (0.5–2)	0.3 (0.3–0.5)	1 (0.8–1.3)	Not tested	0.8	
JWH-305	1.5 (0.2–7.5)	1.8 (1.3–2.5)	5 (5–8)	Not tested	2.8	
JWH-248	Inactive (26)	Inactive (26	Inactive (26)	Not tested	–	
JWH-311	2.5 (out of range)	2.5 (out of range)	1.2 (0.9–1.9)	Not tested	4.2	
JWH-312	6 (5–7)	1.9 (1.2–2.5)	5.6 (5.3–5.9)	Not tested	4.5	
JWH-313	Inactive (9)	Inactive (9)	Inactive (9)	Not tested	–	
XLR-11	0.9 (0.36–1.64)	3.3 (2.22–4.77)	0.6 (0.58–0.91)	0.6 (0.57–0.64)	1.4	[112]
UR-144	1.0 (0.55–2.25)	2.6 (1.83–4.05)	0.6 (0.51–0.74)	1.0 (0.64–1.66)	1.3	

[a] ED_{50} was defined as the dose at which half the maximal effect occurred. The maximal effect was 90% inhibition of spontaneous activity, 100% maximal antinociceptive effect (MPE), –6 °C change in rectal temperature, and 60% ring immobility. Dose is reported as μmol/kg. Potency is the average ED_{50} for all tests and as μmol/kg for comparison between compounds.

Table 4. Evaluation of several non-halogenated vs. halogenated synthetic cannabinoids (single atom substitution)

Parent compound	Halogenated analog	K_i (nM) CB_1	K_i (nM) CB_2	Ref.
THC[a]		41±2	36±10	[15,87]
JWH-018 Series	JWH-018	9±5	2.9±2.6	[5]
	5-Fluoro-pentyl-JWH-018 (AM-2201)	1	2.6	[60]
	4-Fluoro-naphthyl-JWH-018 (JWH-412)	7.2±0.5	3.2±0.5	[113,114]
	4-Chloro-naphthyl-JWH-018 (JWH-398)	2.3±0.1	2.8±0.2	[113,114]
	4-Bromo-naphthyl-JWH-018 (JWH-387)	1.2±0.1	1.1±0.1	[113,114]
AM-679 Series	AM-679	13.5	49.5	[41]
	5-Fluoro-pentyl-AM-679 (AM-694)	0.08	1.44	[60]
	5-Iodo-pentyl-AM-679 (AM-698)	135.8	314.7	[60]
UR-144 Series	UR-144	29	4.5	[112]
	5-Fluoro-pentyl-UR-144 (XLR-11)	24	2.1	[112]

[a] THC binding shown for comparison.

E. Animal Studies

Cannabinoids have been reported as being useful in the treatment of pain, nausea, vomiting, epilepsy, ischemic stroke, cerebral trauma, multiple sclerosis, cancerous tumors, movement disorders such as Parkinson's and Huntington's Disease, mood and anxiety disorders, and other disorders and diseases in humans and animals [72]. Many of these effects are mediated via modulation of CB_1 and CB_2 receptors as discussed above. Synthetic cannabinoids are also known to exhibit pharmacological effects through interaction with both CB_1 and CB_2 receptors located throughout the central and peripheral nervous system. In general, interaction with CB_1 receptors results in alteration of mood (elevation or anxiety and panic), memory, and perception of time as well as auditory and visual cognition [72]. In addition, antinociception, hypothermia, and hypomobility may also be indicated [113]. Agonistic binding to CB_2 receptors, which are mainly located in immune cells but do also exist in the CNS, results in release of immunomodulating agents and immune-cell migration; therefore, ligands interacting with these sites are useful in reduction of inflammatory induced pain resulting in peripheral antinociception [115]. In bone cancer, the pain is associated with different pathologies. These can be assessed in animal models via two types of study. The hot plate test is used as a measure of hyperalgesia, i.e., increased response to painful stimulus and the von Frey test is used to measure mechanical allodynia, i.e., painful response to a normally innocuous stimulus. The von Frey test uses a fine-gauge metal wire, to test a rodent's sensitivity to pinch and mechanical stimuli. Via mice bone cancer models dosed with 0.3–10 mg/kg AM-1241, it has been shown that thermal hyperalgesia and mechanical allodynia are abolished and that the responses are dose related [17].

Studies of the effects of these drugs are mainly limited to animal models with human studies being limited to clinical or forensic observations and user testimonials as discussed later in this review. In general, the toxic effects in humans appear to have the potential to be more severe and unusual than THC and include psychosis, seizures, tachycardia, autonomic hyperactivity, and suicidality. There follow summaries of the animal-based behavioral outcomes for the best studies of synthetic cannabinoid agonists.

1. JWH-018

Initial studies in rats on JWH-018 showed that it produced the tetrad of effects classically associated with cannabinoids (analgesia, catalepsy, hypomobility, and hypothermia) with effective doses ranging from 0.09 mg/kg for analgesia to 1.47 mg/kg for hypothermia [111].

Studies on CB_1 receptors form the majority of research being done on synthetic cannabinoids. The effects of JWH-018 on neurotransmission were investigated by Atwood and Mackie using a neuron model. JWH-018 was found to decrease the probability of neurotransmitter release in a concentration-dependent manner via CB_1 as measured through glutamate release, which is inhibited in a dose-response fashion [4]. As CB_1 receptor stimulation also results in the activation of MAPKs, this was also investigated with JWH-018 with a positive result and maximal activation after 5–10 min of treatment. MAPKs are involved in the response to potentially harmful, abiotic stress stimuli. When JWH-018 was compared to the known CB_1 agonist WIN 55,212 it was found to be more potent by a factor of about 16 (EC_{50} 4.4 nM vs. 69.9 nM).

Observations during repeated dosing with JWH-018 in a rat study include severe lethargy and an unresponsive catatonic state at all doses from 0.1 to 10 mg/kg. The highest dose resulted in respiratory depression and death of one male rat. A rat pharmacokinetic study with bolus IV injection of 5 mg/kg indicates a biphasic distribution suggesting both distribution and elimination phases. A clearance rate of 55 mL/min/kg (as per rat blood flow) and a half-life of 2 h were also observed [106].

2. CP 47,497

CP 47,497 is at least as potent as THC with respect to analgesic, motor-depressant anticonvulsant, and hypothermic effects in mice, rats, and dogs [47]. It has also been shown to elicit vocalization in palpated rats and ataxia in dogs [109]. In drug-discrimination studies in rats, the stimulus properties of THC (3.2 mg/kg) are generalized to CP 47,497 with an absolute threshold dose 3–14 times lower than the threshold dose of THC itself (route dependent). Moreover, the rats were unable to discriminate between the stimulus properties of equated intraperitoneal doses of THC and CP 47,497 after prolonged training. Although behavioral effects have been observed for CP 47,497, similarly to THC it does not resemble standard antipsychotic, antidepressant, or hypnotic drugs in simple drug-interaction tests [76].

3. HU-210

HU-210 ((-)-11-hydroxy-Δ8-THC-dimethylheptyl) is a more potent synthetic analog of THC. HU-210 exhibits similar neuroblast cell membrane CB_1 receptor binding as CP 55,940. In mouse models testing tetrad behavioral responses (hypothermia, analgesia, hypoactivity, and catalepsy) the ED_{50} is 5–20 μg/kg [89].

There is evidence that HU-210 causes impairment of memory and hippocampal activity. Spatial memory deficits are due to abnormalities in hippocampal cell firing [79].

HU-210 also causes an increase in arachidonic acid levels, increased calcium concentrations, and translocation of PLA2. These result in inflammatory responses indicating CB_2 receptor agonism. The effects were found to be dose dependent [36].

Following subchronic and chronic exposure to HU-210, a large dose-dependent CB_1 receptor adaption that appears to be region specific has been observed with development of tolerance to drug-induced body weight loss. The molecular mechanisms appear to be similar to those reported for THC.

The dentate gyrus in the hippocampus in the adult mammalian brain is thought to contribute to the formation of new memories. It contains neural stem progenitor cells (NSPCs) capable of generating new neurons, i.e., neurogenesis, throughout the lifespan of mammals. This is important for understanding mechanisms of psychiatric disorder and drug abuse. Most drugs of abuse examined to date decrease adult hippocampal neurogenesis. However, following chronic, but not acute, HU-210 treatment, neurogenesis in the hippocampal dentate gyrus of adult rats was promoted, resulting in anxiolytic- and antidepressant-like effects [47]. This promotion of neurogenesis may also be responsible for the potential use of cannabinoids in dementia [94].

4. AM-411

AM-411 ((-)-1-adamantyl-Δ8-tetrahydrocannabinol) is a full agonist at cannabinoid CB_1 receptors. AM-411 has been shown to produce dose-dependent behaviors consistent with CB_1 agonism, including analgesia, hypothermia, catalepsy, and reductions in locomotion, which were blocked by a CB_1-selective antagonist. AM-411 also produces a dose-dependent suppression of lever-pressing in a task known to be sensitive to administration of CB_1 agonists. Detailed analysis of the temporal patterns of the responding rats showed that AM-411 altered the distribution of interresponse times. AM-411 also decreases relative interior activity in the open field, which is suggestive of an anxiogenic effect in a rat model [62].

5. UR-144

UR-144 has been shown to have full agonist effects at both CB_1 and CB_2 receptors showing low nanomolar (<30) affinity for CB_1 and CB_2 receptors, activating these receptors as full agonists, and producing dose-dependent effects that were blocked by rimonabant, a cannabinoid antagonist, in mice. The cannabimimetic effects observed included antinociception, hypothermia, catalepsy, and suppression of locomotor activity. More recently this study has been extended to XLR-11, which provided similar results to UR-144 [112].

6. JWH-018 and AM-2201 Active Metabolites

In 2011 it was discovered that in addition to parent synthetic cannabinoids being active, that at least five of the hydroxylated metabolites of JWH-018 also exhibit activity at CB_1 receptors [9].

Five hydroxylated and one carboxyl metabolite of JWH-018 were investigated, with the hydroxylated metabolites exhibiting equal or greater affinity to CB_1 receptors as THC. All five hydroxylated metabolites were also found to exhibit larger K_i values than the parent drug and thus to contribute to the side-effect profile of JWH-018. The carboxylated metabolite was found to be inactive at CB_1 receptors.

These findings have been further supported by a study by Chimalakonda et al., who evaluated the cytochrome P450-mediated oxidative metabolism of JWH-018 and its fluorinated counterpart [13]. The hydroxlated metabolites of both compounds were found to exhibit activity at the CB_1 receptors.

F. Synthetic Cannabinoid Effects in Pregnancy

Evidence suggests that tightly controlled endogenous cannabinoid signaling is required for optimal progression of pregnancy events [93]. The developing embryo expresses cannabinoid receptors early in development that are responsive to the endocannabinoid anandamide in utero [58]. This signaling is important in regulating the timing of implantation of the embryo and receptivity of the uterus. Additionally, in mice, it has been shown that anandamide modulates the probability of implantation to the uterine wall.

During pregnancy, maternal use of synthetic cannabis could upset the balance of cannabinoid signaling and may therefore compromise pregnancy outcome. Maternal use of natural and synthetic cannabinoids has been shown to disturb pregnancy events [74].

Although there is no direct evidence available to show that synthetic cannabinoids compromise the processes the uterus undergoes to prepare for embedding of the embryo or birth, studies in CB_1 knockout mice suggest that both of these are also potential targets of synthetic cannabinoids [82].

II. ADVERSE EFFECTS IN HUMANS

A review was conducted to document specific relationships between the use of unique identified synthetic cannabinoid compounds and observed clinical effects, including toxicity and death. The reports discussed below were identified through systematic review of literature regarding synthetic cannabinoid use in Medline

(PubMed®)[b], perusal of the tables of contents of key journals, review of abstracts from professional meetings and conferences, government reports and alerts, and other Internet searches. In assessing published reports, those of most value include toxicological or chemical confirmation of the specific drug involved (ideally in a biological sample, along with a quantitative measurement) or at least of the material ingested by the subject. Many of the articles and manuscripts reviewed, particularly large case series, lacked this chemical confirmation, and therefore less weight has been attached to their findings in this summary. This lack of chemical confirmation is undoubtedly a reflection of the limited ability of analytical laboratories to keep up with the rapidly changing menu of target compounds, and the need for certain specialized types of testing equipment, most significantly liquid chromatography tandem mass spectrometry (LC-MS/MS). Other factors that hamper efforts to develop robust quantitative tests include the delayed availability of standard reference materials and their deuterated analogs required for quantitative measurement, making it difficult to validate protocols for the identification and quantitation of the emerging synthetic cannabinoid compounds.

Reports were placed in four categories in order of increasing relevance: (a) short (n<50) case series or reports with no toxicological confirmation (**Table 5**); (b) case series with large populations with mixed or no toxicological confirmation (**Table 6**); (c) case series reports with qualitative confirmation in blood or urine (**Table 7**); and (d) case series or reports with qualitative or quantitative confirmation in blood or serum/plasma (**Table 8**). While only the studies in Table 8 are discussed in detail, the symptoms and adverse effects described in Tables 5–7 are qualitatively consistent with the better documented case studies.

Table 8 reflects summary results from those publications that contained either qualitative or quantitative confirmation of the drugs present, and clinical, forensic, or symptomatic reports of their adverse effects. Ten such studies were published between January 2010 and July 2013, and are now appearing in the literature with increasing

Table 5. Case series or reports with no toxicological confirmation

Product	*n*	Patient information	Adverse effects	Ref.
"K2"	10	9 males; 1 female 16–27 years of age	Increased heart rate, increased blood pressure, agitation, hallucinations, pallor, numbness, vomiting, tremors, seizures	[20]
"Pure"	1	17-year-old female	Agitation, visual hallucinations, anxiety, increased heart rate, mild increased blood pressure, low potassium in blood	[107]
"Synthetic weed"	1	19-year-old male	Alveolar infiltrates	[57]
"Elation Déjà Vu"	1	32-year-old male	Anxiety, nausea, and shortness of breath, tachycardia	[24]
	11	10 males; 1 female 15–19 years of age	Irritability (36%); anxiety (27%); numbness (18%); anger (9%); sadness (9%); memory changes (100%); auditory perceptual changes (9%); visual perceptual changes (45.4%); paranoid thoughts (35%); palpitations (27%); blackouts (9%); restlessness (9%)	[11]
"K2"	1	17-year-old male	Vomiting, hyperventilating, responding inappropriately to questions, low potassium in blood	[26]
"Spice"	1	30-year-old male	Withdrawal on first day of abstinence — irritability, emotionally uneasy, anxiety, poor sleep. productive cough — pulmonary exam normal	[33]
Synthetic cannabinoid	1	19-year-old male	Nausea and vomiting, abdominal pain	[67]
Synthetic cannabinoid	1	15-year-old male	Nausea and vomiting, abdominal pain	
Blueberry-flavored	1	21-year-old male	Nausea and vomiting, flank pain	
Synthetic cannabinoid	1	25-year-old male	Nausea and vomiting	
"Synthetic marijuana"	1	30-year-old male	Nausea and vomiting, abdominal pain	
"Spice Gold"	1	33-year-old male	Nausea and vomiting	
"Mad Monkey" or "Clown Loyal"	1	27-year-old male	Flank pain	
Synthetic cannabinoid	1	15-year-old male	Nausea and vomiting, abdominal pain/back pain	
Flame 2.0	1	15-year-old female	Nausea and vomiting	

[b]Search terms used were: synthetic cannabinoid; cannabinoid agonist; cannabinoid antagonist; cannabinoid toxicity; cannabinoid adverse effects; cannabinoid functional assay; synthetic cannabinoid binding; synthetic cannabinoid emergency room; synthetic cannabinoid forensic; synthetic cannabinoid animal studies; synthetic cannabinoid in vitro; synthetic cannabinoid renal; and individual compound names.

Table 6. Case series with large populations with mixed or no toxicological confirmations

n	Patient information	Adverse effects	Ref.
464	Male 73.9%; female 25.4%; unk. 0.6%	Cardiovascular (43.5%) Slow heart rate (1.5%); chest pain (6.7%); low blood pressure (2.2%); high blood pressure (9.7%); conduction disturbance/dysrhythmia/electrocardiogram change (1.7%); increased heart rate (37.3%)	[29]
	≤19 years 40.9%; ≥20 years 57.3%; unk. 1.7%	Dermal (2.6%) Edema (0.2%); erythema — redness of skin (0.2%); hives (0.2%); irritation/pain (0.4%); pallor (1.3%); itchy skin (0.2%); rash (0.2%)	
		Gastrointestinal (21.1%) Abdominal pain (1.1%); anorexia/weight loss (0.4%); dehydration (0.2%); diarrhea (0.6%); vomiting blood (0.2%); nausea (9.9%); throat irritation (0.2%); vomiting (15.7%)	
		Hematological (0.4%) Abnormal bilirubin (0.2%); abnormal liver function test (0.2%)	
		Neurological (61.9%) Agitation (18.5%); uncoordinated movement (2.2%); coma (1.5%); confusion (9.1%); dizziness (8.6%); drowsiness (18.5%); hallucinations (10.8%); sustained muscle contraction (0.2%); headache (3.0%); muscle weakness (0.9%); numbness (1.5%); paralysis (0.2%); seizures (3.7%); slurred speech (1.7%); loss of consciousness (1.9%); tremors (3.9%); ocular (5.0%); blurred vision (0.4%); irritation/pain (0.2% onstriction of the pupil 0.2%); dilated pupils (2.8%); involuntary eye movements (0.6%)	
168	139 male; 9 female	Dry mouth, drowsy/tired, heart racing, anxious, paranoid, nauseous, hallucination, vomiting	[105]
416	Male 74.9%; female 24.4%	Increased heart rate (36.6%); agitation/irritability (19.1%); drowsiness/lethargy (17.5%); vomiting (14.8%); hallucinations/delusion (11.2%); high blood pressure (9.6%); nausea (9.3%); confusion (8.9%); dizziness/ vertigo (8.9%); chest pain (6.9%)	[28]
	≤19 years 40.2% ≥20 years 57.9% unk. 1.9%		
1,898	Males 79.4%	Increased heart rate (40%); agitation/irritability (23.4%); vomiting (15.3%); drowsiness/lethargy (13.5%); confusion (12%); nausea (10%); hallucination/delusion (9.4%); increased blood pressure (8.1%); dizziness/ vertigo (7.3%); chest pain (4.7%); seizures (3.8%); death — 1 case (58-year-old male, due to cardiac arrest)	[40]

frequency. The fact that these reports are among the most recent of those studied reflects the outcome that additional laboratories have acquired the capability of performing this analysis.

A. Physiological Effects

Physical effects reported from a number of different synthetic cannabinoids both individually (JWH-018) [96] and in combination (JWH-018 and CP 47,497 (C8) [37], JWH-018 and JWH-073 [84]) include altered mood and perception, red or bloodshot eyes, nausea, vomiting, listlessness, fever, sweating, and dryness of the mouth. The highest serum concentration of synthetic cannabinoid exhibiting these symptoms was a combination of 20 ng/mL JWH-210, 8.4 ng/mL JWH-081, and 2.1 ng/mL JWH-122. The lowest concentration was a combination of 0.17 ng/mL JWH-122 and 0.10 ng/mL JWH-250. The physiological effects can be wide-ranging, from mild symptoms to severe adverse effects targeting specific organs. Some of the more severe effects are discussed in more detail below.

1. Kidney Damage

Acute kidney injury has been reported, related to the consumption of XLR-11 [67,97]. Effects reported include vomiting, flank pain, abdominal pain, and acute kidney injury (diagnosed by increased urinary creatinine concentrations) [67]. In each case blood or urine was collected on the same day, or two days after the synthetic cannabinoid was consumed. The presence of XLR-11 or its metabolite (UR-144 N-pentanoic acid) was confirmed in both reports. The highest UR-144 N-pentanoic acid concentration measured was 529 ng/mL in the urine, on the day of use [97]. Kidney injury has also been reported in a further 10 cases, but no toxicological analysis was performed in these cases [67]. To date, no quantitative toxicology results are available that support the presence of other synthetic cannabinoids producing this effect. A journal editorial commenting on the paper by Murphy does caution that the identification of XLR-11 may reflect the use of the compound at the time the study was completed, rather than a correlation between XLR-11 and acute

Table 7. Case series reports with qualitative confirmations

Product	*n*	Patient information	Patient sample	Test and qualitative result Type	+ or –	Adverse effects	Ref.
"Spice Gold"	1	21-year-old male	Urine and serum	Toxicol. screen	–	Panic attack, anxiety, blurred vision, unsteady gait, fear, excessive sweating, irritability, weakness, increased heart rate.	[66]
"Spice Gold"	1	20-year-old male	Urine	Toxicol. screen	–	Withdrawal symptoms: profuse sweating, internal unrest, tremor, palpitation, nausea, insomnia, headache, diarrhea, vomiting.	[118]
"Spice" 8 out of 9 reported use	9	13–27 years old	Urine test (3); no test (6)	THC	–	Increased heart rate (66.7%); combination of symptoms: increased heart rate, temperature and pupil size, reduced bowel sounds and sweating (44.4%); agitation (44.4%); tremor (44.4%); confusion (33.3%); pallor (22.2%); dilated pupils (22.2%); high blood pressure (22.2%)	[6]
Unk.	3	2 males; 1 female 22±1 years old	Urine	JWH-018	+	Reddening of eyes, tachycardia, anxiety, paranoia and hallucinations accompanied by short-term memory defects and the impaired sense of time.	[90]
"Banana cream nuke"	2	20-year-old female 22-year-old female	No test Urine	— Toxicol. screen Screen of synthetic cannabinoid	— – JWH-018 JWH-073	Anxiety, increased pulse Anxiety, palpitations	[84]
"Spice"	1	20-year-old male	Urine	Toxicol. screen	–	Severe anxiety and paranoia, increased heart rate, and excessive sweating, with halting speech and avoidant eye contact, auditory and visual hallucinations	[8]
"Spice"	1	25-year-old male 0 day since last use	Not stated	JWH-018 metabolite JWH-073	+ +	Possible seizure, increased heart rate, increased acidity of blood, unresponsiveness	[88]
"Spice"	1	21-year-old male Last use unknown	Not stated	JWH-018 JWH-073	+ +	Agitation, high blood pressure	
"Spice"	1	19-year-old male 0 day after last use	Urine	JWH-018 HWH-073	+ +	Paranoia and delusions	
"Spice"	3	All males 20–30 years old A B C	 Urine Urine Urine	 Toxicol. screen/cannabis Toxicol. screen Toxicol. screen/cannabis	 + – +	Mild effects common to all: disorganized speech, poor concentration Paranoia, delusions, aggression, suicidality Agression, paranoia, delusions Delusions and suicidality	[104]
—	10	All males 21-years old	Urine Blood	Cannabis Synthetic cannabinoid	+ (4) + (2)	Paranoid delusions (90%); disorganized behavior (70); insomnia (60); disorganized speech (60%); suicidal ideation (40%); auditory hallucinations (40%); psychomotor agitation (30%); agitation (20%); visual hallucinations (20%)	[45]
"K2"	3	16-year-old male 16-year-old male 16-year-old male	Urine Urine Urine	THC THC THC JWH-018 JW-071	+ – + – –	All three patients reported: chest pain, ST elevations, high level so troponin (protein released when heart has been damaged)	[65]
"Happy Tiger Incense"	1	19-year-old male sample unknown	Drugs screen	Benzodiazepines	+	Convulsion, vomiting, confusion,	[83]

Table 7. (Contiuned)

Product	*n*	Patient information	Patient sample	Test and qualitative result Type	+ or –	Adverse effects	Ref.
"K2"	1	36-year-old male	Urine	Opioids Cannabinoids Ephedrine Promethazine Dextromethorphan	– – + + +	Irritable, restless, poor sleeping, mental disturbance — thought and behavior disorganized, irrelevant speech	[99]
"K2"	1	16-year-old female	Urine	THC (no synthetic cannabinoid test)	+	Altered mental status, vertical involuntary eye movement	[14]
"Spice"	1	18-year-old male	Urine	THC	–	Agitated and restless, headache, dizziness, excessive sweating, increased heart rate,	
"Spice"	1	16-year-old male	Urine	THC	–	Altered mental status, hallucination, agitated motor speech disorder, sustained muscle contraction	[84]
"K2"	2	17-year-old male	Urine/blood	Cannabinoids	+	Altered mental status, confused speech and somnolence, chest and back pain, increased heart rate, high creatinine kinase	[34]
		15-year-old male		Cannabinoids	–	Unconscious, increased heart rate, high serum potassium	
"Spice"	1	59-year-old male	Serum	Toxicol. screen	–	Admitted to an inpatient psychiatric until 3 times over 60 days, visual hallucination, disorganized and bizarre behavior	[75]
"Spice"	1	48-year-old male 0 days after use	Urine	JWH-018 metabolites	+	Seizure, increased heart rate, high respiratory rate, dilated pupils, excessive sweating, lightheaded/confused, high creatine kinase	[73]
"K9", co-ingestion of Oxyelite (caffeine/herbs)	1	17-year-old male		JWH-018 JWH-073	+ +	Chest pain, increased heart rate and low heart rate, hallucinations	[117]
"K2 summit blend" then "JWH-018"	1	48-year-old male	Urine	Toxicol. screen	–	Unconscious, followed by screaming then an episode of tonic-clonic seizures, incontinence, tongue-biting, and excessive sweating, 14 h later – increased body temperature and increased heart rate	[98]
"K2"	2	16-year-old male	Urine	Toxicol. screen	–	Psychosis, low mood, insomnia, hyperactivity, anxiety, paranoid delusion, musical auditory hallucinations	[71]
		17-year-old male	Urine	Toxicol. screen	–	Severe anxiety, insomnia, disorganized thoughts, paranoid delusions, agitation, and mild cognitive impairment	
"Space"	3	19-year-old male 19-year-old female 23-year-old male	Urine Urine Urine	Toxicol. screen Toxicol. screen Toxicol. screen	– – –	Paranioa, aggression, agitation, hallucinations Mild somnolence, amnesia, mild agitation Panic, agitation, difficulty breathing, red eye, delusions	[7]
K2 powder "Silver K2"	2	19-year-old male 15-year-old male	Not provided Not provided	Toxicol. screen Toxicol. screen	– –	Respiratory depression Respiratory depression	[48]
"Black Mamba"	1	20-year-old male	Urine	AM-2201 metabolites	+	Convulsions	[63]
"Scooby Snacks"	1	30-year-old male	Urine	JWH-018, JWH-073 AM-2201	+	Intractable abdominal pain, nausea, vomiting	[38]

Table 8. Summary of case reports of adverse effects with quantitative analysis

Product	*n*	Patient information	Patient sample	Drug detected	Drug conc. (ng/mL)	Adverse effects	Ref.
Smoke	2	33-year-old female	Serum			Sedation, sickness, dry mouth	[96]
		Time since smoking	5 min	JWH-018	8.1		
			10 min	JWH-018	4.6		
			1.33 h	JWH-018	1.7		
			3 h	JWH-018	0.41		
			6 h	JWH-018	0.16t		
			24 h	JWH-018	Present		
			48 h	JWH-018	Present		
		47-year-old male	Blood			Hot flushes, burning eyes, thought disruption, increased pulse, residual tiredness lasting 6–12 h	
		Time since smoking	5 min	JWH-018	10.2		
			10 min	JWH-018	6.1		
			1.33 h	JWH-018	1.8		
			3 h	JWH-018	0.25		
			6 h	JWH-018	0.13		
			24 h	JWH-018	Present		
			48 h	JWH-018	Not present		
K2	1	48-year-old, male	Urine	JWH-018 metabolites	200 nM	Agitation, seizure, increased heart rate	[53]
"Spice"	1	16-year-old male 2.7 h after use	Serum	CP-47.497-C8 JWH-018	2.3 <0.10	Poison severity score 1 (PSS1): Drowsiness, vertigo, restlessness, mild pain, increased heart rate, high/low blood pressure, coughing, vomiting, mild electrolyte and fluid disturbances	[37]
"Smoke"	1	21-year-old male 3.5 h after use	Serum	JWH-018	0.45	PSS1	
"Smoke"	1	18-year-old male 3.0 h after use	Serum	JWH-018	13	Poison severity score 2 (PSS2): Unconsciousness, confusion, hallucination, delirium, pain, igidity, cramping, slow heart rate, increased heart rate, pronounced high/low blood pressure, vomiting, diarrhea, pronounced low blood sugar, increased body temperature	
"Spice"	1	18-year-old male 5 h after use	Serum	JWH-018	0.38	PSS2	
"Jamaican gold"	1	17-year-old male 2.8 h after use	Serum	JWH-081	42	PSS2	
"Ninja strong"	1	20-year-old female	Serum unknown	JWH-081 JWH-018 JWH-250	4.0 0.40 0.33	Poison severity score 3 (PSS3): Coma, respiratory depression, agitatio generalized paralysis, blindness, deafness, slow or fast heart rate, haemorrhage, severe electrolyte and fluid disturbances, severe low blood sugar, dangerous reduced or increased body temperature.	
"Monkees go bananas tropical car perfume"	1	28-year-old male 10 h after use	Serum	JWH-122 JWH-250	0.17 0.10	PSS1	
"Bonzai"	1	17-year-old male 1 h after use	Serum	JWH-081 JWH-250	3.0 1.1	PSS1	
"Monkees go bananas tropical car perfume"	1	18-year-old male 1.5 h after use	Serum	JWH-122 JWH-250 JWH-018	40 0.26 <0.10	PSS2	
"Jamaican gold"	1	19-year-old male 40 h after use	Serum	JWH-081	1.2	PSS2	
"Bonza"	1	17-year-old male 1 h after use	Serum	JWH-018	11	PSS1	
"Monkees go bananas tropical car perfume"	1	14-year-old male 1 h after use	Serum	JWH-122	1.7	PSS3	

Table 8. (Continued)

Product	*n*	Patient information	Patient sample	Drug detected	Drug conc. (ng/mL)	Adverse effects	Ref.
"Monkees go bananas tropical car perfume"	1	15-year-old male 1 h after use	Serum	JWH-122	0.29	PSS1	
"Lava red"	1	17-year-old male 1 h after use	Serum	JWH-122	0.34	PSS1	
"Lava red"	1	28-year-old male 1 h after use	Serum	JWH-122	15	PSS2	
"OMG"	1	19-year-old male 18 h after use	Serum	JWH-122	0.56	PSS2	
"Maya"	1	24-year-old male 5 h after use	Serum	JWH-210 JWH-73 JWH-015	2.5 0.11 <0.10	PSS1	
"Maya"	1	23-year-old male 1 h after use	Serum	JWH-210 JWH-081	3.9 0.25	PSS1	
"Sweed"	1	29-year-old male 4.5 h after use	Serum	JWH-122 AM-694	9.0 0.20	PSS2	
"Jamaican gold extreme"	1	23-year-old male unk.	Serum	JWH-210 JWH-081	7.7 1.8	PSS2	
"Push"	1	16-year-old male 2 h after use	Serum	JWH-210	5.6	PSS2	
"Maya"	1	26-year-old male 0.75 h after use	Serum	JWH-210 JWH-122 JWH-018	190 0.22 0.12	PSS2	
"Maya"	1	27-year-old male 9.5 h after use	Serum	JWH-210	68	PSS2	
"Bonzai remix"	1	30-year-old female unk.	Serum	JWH-210 JWH-081 JWH-122	20 8.4 2.1	PSS1	
"Spice"	1	19-year-old male 2 h after use	Serum	JWH-210	0.65	PSS2	
"Jamaican gold"	1	19-year-old male 10 h after use	Serum	JWH-210	1.0	PSS2	
"Sweed"	1	22-year-old male unk.	Serum	JWH-210	0.27	PSS1	
"Spice"	1	19-year-old male 1 h after use	Serum	JWH-210	35	PSS2	
"Spice"	1	15-year-old male 20 h after use	Serum	JWH-210	0.2	PSS2	
"Bonzai"	1	15-year-old male 2 h after use	Serum Urine	JWH-122 JWH-210 JWH-018 JWH-018 metabolite *N*-(3-OH-pentyl) *N*-(4-OH-pentyl) *N*-(5-OH-pentyl) *N*-(5-OH-carboxypentyl) JWH-073 metabolite *N*-(4-OH-carboxybutyl) JWH-122 metabolites *N*-(4-OH-pentyl) *N*-(5-OH-pentyl) OH-indole OH-naphthyl	230 7.8 0.39 0.03 0.49 0.28 0.12 0.10 ~11 3.5 Positive Positive	Seizure, coma, insufficient respiration, mild increase of blood glucose, vomiting, increased creatinine kinase, mild increase in platelet	[36]

Table 8. (Continued)

Product	*n*	Patient information	Patient sample	Drug detected	Drug conc. (ng/mL)	Adverse effects	Ref.
Not provided	1	17-year-old male 4 h after use	Serum	JWH-210 metabolite *N*-(4-OH-pentyl)	0.06		
			Urine	MAM-2201	0.15		
				UR-144	0.24		
				JWH-018 metabolite *N*-(5-OH-carboxypentyl)	0.11		
				JWH-122 metabolite *N*-(5-OH-pentyl)	1.6		
"Jamaican gold"	1	17-year-old male 3 h after use	Serum	UR-144 metabolites		Nausea, vomiting, mild agitation, panic attacks, involuntary muscle twitching, confusion, somnolence, dilated pupils, increased heart rate, low potassium in blood, mild increase in blood glucose	
				OH-indole	Positive		
				OH-pentyl	Positive		
			Urine	JWH-081	42		
				JWH-018 metabolites			
				N-(3-OH-pentyl)	0.03		
				N-(4-OH-pentyl)	0.28		
				N-(5-OH-pentyl)	0.12		
				N-(5-OH- carboxypentyl)	0.11		
				JWH-073 metabolite *N*-(4-OH-carboxybutyl)	0.10		
"Lava red" 2 h after use	1	20-year-old male	Serum	JWH-081 metabolites		Vomiting, unable to communicate, pale pale skin dilated pupils, mild increase in heart rate somnolence, mild reduction in potassium in blood, mild increase in creatine kinase, increase in white blood	
				N-(5-OH-pentyl)	~13		
				OH-indole	Positive		
				OH-naphthyl	Positive		
			Urine	JWH-122	15		
				JWH-018 metabolites			
				N-(4-OH-pentyl)	0.06		
				N-(5-OH-pentyl)	0.04		
				N-(5-OH-carboxypentyl)	0.03		
				JWH-122 metabolites			
				N-(4-OH-pentyl)	4.8		
				N-(5-OH-pentyl)	0.74		
				OH-indole	Positive		
				OH-naphthyl	Positive		
Blueberry-flavored or bubblegum-flavored	1	18-year-old male 2 days after last use	Urine	XLR-11 metabolite	400	Nausea, vomiting, and flank pain	[67]
Phantom Wicked Dreams	1	30-year-old male 2 days after last use	Blood	XLR-11 metabolite	42	Nausea and vomiting	
Mr. Happy	1	26-year-old male 0 day after last use	Serum	XLR-11	35	Nausea, vomiting, and abdominal pain	
				XLR-11 metabolite	102		
				UR-1441	6		
			Urine	XLR-11 metabolite	529		
Lava	1	18-year-old male 2 days after last use	Blood	XLR-11	33		
				XLR-11 metabolite	38		
"Mr. Happy"	1	26-year-old male	Urine	XLR-11	529	Acute kidney injury, high white blood cell count, high creatine, high blood urea nitrogen, protein and trace of blood in urine	[97]
			Serum	XLR-11	36		
"Jamaican extreme"	1	18-year-old male 30 min after use	Blood	AM-2201	4.6	Unable to follow instructions, retarded sequence of movement, confused and disoriented, slurred and babbling speech	[68]
				JWH-018	0.17		

Table 8. (Contiuned)

Product	*n*	Patient information	Patient sample	Drug detected	Drug conc. (ng/mL)	Adverse effects	Ref.
"BooM"	1	14-year-old female	Blood	JWH-210 JWH-122	4 0.33	Inappropriate freezing, enlarged pupils	
"BooM"	1	14-year-old female	Blood	JWH-210	0.80	Unconscious, confused speech, instable appearance	
Not provided	1	20-year-old male 80 min after use	Blood	JWH-019 JWH-122 JWH-210 AM-2201	1.7 7.6 4.4 0.31	Confused speech, instable appearance	
"BooM" and motor "OMG"	1	29-year-old male 50 min after use	Blood	JWH-210 JWH-122	6.2 1.0	Vestibular disorder, disturbance to fine skill, enlarged pupils, blunt mood	
Not provided	1	21-year-old male 81 min after use	Blood	JWH-018 JWH-122 JWH-210	0.52 0.26 0.66	Enlarged pupils, delayed reaction of pupils to light, retarded behaviour	
Not provided	1	21-year-old	Blood	JWH-307 Blood alcohol	1.1 1.74%	Delayed reactions, retarded movement sequence, nervous, constricted pupil, no reaction to light, depressed mood	
Not provided	1	22-year-old 1 h 35 min after use	Blood	AM-2201 JWH-018 JWH-122 JWH-210 JWH-307 MAM-2201 UR-144	<0.1 1.9 28 2.5 <0.1 <0.1 <0.1	Impaired driving, retarded movement sequence, apathetic, nervous, delayed reaction of pupils to light, death	
Herbal blends	1	59-year-old male Postmortem interval of 4 days	Blood Liver Kidney Brain Adipose tissue	MAM-2201 MAM-2201 MAM-2201 MAM-2201 MAM-2201	12.4 18.1 ng/g 11.2 ng/g 4.3 ng/g 1,535 ng/g	Death	[81]
Not provided	12	Male	Blood	JWH-018	1.1	No adverse effect	[116]
Not provided		18-year-old male	Blood	JWH-018	0.24	Pupils dilated, red eye	
Not provided		22-year-old male	Blood	JWH-018 JWH-250	9.9 2.7	Pinpoint pupils, red eye	
Not provided		25-year-old male	Blood	JWH-018	Positive	Red eye, watery eyes, increased pulse rate	
Not provided		18-year-old male	Blood	JWH-018	Positive	Red eye, slow speech, increased pulse rate	
Not provided		31-year-old male	Blood	AM-201 JWH-081 JWH-122 JWH-210	1.4 0.12 2.5 0.10	Red eye, increased pulse rate	
Not provided		27-year-old male	Blood	JWH-018 AM-2201 JWH-122 JWH-210	0.1 0.43 Positive Positive	Red eye, increased pulse rate	
Not provided		21-year-old male	Blood	AM-2201 JWH-250	3.1 0.38	Droopy eyelids, low and slow speech	
Not provided		26-year-old male	Blood	AM-2201	0.94		
Not provided		18-year-old male	Blood	AM-2201	3.6	Low and slurred speech, red eye, watery eyes, closed eyes, emotional, increased pulse rate	
Not provided		21-year-old male	Blood	AM-2201 JWH-081 JWH-122 JWH-210	2.8 Positive Positive Positive	Red eye, droopy eyelids, increased pulse rate	
Not provided		19-year-old male	Blood	AM-2201 JWH-210	4.0 Positive	Slow and slurred speech, red eye, droopy eyelids, lethargic, increased pulse rate	

Table 8. (Continued)

Product	*n*	Patient information	Patient sample	Drug detected	Drug conc. (ng/mL)	Adverse effects	Ref.
"Spice" product	1	21-year-old male 4th day in hospital	Blood	AM-2201 JWH-122 JWH-210	0.75 Positive Positive	Diffuse pulmonary infiltrates	[2]
			Urine	AM-2201 metabolite JWH-018 metabolite	Positive Positive		
			Saliva	AM-2201 JWH-018	Positive Positive		

kidney infection [102]. A cohort of 22 patients admitted to an emergency room in Brunswick, Georgia, reported adverse effects including hyperglycemia (13 cases) and hypokalemia (9 cases) among their symptoms. These cases were linked to ADB-PINACA (*N*-(1-amino-3,3-dimethy-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide) through toxicological testing [21].

2. Pulmonary Effects

There have been a number of reports linking cannabis to pulmonary dysfunction [95]. However, to date there has been only one case report with toxicology data that shows a link between synthetic cannabinoids and respiratory dysfunction [2]. This report was of a 21-year-old male who developed diffuse pulmonary infiltrates (the accumulation of liquids in the lung, for example fluid or pus) after chronic inhalation of multiple synthetic cannabinoid-containing products over a period of 4 months. AM-2201 was quantified in the blood sample; JWH-122 and JWH-210 were detected in the blood but not quantified. Diffuse alveolar infiltrates was also reported in a single case, where a 19-year-old male admitted to using "synthetic weed"; however, in this case no toxicological testing was performed [57]. These case reports offer some limited preliminary evidence of a link between synthetic cannabinoid use and lung injury; however, more data are needed with respect to the frequency and severity of this phenomenon. Two patients in Brunswick, Georgia developed pneumonia after using ADB-PINACA [21].

3. Cardiovascular Effects

Adverse cardiovascular effects associated with synthetic cannabinoid use are largely limited to increases in resting heart rate (tachycardia), which has been reported in many case studies, and has involved many synthetic cannabinoid compounds both in isolation: JWH-018, JWH-122, JWH-073, JWH-015, JWH-081 [36,37]. JWH-018 metabolites [53], and in combination: CP 47,497(C8) and JWH-018, JWH-122 and JWH-250, JWH-210, JWH-071, and JWH-015, JWH-210, JWH-081, and JWH 122, JWH-210 and JWH-081 [37], and MAM-2201 and UR-144 [36]. A reduction in resting heart rate (bradycardia) was also reported less frequently and only noted in one of the studies where toxicology analysis was performed [37].

Both increases (hypertension) and decreases in blood pressure (hypotension) have been reported [37]. These effects were reported in a range of individuals who had consumed different synthetic cannabinoid compounds: JWH-018, JWH-122, JWH-250, JWH-081, AM-694, and JWH-210. In the cases where only a single synthetic cannabinoid was reported, the lowest serum concentration to induce changes to the blood pressure was 0.2 ng/mL of JWH-210, and the highest serum concentration was 190 ng/mL of JWH-210. Whether hypotension or hypertension predominates may be related to the interval between ingestion and the blood pressure being taken. Marijuana (THC) causes an acute increase in blood pressure following ingestion, but subsequently drops. Yeakel and Logan reported a tendency toward increased pulse and systolic blood pressure in drivers found to be under the influence of synthetic cannabinoids [116]. Of the case series in Brunswick, Georgia linked through toxicological testing to ADB-PINACA, 13 (59%) experienced tachycardia, and one patient experienced a myocardial infarction [21].

4. Gastrointestinal Effects

Cannabinoid hyperemesis syndrome (CHS) consists of recurrent bouts of intractable abdominal pain and severe nausea and vomiting that occur over several months and resolve when cannabis use is discontinued [91]. In addition, patients with CHS report frequent hot baths relieve symptoms. Hopkins and Gilchrist [38] describe a case of CHS involving a heavy chronic user of synthetic cannabinoids. The patient's symptoms began while he was routinely using marijuana and continued after he discontinued marijuana and began using synthetic cannabinoids. Analysis of the product he was using revealed JWH-018, JWH-073, JWH-122, AM-2201 and AM-694. Urine analysis confirmed metabolites of JWH-018, JWH-073 and AM-2201. Complete resolution of symptoms was reported after two weeks of abstinence.

5. Central Nervous System Effects

Reports of severe toxicity of synthetic cannabinoids in the literature are, as yet, infrequent. Serious central nervous system effects include confusion, psychosis, agitation, loss of consciousness or memory, and seizures [25,36,83,85,88]. Serious cognitive impairment has also been described with chronic daily use [118]. Mild neurological effects that are commonly reported include drowsiness, dilated pupils, droopy eyelids, involuntary eye movement, and slow speech [68,96,116]. In a case series of 22 patients admitted to the emergency room after confirmed use of ADP-PINACA, several patients reported significant CNS effects including confusion/disorientation (32%), somnolence/unresponsiveness (32%), and aggression (32%) [21]. Although these symptoms may appear minor, they can have a negative impact on an individual's ability to perform daily tasks; this impairment has been studied in relation to driving [68,116].

6. Seizures

Comparison of the synthetic cannabinoids confirmed in biological samples from seizure patients (with no prior history of seizures) with the presence of synthetic cannabinoids in the product, suggest that JWH-018, JWH-122, JWH-210, and AM-2201 may have an involvement in lowering seizure thresholds. The mechanism linking these synthetic cannabinoids to seizures is currently unclear. It may be due to the synthetic cannabinoids themselves, or due to another substance present within the synthetic cannabinoid product [59].

Seizures have been reported in four cases where individuals have ingested JWH-018 [33,49,67,80] or AM-2201 [63]. Lapoint et al. reported clinical results of approximately 200 nM of JWH-018 metabolites in the urine [53]. In Hermanns-Clausen et al., a combination of compounds were present: JWH-122, JWH-210, and JWH-018 [36]. The highest concentration was of JWH-122, with 230 ng/mL in the serum and approximately 11 ng/mL of the parent compound measured in the urine. This individual also showed other symptoms of severe neurological dysfunction, including being found in a comatose state with insufficient respiration. Three patients from a cohort of 22 experiencing toxicity related to use of ADP-PINACA, experienced seizures [21].

There have been two further cases of convulsions associated with individuals who smoked synthetic cannabinoid products ("Spicy XXX" [88], "Happy Tiger Incense" [83]. In the second case analysis of the product identified JWH-018, JWH-081, JWH-250, and AM-2201; however, no analysis on biological samples collected in either of these two cases was performed. The effect of multiple synthetic cannabinoids in a sample is unknown.

Chemically related naturally occurring cannabinoids in cannabis (phytocannabinoids) such as cannabinol and cannabidiol, have been shown in mouse models to be anticonvulsant. The absence of phytocannabinoids in synthetic cannabinoid products may result in an increased risk of seizures in users of synthetic cannabinoids [83].

7. Psychosis

Psychosis is a mental health condition in which an individual has difficulty thinking clearly, and is unable to distinguish between reality and delusions or false beliefs. This can take the form of hallucinations, where a person thinks they can hear and see things that are not there. Psychosis has been reported rarely with cannabis [35], and the psychotic symptoms are related to the dose of THC with greater risk occurring with high-potency marijuana [18]. However, there is an increasing number of case reports linking synthetic cannabinoid use to psychosis. Every-Palmer proposes that these psychotic effects may be due to the use of JHW-018, which has been shown to have similar effects to THC in animal studies. JHW-018 may even have more potent effect because it is a full agonist at the CB_1 receptor, compared to THC which is only a partial agonist [25], and a possible neuroprotective effect of other phytocannabinoids.

Individuals who have had previous psychosis, or who were particularly vulnerable to mental health problems, have been reported to have relapses after taking synthetic cannabinoids. Combined results from these studies show that there are six cases where there were psychotic relapses following the use of synthetic cannabinoid products [25,66]. In a further study, 69% of participants reported or exhibited psychotic symptoms following the use of synthetic cannabinoids [25]. However, toxicology analysis was not performed in these cases.

One case study confirmed the presence of metabolites of JHW-018 in urine samples, 12 h after smoking. These three individuals were showing symptoms of paranoia and hallucinations [90]. Two further cases were reported of individuals becoming disoriented 90 min after smoking the synthetic cannabinoid product. The toxicology screens (whose analytical scope is not reported) for both individuals were negative, but analysis of the product that was found in the possession of the individuals identified the presence of JHW-018 and JHW-073 [117].

Hallucinations have been reported after the ingestion of JWH-018, JWH-081, JWH-112, JWH-250, JWH-210, or AM-694. This was confirmed with toxicological analysis. In addition to hallucinations these individuals showed symptoms of delirium and confusion [36]. Confusion was also reported in a case where an 18-year-old male displayed agitation, panic attacks, muscle twitching, and

an increased heart rate, and was subsequently found to have a serum concentration of 42 ng/mL of JWH-081. Many synthetic cannabinoid products have been shown to contain multiple different compounds, and these may result in a variety of overlapping and discrete symptoms, making it difficult to draw conclusions regarding specific compounds and their individual adverse effects on the user.

B. Effects of Synthetic Cannabinoids on Driving Ability

Synthetic cannabinoids are increasingly being tested for in cases of impaired driving. Results from these reports are summarized in Table 8. Yeakel and Logan reported 12 cases of suspected impaired driving in which the drivers subsequently tested positive for synthetic cannabinoids in blood samples [116]. Many of the drivers underwent a psychophysical examination routinely used by law enforcement to assess impairment, and although the drivers were cooperative and relaxed, they showed objective signs of being under the influence in terms of performance in field sobriety tests, cognitive indicators, and body sway. Pulse and blood pressure were generally elevated. Observed effects included slow and slurred speech, reddened conjunctiva, and increased pulse rate. The most consistent indicator present in the subjects was a marked lack of convergence, or inability to cross their eyes in response to following a stimulus. In all cases where a DRE officer evaluated and documented impairment (n=10) it was attributed to the Drug Recognition Expert (DRE) cannabis category. Drugs detected in toxicological examinations included JWH-018, JWH-081, JWH-122, JWH-210, JWH-250, and AM-2201. Concentrations ranged from the limits of detection (0.1 ng/mL) to 9.9 ng/mL. In seven cases a single synthetic cannabinoid was present. In the seven cases in which information concerning accidents was obtained, four of the drivers were identified as having been involved in accidents, and all were considered to be the causing driver. Musshoff et al. described a series of seven subjects, some of whom exhibited impairment in their driving following toxicologically confirmed synthetic cannabinoid use [68]. The drugs involved included JWH-018, AM-2201, JWH-210, and JWH-122. The concentrations and psychophysical effects were similar to those in the report by Yeakel and Logan [116], including slurred speech, dilated pupils, confusion, instability, and slowed movement. The authors concluded that synthetic cannabinoids can lead to impairment similar to typical performance deficits caused by cannabis use, which are not compatible with safe driving.

C. Synthetic Cannabinoid-Related Deaths

To date, three deaths have been reported that were attributed to synthetic cannabinoids. The deaths were separate incidents. One death was due to a coronary ischemic event and another individual committed suicide due to anxiety [31]. These two deaths were reported to have occurred after the ingestion of a Spice product labeled “K2”, but no toxicology results were published in relation to either death, so the synthetic cannabinoids present and their concentrations were not determined. The third death was reported by Saito et al. in 2013: a case of fatal MAM-2201 poisoning in a 59-year-old man [81]. The concentration of the compound in the blood was 12.4 ng/mL. The postmortem interval was four days, and the potential for postmortem redistribution for synthetic cannabinoid drugs has not been assessed. The report does not go into any further detail about the symptoms or the effect that the MAM-2201 had on this individual.

III. LEGAL STATUS OF SYNTHETIC CANNABINOIDS

A. US Approaches to Scheduling Synthetic Cannabinoids

Because the products available on the market change so rapidly (currently these drugs appear to have a life cycle of about 12–24 months before being replaced by the next wave), efforts to schedule the drugs at the federal and state levels lag behind what is available on the street. Approaches to scheduling fall into three broad categories including, adding specific compounds to the Schedule, scheduling by chemical class or family, and scheduling through reference to state and federal analog acts. Some of these analog acts include language that references the pharmacological activity of the drug, requiring it to be “substantially similar” to other scheduled compounds, and some even go so far as to require that the compounds be demonstrated to be agonists as demonstrated through binding studies and functional assays [103]. This makes it all the more important for researchers to obtain the binding and functional-effect data described in the experiments outlined in this review.

B. Review of Non-American Legal Policies

Legislation controlling synthetic cannabinoids has been introduced in many countries in an attempt to limit the spread of existing drugs and control potential new analogs. A recent review by the UK Drug Policy Commission (UKDPC) of the analog approach to scheduling called

it "an imperfect law" and came out strongly against that approach [51], favoring a speedier addition of specifically listed compounds to the Schedule. Synthetic cannabinoids represent the largest group of compounds currently monitored in Europe by the EU's early warning system on new psychoactive substances, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [23]. As of May 2013, a total of 84 synthetic cannabinoids had been reported to the EMCDDA.

In December 2009, the UK Misuse of Drugs Act of 1971 was amended to include a range of synthetic cannabinoids [101]. This was updated in 2013. The synthetic cannabinoids captured by these new generic definitions were also "designated" and inserted into Schedule 1 of the 2001 Regulations.

The Advisory Council on the Misuse of Drugs (London, UK) proposed five generic definitions for the synthetic cannabinoid agonists and initially in 2009, five substances were listed by name (HU-210, Nabilone, WIN-55,212-2, HU-243, CP 50,5561). The cannabinoids targeted for control under these generic definitions were CB_1 receptor agonists. In 2013, three new generic definitions were added and the following compounds listed as Class B, Schedule I drugs: AM-694; MAM-2201; Cannabipiperidiethanone; AM-2233; AM-1220; AM-679; RCS-4 and its C4 homolog; RCS-4 C2-isomer; WIN 48,098 (Pravadoline); AM-1248; AB-001; UR-144.

In 2006, the Pharmaceutical Affairs Law in Japan was amended to establish a new category, "Designated Substances", in order to more strictly control so-called new psychoactive substances. As of July 2012, 78 substances including 23 synthetic cannabinoids were listed [50]. The first synthetic cannabinoids to be listed under this law in 2009 were CP-47,497(C7), cannabicyclohexanol (CP-47,497(C8)) and JWH-018, followed in 2010 by JWH-073 and JWH-250. In 2011, an additional 11 compounds were added (JWH-015, JWH-081, JWH-122, JWH-200, JWH-251, JWH-019, JWH-203, JWH-210, AM-694, AM-2201, and RCS-4). In 2012, JWH-022, AM-1220, AM-2233, CB-13, cannabipiperidiethanone, APICA, APINACA, RCS-4 *o*-isomer, MAM-2201, JWH-122 N-(4-pentenyl) analog, AM-2232, UR-144, XLR-11, JWH-398, JWH-182, and JWH-007 were added. Finally, in 2013 an additional 14 substances have been added, namely AB-FUBINACA, JWH-213, AM-1241, AB-001, AM-1248, JWH-030, JWH-307, 5-fluoropentyl-3-pyridinoylindole, APINACA *N*-(5-fluoropentyl) analog, APICA *N*-(5-fluoropentyl) analog, ADB-FUBINACA, AB-PINACA, ADBICA, and QUPIC (PB-22). This latter entry is of interest as it is not currently restricted in the United States. In March 2013 a generic definition covering naphthoylindoles was introduced to the Japanese Narcotics Control Law. As with US and UK laws, the Designated Substances category is a temporary "holding" station for substances awaiting full legislation. In August 2012, cannabicyclohexanol and JWH-018 received full narcotics status; in March 2013, JWH-073 and JWH-122 were listed as narcotics and in May 2013 AM-2201, and MAM-2201 received the same status.

In addition to the United Kingdom, across Europe many synthetic cannabinoids are now controlled. Countries whose drug legislation now controls for these drugs include Austria, Switzerland, Germany, the Netherlands, France, Hungary, Poland, Luxemburg, Lithuania, Estonia, and Sweden [24]. The majority of these countries have modified their systems to allow for early monitoring in addition to their existing legislation.

CONCLUSION

Synthetic cannabinoids have evolved rapidly since first appearing on the world market. The speed with which manufacturers can create new compounds has presented an ongoing challenge to the forensic toxicology community. Methods to detect compounds in blood and identify their metabolites in order to detect their use through urine testing have to be rapidly developed as new analytes appear. Inevitably, with limited abilities by human performance and postmortem forensic toxicology laboratories to keep up with this changing market, detection rates of synthetic cannabinoid use are likely very low, and the information needed to interpret these results has been correspondingly slower to develop.

Because the safety profile of the compounds is largely unknown, the ability to do human studies to determine their effects presents an ethical challenge. By considering how these compounds bind to and act at cannabinoid receptors, and by evaluating existing information on their effects in animal models, scientists can begin to develop a picture on their effect profile. This information provides a basis for interpreting human effects of synthetic cannabinoids in the absence of controlled administration studies. A review of the literature that exists to date suggests that synthetic cannabinoids may have side effects that are more severe than that of marijuana. In addition to the expected CNS effects, some compounds have been associated with seizures, tachycardia, kidney damage, and death. The cognitive effects have been demonstrated to cause impairment that is not compatible with safely operating a motor vehicle. This review provides important data for interpreting toxicology casework while highlighting the need for continued vigilance in studying synthetic cannabinoids and their effects on humans.

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