Published in final edited form as:
Drug Alcohol Depend. 2014 November 1; 0: 12–41. doi:10.1016/j.drugalcdep.2014.08.005.

Synthetic Cannabinoids: Epidemiology, Pharmacodynamics, and Clinical Implications*

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Abstract

Background—Synthetic cannabinoids (SC) are a heterogeneous group of compounds developed to probe the endogenous cannabinoid system or as potential therapeutics. Clandestine laboratories subsequently utilized published data to develop SC variations marketed as abuseable "designer drugs." In the early 2000's, SC became popular as "legal highs" under brand names such as "Spice" and "K2," in part due to their ability to escape detection by standard cannabinoid screening tests. The majority of SC detected in herbal products have greater binding affinity to the cannabinoid CB_1 receptor than does Δ^9-tetrahydrocannabinol (THC), the primary psychoactive compound in the cannabis plant, and greater affinity at the CB_1 than the CB_2 receptor. *In-vitro* and animal *in-vivo* studies show SC pharmacological effects 2-100 times more potent than THC, including analgesic, anti-seizure, weight-loss, anti-inflammatory, and anti-cancer growth effects. SC produce physiological and psychoactive effects similar to THC, but with greater intensity, resulting in medical and psychiatric emergencies. Human adverse effects include nausea and vomiting, shortness of breath or depressed breathing, hypertension, tachycardia, chest pain,

*Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:….

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Author Disclosures
Conflict of Interest
No conflict declared.

Contributors
Marisol Castaneto, David Gorelick, Nathalie Desrosiers, and Rebecca Hartman reviewed and selected articles as part of the comprehensive literature review. Marisol Castaneto organized the data included in this review and wrote the first draft of the manuscript with the assistance of David Gorelick, Sandrine Pirard, and Marilyn Huestis. All authors contributed and approved the final manuscript.

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muscle twitches, acute renal failure, anxiety, agitation, psychosis, suicidal ideation, and cognitive impairment. Long-term or residual effects are unknown. Due to these public health consequences, many SC are classified as controlled substances. However, frequent structural modification by clandestine laboratories results in a stream of novel SC that may not be legally controlled or detectable by routine laboratory tests.

Methods—We present here a comprehensive review, based on a systematic electronic literature search, of SC epidemiology and pharmacology and their clinical implications.

Keywords

synthetic cannabinoids; designer drug; epidemiology; pharmacodynamics; CB_1/CB_2 agonists; Spice; K2

1. INTRODUCTION

Synthetic cannabinoids (SC) interact with CB_1 and CB_2 cannabinoid receptors and elicit cannabimimetic effects similar to Δ9-tetrahydrocannabinol (THC), the primary psychoactive constituent in cannabis (Wiley et al., 2013b). SC were developed as research tools to explore the endocannabinoid system and as potential therapeutics (Pertwee, 2006). CB_1 receptors are expressed in the central and peripheral nervous systems, bone, heart, liver, lung, vascular endothelium, and reproductive system (Howlett et al., 2002). CB_2 receptors are primarily in the immune system, but also in the central nervous system at lower levels than CB_1 (Ashton et al., 2006; Onaivi et al., 2008; Van Sickle et al., 2005). SC activate CB_1 receptors, G-protein coupled receptors predominantly located at pre-synaptic terminals. CB_1 receptor activation decreases cellular cyclic adenosine monophosphate (cAMP) levels and elicits cannabimimetic responses (Pertwee, 2010). SC agonists interact with voltage-gated ion channels and inhibit potassium, sodium, and N- and P/Q-type- calcium channels by reducing membrane potentials.

Cyclohexylphenols (CP) were synthesized between 1970 and 1980 with CP55,940 (2-[(1R, 2R,5R)-5-Hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-5-(2-methyl-octan-2yl)-phenol), commonly utilized to localize cannabinoid receptors (Johnson MR and Melvin LS, 1986). Created in Dr. Raphael Mechoulam's laboratory at Hebrew University (HU), Jerusalem, HU-210 [(6aR)[-trans-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6Hdibenzo[b,d]pyran-9-methanol] is a dibenzoypyran, structurally similar to THC, and a highly potent CB_1 and CB_2 agonist (Mechoulam et al., 1990; Howlett et al., 1995; Ovadia et al., 1995; Rodriguez de Fonseca et al., 1995). In the 1990s, aminoalkylindoles such as WIN55,212 [(R)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[(1,2,3.de)-1,4-benzoxazin-6-yl]-1-naphthalen-ylmethanone] were investigated as potentially safer (non-psychotropic) pharmacotherapies (Bell et al., 1991). John W. Huffman (JWH) created the most extensive SC series with chemical structures different from the classical dibenzopyran, but eliciting cannabimimetic effects in animals (Huffman and Dai, 1994). Other SC developed in the last two decades were the AM-series (Alexandros Makriyannis) (Makriyannis A and Deng, 2000) and indazole-carboxamide derivatives, e.g. AB-FUBINACA [N-[(2S)-1-Amino-3-methyl-1-oxo-2-butanyl]-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide] (Buchler et al., 2009). To date

hundreds of SC were categorized into the following structural groups (Figure 1): adamantoylindoles, aminoalkylindoles, benzoylindoles, cyclohexylphenols, dibenzopyrans, naphthoylindoles, naphthylmethylindoles, naphthylmethylindenes, naphthoylpyrroles, phenylacetylindoles, tetramethylcyclopropyl ketone indoles, quinolinyl ester indoles, and indazole carboxamide compounds.

SC, synthesized in clandestine laboratories and sprayed on dried plant materials, were first marketed as legal cannabis alternatives in Europe in the early 2000's (United Nations Office on Drugs and Crime, 2011). SC sold on the Internet, in head shops and convenience stores as Spice and K2 are labeled "not for human consumption." Many SC are Schedule I drugs under the US Controlled Substance Act (US Drug Enforcement Administration, 2014; US Drug Enforcement Administration, 2013a, b). As new SC groups are scheduled, more structurally-diverse cannabimimetic compounds emerge, which may not be covered under current regulations.

SC popularity are attributed to intense psychoactive effects, lack of detectability in routine urine drug tests, and, until recently, legal status in most jurisdictions (Gunderson et al., 2012; Vandrey et al., 2011; Winstock and Barratt, 2013). Documented serious adverse effects and limited human pharmacology data make SC intake an important public health and safety concern. We present SC epidemiology, pharmacodynamic profiles, and clinical implications, based on a systematic and comprehensive electronic literature review.

2. METHODS

We conducted a comprehensive literature search of 7 electronic bibliographic databases (PubMed®, Embase™, Web of Science™, Scopus™, Cochrane, Biological Abstracts, and Chemical Abstracts via STN® and SciFinder® platforms) up to December 31, 2013, except that Biological Abstracts (Biosis) and Chemical Abstracts searches ended November 30, 2011. In addition, we expanded our query employing Google and Google Scholar, and hand-searched reference lists of identified articles. We employed database-specific search strategies with multiple keywords (e.g. "synthetic cannabinoids", "JWH-018," JWH-073," "Spice," and "K2"), utilizing word truncation/wild card symbols and index terms as appropriate for each database (see Supplementary Material Table 1)[1]. Each identified article was categorized into the following topics (based on title and abstract review): animal and human pharmacology (pharmacodynamics and pharmacokinetics), chemistry, commercial sources, detection and identification, epidemiology, legal status, receptor interactions, and street use and marketing.

Of 3,161 potentially relevant records, 2,343 were excluded because they pertained to plant-derived cannabinoids (e.g., cannabinol, cannabidiol, nabiximols [Sativex®]), synthetic THC (dronabinol [Marinol®], nabilone [Cesamet®]), or endogenous cannabinoids (e.g., anandamide, 2-arachidonoylglycerol), or were not English language. Articles (n=818) related to SC analytical methods, chemical synthesis, legal status, pharmacokinetics, and street use and marketing will be reviewed elsewhere; this review covers SC epidemiology

[1]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:….

(9), animal and human pharmacodynamics (338), and receptor interactions (42). Articles older than 10 years were included only if the study was not replicated more recently, yielding 215 articles included in this review.

3. RESULTS

3.1 Epidemiology

We identified 9 SC epidemiological studies, none population- or community-based. Two worldwide surveys of self-selected convenience samples were conducted between 2011-2012. The first, collecting data online between January 4th and February 7th, 2011 recruited participants primarily from Internet drug forums providing SC information (Vandrey et al., 2011). Of 391 participants, 168 met inclusion criteria (self-reported SC intake, English speaking, and ≥18 years), representing 13 countries and 42 US states. The majority were Caucasian (90%), single (67%), men (83%), with at least high school education (96%), with mean first SC use at 26 years. Almost all (92%) reported alcohol and 84% cannabis intake, both frequently combined with SC. The most common route of administration was smoked (via water pipe/bong, cigarette, blunt or pipe); however, oral, rectal and vaporized administration also were mentioned. Curiosity was the primary reason (78%) for SC intake, while 58% favored the drugs' effects. About one-third sought intoxication while avoiding a positive cannabinoid test. SC abuse was reported by 37%, dependence 15%, and withdrawal 15%. Discontinued SC intake produced similar cannabis withdrawal symptoms including headaches, anxiety/nervousness, depression, irritability.

The second worldwide anonymous online survey collected data between November 23 and December 21, 2011, yielded 14,966 participants, two-thirds men, median age 26 years, of whom 17% (n=2,513) reported SC intake (Winstock and Barratt, 2013). Of those using SC within the last year (n=980), 98% also used cannabis, and commonly other drugs. Although SC onset of effects was faster than for cannabis, 92.8% (n=887) preferred cannabis to SC due to the latter's undesirable effects. However, 7.2% reported preference for SC over cannabis for reasons such as accessibility, cost, non-detection, and effects.

Several single-country surveys of self-selected convenience samples were conducted. An anonymous email survey (n=852) at the University of Florida in September, 2010 found that 8.1% reported lifetime SC use and 68% were male and 32% female. Smoking in a cigarette was most frequent (88%), with 25% consuming with a hookah and/or joint (Hu et al., 2011). A majority (91.3%) also smoked cannabis. There was no significant association between SC use and race, marital status, or campus living arrangement.

Between December, 2011-January, 2012, 316 Australian SC users (≥18 years, 77% male, 86% high school graduates, and 30% college graduates) completed an online survey (Barratt et al., 2013). The majority (78%) were employed, 19% were students, and <10% unemployed (or actively looking for work). About 10% sought aid for illicit drug and 3% for alcohol-related problems. Almost all (94%) reported SC intake within the past year, 45% within 30 days. SC daily use was reported by 7% and weekly intake by >33%. 96% reported lifetime cannabis intake, 94% within the last year, and 61% the past month. Polydrug use was reported by 64% and 27 different SC brands were consumed.

A field-based survey interviewed 1,740 adults between May-October, 2012 at clubs in New York City (Kelly et al., 2013). Mean age was 26.4 (range 18–40) years, with 55.2% male, 35.5% homosexual, 61% Caucasian, 15% African-American, 15% Latino, 6.0% Asian, and 12% mixed race. Of those reporting past year SC intake (8.2%), 41.2% were heterosexual men and 17.4% lesbian and bisexual women. SC prevalence in this US sample was lower than self-reported prevalence (12.6%) among those participating (n=2,700) in an online survey in UK dance clubs between November 17–30, 2009 (Winstock et al., 2011).

The annual Monitoring the Future survey of approximately 50,000 US high school students included questions related to lifetime and past year SC intake in 2011-2013 (O'Malley et al., 2014). For 2013, 25.8% reported past-year cannabis intake and 6.4% SC intake. In 2012, students reported 24.7% cannabis and 8.0% SC consumption, with 14.8% and 23.5% of 12th graders perceiving cannabis and SC intake (once or twice), respectively, as less harmful than other drugs. By 2013, SC perceived harmfulness increased to 25.9% (not significant), while perceived harmfulness of most other illicit drugs, aside from synthetic cathinones (59.5%), did not significantly change.

SC possession and use were prohibited for US military personnel as early as 2010 (Cole, 2011; Gould, 2010, 2013; Live, 2011; Loeffler G, 2011). Between March, 2011 and March, 2012, the Armed Forces Medical Examiner System received 1,635 urine samples from service members suspected of SC intake (Brantley, 2012). Of these, 1,148 (70.2%) specimens confirmed positive for SC. An Army Substance Abuse Program 2012 SC prevalence study of 10,000 randomly collected urine specimens, previously screened negative for routinely-tested drugs, reported 2.5% positivity rate (Gould, 2013). The 2011 Health Related Behaviors Among Active Duty Military Personnel web-based survey reported a 1.1% past month SC use among 39,877 non-deployed member respondents, which was higher than cannabis (0.9%) (Barlas et al., 2013). Though some service members claimed that SC sold in convenience stores were perceived as legal (Effron, 2013; Logico, 2012), military officials believed that limited SC testing was a major factor in their illicit use (Cole, 2011; Gould, 2013). SC are now included in routine military drug testing (Army Center for Substance Abuse Program, 2013).

In 2012, the World Anti-Doping Agency (WADA) reported 8 samples positive for JWH-018 [naphthalen-1-yl-(1-pentylindol-3-yl)methanone] (n=6) and JWH-073 [naphthalen-1-yl-(1-butylindol-3-yl)methanone] (n=2) among 4,500 samples positive for prohibited substances under the Anti-Doping Administration and Management System (World Anti-Doping Agency, 2012). HU-210 or THC-like cannabinoids were identified in the 2010 Prohibited List (World Anti-Doping Agency, 2010), which further expanded in 2011 to include "Spice" cannabimimetics (World Anti-Doping Agency, 2011).

In summary, SC appealed to young cannabis and polydrug users. US high school students perceive SC as safer than other drugs of abuse. Military personnel and athletes smoke SC to avoid a positive drug test. However, most SC smokers preferred cannabis due to SC' negative effects.

3.2 Animal Pharmacodynamics

There were 265 peer-reviewed journal articles published between 1989 and 2013 relating to SC animal pharmacodynamics. The most frequently studied SC were the aminoalkylindole WIN55,212-2 (134 studies), cyclohexylphenol CP55,940 (54), and HU-210 (39). We identified few studies with the naphthoylindoles (JWH-018 and analogs) and the newer SC structural families that now dominate the market.

3.2.1 Physiological and Behavioral Effects—Acute SC intraperitoneal (i.p.), intravenous (i.v.), or oral (p.o.) administration produced dose-dependent physiological effects similar to THC in rodents and non-human primates, such as anti-emesis, cannabinoid tetrad (analgesia, catalepsy, hypomotility, hypothermia), and hypotension (see Table 1). Some SC act as anti-epileptics or enhance anti-convulsant drug actions in rodents. SC activity at the CB_2 receptor mediates anti-cancer, anti-inflammatory, anti-oxidative cardio-protective, and immunosuppressive properties (Table 1).

Few SC studies evaluated effects on more complex animal behavior. Chronic CP55,940 (0.15-0.3mg/kg, i.p.) exposure in adolescent rats impaired short-term and working memory as adults, while chronic exposure in adulthood had no long-lasting effect (Renard et al., 2013). Acute administration of 1.2mg/kg i.p. WIN55,212-2 to adolescent and adult rats affected object and social discrimination; rats continuously exposed to WIN55-212-2 since puberty showed persistent discrimination deficits as adults (Schneider et al., 2008). Behavioral deficits (socialization, self-grooming) were more pronounced in WIN55,212-2 (1.2mg/kg i.p.) chronically-treated adolescent rats than adults (Schneider and Koch, 2005).

Chronic exposure to HU-210 (25, 50, or 100μg/kg i.p.), a CB_1/CB_2 agonist 100 times more potent than THC *in vivo*, reduced body weight in adult rodents during the first 4 days, with slow weight gain thereafter, although still lower than controls after 14 days (Dalton et al., 2009). Weight loss was associated with dose-dependent CB_1 receptor down-regulation continuing throughout chronic exposure. In contrast, adolescent rats gained weight over the entire study, but also showed some CB_1 receptor down-regulation over 14 days. Single 100μg/kg i.p. HU-210 doses significantly decreased CB_1 binding in the caudate putamen and hippocampus of adolescent rats and increased brain glucose metabolism in young adult rats, with metabolism returning to normal the following day (Nguyen et al., 2012). These studies suggest that SC's chronic effects are influenced by age, dose, and exposure duration, and that drug tolerance can develop over time.

Animals exposed to 100μg/kg i.p. HU-210 for 12 days manifested increased anxiety, correlating with higher plasma cortisone concentrations compared to controls (Hill and Gorzalka, 2006). Repeated 3.0mg/kg i.p. WIN55,212-2 induced anxiogenic-like behaviors in rats, associated with increased cathecholamine expression in locus coerulus, which is involved in norepinephrine synthesis (Page et al., 2007). CP55,940, a nonselective cannabinoid agonist, administered acutely (10-50μg/kg i.p.) to an anxiety-prone rat strain elicited anxiogenesis (Arnold et al., 2010; Boucher et al., 2011), which diminished as tolerance developed (Boucher et al., 2011). Repeated 7-day exposure to 50μg/kg i.p CP55,940, was associated with 5-HT2A receptor upregulation in rat prefrontal cortex (Franklin and Carrasco, 2013) and hypothalamic paraventricular nucleus (Franklin et al.,

2013), as well as enhanced anxiety-like behaviors. These observations suggest a link between SC and anxiety that is mediated by brain serotoninergic activity, which is influenced by baseline anxiety level.

3.2.2 Drug discrimination and drug re-instatement studies—In rat discrimination studies, AM5983 [(1-[(1-methylpiperidin-2-yl)methyl)]-1Hindol-3-yl)(naphthalen-1-yl)methanone)] and AM2389 [9β-hydroxy-3-(1-hexyl-cyclobut-1-yl)-hexahydrocannabinol] with ED_{50} 0.06 and 0.03mg/kg, respectively, potency was 4–105 times higher than THC's (0.26mg/kg) (Järbe et al., 2011a). In non-human primates, JWH-073 and JWH-018 induced THC-like subjective effects at concentrations as low as 0.032mg/kg (JWH-018), compared to 0.1mg/kg THC with a shorter duration of action (1.5–2.3h versus 3h for THC). Rimonabant (0.32-1mg/kg i.v.), a CB_1 receptor antagonist/inverse agonist, dose-dependently attentuated SC discriminative stimulus effects (Ginsburg et al., 2011), suggesting mediation through the CB_1 receptor.

Rimonabant-elicited withdrawal symptoms (head shakes, increased heart rate) in monkeys previously exposed to THC were dose-dependently attenutated by 0.032–0.32mg/kg CP55,940 or 1-10mg/kg WIN55,212-2 i.v. administration. CP55,940 (0.4mg/kg i.p.) and WIN55,212-2 (2.0–8.0mg/kg i.p.) exposure of adolescent rats facilitated desensitization to other illicit drugs (Biscaia et al., 2008; Pistis et al., 2004). HU-210 (4-100μg/kg i.p.) dose-dependently reinstated previously extinguished cocaine self-administration (animal relapse model) in rats, which was blocked by 1mg/kg rimonabant (De Vries et al., 2001).

3.2.3 *In utero exposure*—In contrast to adolescent exposure, there appear to be little or no adverse effects from SC exposure *in utero*. Daily oral 1, 5 and 25μg/kg HU-210 exposure to pregnant rats had no significant effect on gestational progression or post-natal food and water intake when compared to controls (del Arco et al., 2000). Offspring exposed to HU-210 *in utero* showed no significant difference from the non-exposed control group in average birth weight, body length, and lymphocyte immune function; however, 1μg/kg HU-210-exposed rats had a 17% increase in spleen size. WIN55,212-2 (0.5mg/kg s.c.) daily administration to rats during gestation had no effect on gestational progression, birthweight, or brain development into adulthood; however, glutamic acid decarboxylase (GAD-65/67) and γ-aminobutyric acid (GABA) expression in the cerebellar cortex was significantly higher than in controls (Benagiano et al., 2007).

In summary, animal studies indicate that SC acute or chronic exposure during adolescence or adulthood, but not *in utero*, induces dose-dependent physiological and behavioral effects and brain CB_1 receptor downregulation. Chronic SC exposure during adolescence can have detrimental behavioral effects as an adult.

3.3 Human Pharmacodynamics

The American Association of Poison Control Call Centers received 2,906 SC-related calls in 2010, 6,968 in 2011, and 5,230 in 2012, and 2,639 in 2013 (Supplementary Material Figure 1)[2] (American Association of Poison Control Centers, 2013; Bronstein et al., 2012). There were 11,406 SC-related emergency department (ED) visits in 2010, increasing to 28,531 in 2012 (Substance Abuse and Mental Hearlth Services Administration, 2012). In 2010, Texas

poison control centers received 464 reports of SC-related exposures: 73.9% men and 25% women, ranging in age from 12-67 years (Forrester et al., 2012). Adverse clinical effects were categorized as neurological (61.9%), cardiovascular (43.5%), gastrointestinal (21.1%), respiratory (8.0%), ocular (5.0%), dermal (2.6%), renal (0.9%), hematological (0.4%) and miscellaneous, e.g., acidosis, hyperglycemia, diaphoresis (25.9%). No SC-related fatality was reported, although 59.9% of patients manifested “moderate or major” toxicity symptoms. Treatments included i.v. fluids (38.8%), benzodiazepines (18.5), oxygen (8.0%), and anti-emetics (6.0%).

We identified 63 peer-reviewed articles and 4 meeting abstracts, which included case reports/series, retrospective toxicological data reviews, driving under the influence of drugs (DUID) reports, criminal/forensic cases, and self- and controlled drug administration studies. The majority of case reports were ED visits; other toxicity data came from poison control center calls, inpatient psychiatric cases, and law enforcement drug recognition examiner (DRE) evaluations.

3.3.1 Acute Intoxication—We identified 51 articles from 5 continents reporting >200 acute intoxication cases (summarized in Table 2). ED patients presenting with SC intoxication were ages 13-59 years (mean 22, median 20). Acute SC-intoxication psychoactive symptoms included agitation or irritability, restlessness, anxiety, confusion, short-term memory and cognitive impairment, and psychosis. Physical signs included dilated pupils, reddened conjunctivae, nausea and vomiting, slurred speech, shortness of breath, hypertension, tachycardia (up to 180 bpm), chest pain, muscle twitches, and sweating or skin pallor. Physical examination (except as noted above), clinical laboratory tests, and electrocardiogram (ECG) were generally normal, except for some patients with mild leucocytosis (WBC count 13,000-14,000) or hypokalemia (<3.5meq/L). Hyperglycemia also was observed. Urine toxicological screens were often negative for illicit drugs. Only 26 acute intoxication articles reported SC detection in serum, blood, oral fluid or urine, including ADB-PINACA [*N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1*H*-indazole-3-carboxamide], AM2201 [N-(5-Fluoropentyl)-3-(1-naphthoy)lindole], CP47,497 C8 homolog [5-(1,1-Dimethyloctyl)-2-[(1R,3S)-3-hydroxycyclohexyl]-phenol], JWH-018, JWH-019 [(1-Hexylindol-3-yl)naphthalene-1ylmethanone], JWH-073, JWH-081 [4-Methoxy-1-napthalen-1-yl-(1-pentyindol-3-yl)methanone], JWH-122 [1-Pentyl-3-(1-(4-methylnaphthoyl))indole], JWH-210 [4-Ethylnaphthalen-1-yl-(1-pentylindol-3-yl)methanone], JWH-250 [1-Pentyl-3-(2-methoxyphenylacetyl)indole], JWH-307 [(5-(2-Fluorophenyl)-1-pentylpyrrol-3-yl)-1-(naphthalenylmethanone)], MAM2201 [1-(5-Fluoropentyl)-3-(4-methyl-1-napthoyl)indole], RCS-4 [4-Methoxyphenyl-(1-allyl-1H-indol-3-yl)methanone], XLR-11 [(1-(5-Fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone], and UR-144 [(1-Pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone]. Metabolites were identified in urine except following ADB-PINACA, JWH-250, JWH-307, and RCS-4 intake. Patients generally received supportive care, benzodiazepines, and i.v. saline, except in cases with serious complications

[2]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:….

such as seizures that often also required intubation. Some patients reported effect onset within minutes of smoking and intoxication for 2-5h, with most recovering in <24h.

Serious medical complications developed after subacute exposures (>24h after intake), including myocardial infarction, ischemic strokes, seizures, and acute kidney injury (AKI). Among patients with AKI, XLR11 and/or UR-144 (parent and metabolites) were detected in urine, blood, or serum and implicated as causing injury. Some patients with AKI required hemodialysis and corticosteroid treatment, while others recovered within 3 days of hospital admission.

3.3.2 Controlled administration studies—We identified five peer-reviewed articles and one conference proceeding abstract describing SC controlled administration (Table 3). Two German investigators smoked a shared cigarette containing 0.3g “Spice Diamond,” a mixture of a dimethyl CP47,497 [2-[(1R,3S)-3-hydroxycyclohexyl]-5-(2-methyloctan-2-yl)phenol] homologue, the trans-diastereomer of the CP47,497 homologue, and small amounts of JWH-018 (Auwärter et al., 2009). Acute effects, noticeable 10 min after smoking, included altered mood and perception, tachycardia, dry mouth, and reddened conjunctivae. There was no impairment in objective psychomotor tests, although the subjects felt they were moderately impaired. Objective effects resolved over 6 h; however, the investigators reported noticeable “minor after-effects” the next day. Two other investigator-involved studies included oral AB-001 [(1-Pentyl-1H-indol-3-yl)adamantylmethanone] and oral and smoked AM694 [1-(5-fluoropentyl)-3-(2-iodobenzoyl)indole]. AB-001 was ingested by 1 male (13mg) and 1 female (26mg) (Grigoryev et al., 2012b). AM694 (10mg) was first ingested by one male investigator, who later smoked a drug-laced cigarette soaked in acetone containing 1g/L AM694) (Grigoryev et al., 2012a). In these studies, investigators reported no physiological effects. After 5mg oral AM2201, no psychological or physiological effects were reported, with serum concentrations of AM2201 (0.04μg/L), 6-hydroxyindole AM2201 (0.2μg/L), JWH-018 pentanoic acid (0.7μg/L), and JWH-018 5-hydroxypentyl (0.3μg/L), 1.5h after ingestion (Hutter et al., 2013). AM2201 was not present after 28h, while AM2201 6-hydroxyindole and JWH-018 metabolites were present up to 28 and 57h, respectively.

In a German study, a 33-year old woman and a 47-year old man smoked 100 and 150mg, respectively, of a 2.9% JWH-018 cigarette, yielding 50μg/kg body weight JWH-018. Immediate effects included sedation, dry mouth, feeling sick, subjective thought disruption, burning eyes, hot flushes, and tachycardia (Teske et al., 2010). No significant change in blood pressure or pupil reaction was noted. After acute effects resolved, subjects felt tired and exhausted for 6–12h after smoking. JWH-018 serum concentrations after 5min were 8.1 (Subject 1) and 10.2 (Subject 2) μg/L. Concentrations rapidly declined at 1h after intake and were undetected at 24h.

An unpublished controlled drug administration study was conducted at the University of Central Missouri (Warrensburg, MO) in collaboration with NMS Laboratories (Willow Grove, PA; Logan et al., 2011). Six healthy research volunteers took up to three inhalations from a water pipe containing 0.3g SC-laced herbal product. Two subjects each smoked either K2 Standard (9mg/g JWH-018 and 9mg/g JWH-073), K2 Citron (10mg/g of each), or

K2 Summit (11mg/g JWH-018 and 9mg/g JWH-073). There was no placebo condition and it is not clear whether raters were blinded to study conditions. Impairment was assessed by a DRE. Acute subjective effects began at 2-3min and peaked 5-10min after smoking and included changes in mood and perception (5 subjects), self-assessed impairment (5), mild anxiety (4), impaired sense of time (4), loss of concentration (4), sedation (3), and paranoia (2). No subject experienced hallucinations. Physical effects included tachycardia (6 subjects), reddened conjunctivae (6), dry mouth (4), and burning eyes (1). Increased systolic blood pressure, body sway and other signs of impaired balance and motor coordination, leg and body tremor, and lack of eye convergence occurred in some subjects. Pupil size and reactivity, muscle tone, and body temperature remained normal; no horizontal or vertical gaze nystagmus was observed. Acute effects resolved within a few hours, but three subjects experienced fatigue and exhaustion (hangover-like effect) for 6-12h after smoking. JWH-018 and JWH-073 were quantified in blood at 4–5μg/L after 1 h, while metabolites were detected in urine (concentrations not specified).

3.3.3 Driving Impairment—We identified 3 peer-reviewed articles documenting DUID with SC. The first involved 8 drivers in Germany stopped by police for suspected DUID (Musshoff et al., 2013). Somnolence and retarded movements were the most commonly observed symptoms. SC were identified in serum (collected within 2h) in all suspected cases, with concentrations ranging from 0.33μg/L to 28μg/L. Six of 8 suspects' serum contained multiple SC. One motorcyclist's serum contained 7 SC: JWH-122 (28μg/L), JWH-210 (2.5μg/L), and JWH-018 (1.9μg/L). AM2201, JWH-307, MAM2201, and UR-144 also were detected in low concentrations (<0.1μg/L). The examining physician reported "no abnormalities" 1.5h after arrest.

In the US, NMS Laboratories confirmed SC in blood from 12 suspects receiving DRE evaluations between 2010 and 2011 (Yeakel and Logan, 2013). AM2201, JWH-018, JWH-081, JWH-122, JWH-210, JWH-250 blood concentrations were 0.24-9.9μg/L. The predominant SC was AM2201 (7 samples, 0.4–4.0μg/L). All suspects failed their DRE examination, with general poor motor coordination, but the majority were "cooperative and relaxed." About 25% were involved in motor vehicle accidents; none were positive for alcohol. These symptoms were different from ED reports of agitation, aggression, and panic attacks associated with SC intoxication.

In a Norwegian study conducted between November, 2011 and April, 2012, 2.2% of 726 blood samples collected from DUID suspects confirmed positive for SC (Tuv et al., 2014). Each sample quantified for only one SC, with AM2201 (0.07–1.33μg/L) and JWH-018 (0.08–0.46μg/L) the most prevalent (n=5 each). All samples also were positive for other psychoactive drugs: THC (12), benzodiazepines (12), methamphetamine and amphetamine (4), methamphetamine only (3), LSD (2), ketamine (1), methadone (1), methylphenidate (1), and alcohol (1). The majority (11) were impaired and/or involved in traffic accidents

3.3.4 Subacute psychiatric effects—Five reports from psychiatric inpatient units and two ED visits suggested that some SC smokers experienced longer-lasting psychiatric effects. Fourteen apparently healthy men (20-30 years) with no prior psychiatric history developed new onset psychosis after smoking SC, including paranoia, thought disorder, and

suicidal ideation (5 patients) (Hurst et al., 2011; Thomas et al., 2012; Van Der Veer and Friday, 2011). Treatment required psychiatric hospitalization and anti-psychotic medications. The episode lasted up to one week in 8 patients, two weeks in 3 patients, and more than 5 months in 3 patients.

Fifteen men hospitalized in a New Zealand psychiatric ward were interviewed about SC use (Every-Palmer, 2011). All had a history of cannabis intake, while the majority (13) reported smoking SC (JWH-018) within the past year and experiencing rapid onset of psychoactive effects after smoking SC alone. Of the 13 SC smokers, 9 admitted to experiencing psychotic symptoms. Although none reported experiencing withdrawal, 5 patients experienced psychotic relapse after smoking SC for a day and effects lasted as long as "several weeks." A retrospective audit of SC-related admissions in a New Zealand acute psychiatric ward reported 17 patients with severe psychotic symptoms hospitalized for up to 13.1 days (Glue et al., 2013).

One 59-year old man with a history of post-traumatic stress disorder and polydrug abuse experienced "flashbacks" immediately after smoking SC (Peglow et al., 2012). He had three hospital admissions over 60 days, recovering within 24h with each subsequent visit. All his drug toxicological screens were negative for alcohol, THC, cocaine, opiates, barbiturates, benzodiazepines, and PCP. His episodes ceased after discontinuing SC intake. Another case involved a 25-year old man with a history of recurrent psychosis who developed anxiety and paranoid psychosis with auditory command hallucinations after smoking 3g "Spice" on three occasions, despite being on stable anti-psychotic treatment (amisulpiride 800mg daily) for 2 years (Muller et al., 2010). Symptoms persisted for one month and required psychiatric hospitalization. The patient described previous similar psychotic exacerbations induced by smoking cannabis.

3.3.5 Withdrawal—We identified 3 peer-reviewed articles addressing SC withdrawal. A 20-year-old man who smoked "Spice Gold" 3g/day for 8 months was hospitalized about 1.5 days after last use with a severe withdrawal syndrome, including increased craving, restlessness, nightmares, tachycardia (maximum heart rate 125 bpm), hypertension (180/90), nausea, sweating, and muscle twitches. The syndrome resolved within one week with symptomatic treatment (Zimmermann et al., 2009). A 22-year-old woman smoking 3g/day SC presented to the ED complaining of severe anxiety, "vivid" dreams, headache, cramping of extremities, "sweats and chills", anorexia, and craving 6 days after last use (Nacca et al., 2013). She was discharged within 3h of receiving i.v. saline and 2mg lorazepam. A 20-year-old man, with a history of smoking "Mr. Nice Guy" for 18 months, ceased smoking 6 days prior to ED presentation for headache, chest pain, profuse sweating, and body tremors. Prior to his ED visit, he attempted to alleviate symptoms by smoking cannabis, which was ineffective, but taking his roommate's quetiapine provided relief. Benzodiazepines did not alleviate his symptoms, and after inpatient admission, subsequent hydroxyzine and diphenhydramine administrations also were unsuccessful. The patient's symptoms subsided after the physician administered 50mg quetiapine, and he was released with an unspecified quetiapine dose.

A 23-year-old man, admitted to a German inpatient detoxification clinic for SC withdrawal symptoms, underwent positron emission tomography (PET) scans with the dopamine (D_2/D_3) receptor ligand [^{18}F] fallypride one day after admission and after one week of SC abstinence (Rominger et al., 2013). Compared to controls (three healthy males ages 20, 21, and 25), the patient's first PET scan showed globally decreased D_2/D_3 binding, with the lateral temporal cortex and hippocampus least (−15%) and most (−62%) affected, respectively. The second scan showed marked increases in several areas, with the majority returning to control values. Effects from cannabis were considered unlikely, as the patient's urine drug screen was negative for cannabinoids.

It is difficult to directly compare SC and cannabis withdrawal symptoms because data are limited and patients often had a history of smoking cannabis before and/or after SC. However, many of the symptoms reported by patients after cessation of SC use are also reported during cannabis withdrawal, e.g., disturbed sleep and dreaming, anxiety, craving, nausea, muscle twitching or cramping, and chills (Levin et al., 2010; American Psychiatric Association, 2013).

3.3.6 Mortality—We identified only 4 fatalities associated with SC intake. MAM2201 (dose and route of administration unknown) was linked to the death of a 59-year-old Japanese man who was found dead at home (Saito et al., 2013) with MAM2201 detected in his femoral blood (1.24μg/L), brain, body organs, and adipose tissues. Because there were no signs of physical injury and the deceased was assumed healthy, MAM2201 intoxication was considered cause of death.

In Sweden, a 17-year-old man was found alone outside (6–8°C ambient temperature), dead from hypothermia and acute SC intoxication (Kronstrand et al., 2013). Prior to the man's death, his friend reported smoking a foil of herb with the deceased. The friend took two whiffs, became light-headed and felt numbness in his hands. The friend went indoors afterwards, while the deceased continued smoking outside. JWH-210 was found in post-mortem femoral blood (12.3μg/L).

A 26-year old man was found dead in his apartment with several bags containing methoxetamine (Wikstrom et al., 2013). Femoral blood concentration of 8.6μg/kg methoxetamine and three SC (AM694, AM2201, and JWH-018, all <1pg/g) were confirmed. Although death was attributed to methoxetamine overdose, SC presence also may have contributed.

A 23-year-old man died from self-inflicted injuries sustained during a violent severe psychosis episode after smoking AM2201 (Patton et al., 2013). Prior to his death, a family member heard "stomping noises" for 30min coming from his room. The man was eventually found dead on the floor with multiple injuries, including a fatal stab wound to his neck. A bag of "Mad Hatter" incense, smoke pipe, and a bag of white pills (labeled "ZAN-X") were found in his room. AM2201 (12.0μg/L) was identified in post-mortem heart blood. No other drugs were found. AM2201 also was detected in the "Mad Hatter" incense" and pipe residue. Traces of JWH-073 also were detected. "ZAN-X" did not contain any illicit or prescription drugs.

Reported SC blood concentrations in these cases were 1.2–12.3μg/L compared to impaired driver concentrations of 0.1-28 μg/L. This overlap between lethal and DUID SC concentrations precludes ready identification of a fatal SC concentration. Other factors also could have contributed to death, such as undetected additional SC and/or other drugs of abuse, dose and route of administration, individual variation in SC metabolism, and lack of drug tolerance.

In summary, SC intake produced physiological and psychological effects in humans, which were qualitatively similar but of greater magnitude and duration than cannabis' effects. Acute adverse effects generally subsided within 24-48h, with patients treated with benzodiazepines and supportive care. Rarely, SC intake also caused acute kidney injury and death. In DUID suspects, SC blood concentrations were 0.7-28μg/L, with no clear correlation between impairment and blood concentrations. Withdrawal symptoms similar to those following chronic frequent cannabis intake were observed in chronic SC smokers after at least 1 week of abstinence.

3.4 Receptor affinity

We identified 42 peer-reviewed journal articles on the interaction of SC with cannabinoid receptors; the majority were *in vitro* receptor binding studies and functional assays. SC psychoactive properties are attributed to CB_1 receptor activation (Pertwee, 2004). SC binding affinities were studied in a variety of *in vitro* models and further assessed with *in vivo* studies (i.e., animal administration).

3.4.1 Binding affinity at cannabinoid receptors—Most cannabinoid receptor competitive binding affinity studies in rodent brain employed tritium [^{3}H]-labeled CP55,940 or WIN55,212-2 (Pertwee, 2010) to evaluate receptor binding. Data were presented as the SC concentration displacing 50% of the radiolabeled compound from the receptor (IC_{50}), which is utilized to calculate the binding affinity, Ki (lower Ki represents greater affinity). In general, SC binding affinity to CB_1 and/or CB_2 was compared with THC affinity. THC CB_1 and CB_2 binding affinities were 40.7 and 36.4nM, respectively (Showalter et al., 1996).

The majority of SC detected in herbal products possessed higher affinity and lower Ki values than THC at the CB_1 receptor (Table 4). JWH-018 metabolites retained CB_1 binding affinity *(in vitro)* in mouse brain homogenates expressing CB_1 receptors (Brents et al., 2011). JWH-018, and its 4- and 5-hydroxyindole metabolites had Ki values of 8.0, 2.6±0.3 and 4.2±1.2nM, respectively, 5-6 times lower than THC's Ki (15.3±4.5nM) in this preparation. JWH-018 6-hydroxyindole, 7-hydroxyindole and *N*-5-hydroxypentyl had equipotent (17.2±3.6, 20.8±4.9, and 25.2±5.0nM) binding affinities to THC. However, JWH-018 *N*-pentanoic acid CB_1 Ki was >10,000nM. JWH-018 4-hydroxyindole 10mg/kg i.p. produced cannabinoid tetrad in mouse much greater than THC (Brents et al., 2011). Thus, some SC metabolites may be active and prolong the parent compound's psychoactive and physiological effects and contribute to intoxication severity.

SC receptor binding affinities and selectivity vary based upon functional group substitution (Aung et al., 2000; Wiley et al., 2013b). For example, JWH-018 (naphthoylindole with a *N*-pentyl side chain) and its *N*-butyl analog (JWH-073) CB_1 Ki values are 9.0±5.0 and

8.9±1.8nM, respectively (Aung et al., 2000). However, AM2201 (JWH-018 5-fluoropentyl analog) has a CB_1 Ki of 1nM (Makriyannis A and Deng, 2000). This single halogenated analog is frequently encountered in newly emerging SC. Table 4 summarizes published SC binding affinities at CB_1 and CB_2 receptors.

3.4.2 Intrinsic activity at cannabinoid receptors—Ki presents only ligand-binding interaction. *In vitro* or *in vivo* functional assays, which evaluate the drug's efficacy (e.g., EC_{50}) and potency, are needed to determine a drug's intrinsic activity as a receptor ligand, i.e., full partial, or inverse agonist, or neutral antagonist. However, we identified few published data on SC efficacy or intrinsic activity. SC intrinsic activities were studied in a variety of *in vitro* models, making direct comparisons challenging. CB_1 agonist activation down regulates adenylyl cyclase and decreases cellular cAMP levels, which triggers a cascade of reactions that affects cellular signaling and neurotransmitter inhibition, including acetylcholine, dopamine, noradrenaline, and glutamine, and γ-aminobutyric acid (GABA) (Mechoulam and Parker, 2013; Pertwee, 2010).

Reduced cellular cAMP levels also were observed with CB_2 activation (Slipetz et al., 1995). Moreover, CB_1 or CB_2 receptor activation was measured with [^{35}S]GTPγS functional assay, which involved G-protein conformational change (Breivogel et al., 1997).

CP55,940 inhibited adenylate cyclase production more effectively at 25nM compared to THC (430nM) (Howlett et al., 1988). CP55,940, HU-210, and WIN55,212-2 concentration-dependent inhibited forskolin-induced cAMP production by activating CB_2 receptors expressed in Chinese hamster ovarian cells, which were blocked by pertussis toxin at 10ng/mL maximal inhibition (Slipetz et al., 1995).

HU-210, CP55,940, and WIN55,212-2 activated CB_1 receptors in a [^{35}S]GTPγS binding assay with a potency order of: HU-210>CP55,940>THC>WIN55,212-2 (Breivogel et al., 2001). JWH-018 and its mono-hydroxylated metabolites produced partial G-protein activation in a mouse CB_1 receptor preparation with greater potency than THC (Brents et al., 2011). Naphthoylindoles identified in seized herbal products activated CB_1 receptors (Nakajima et al., 2011). Tetramethylpropylindoles, XLR-11 and UR-144 also were reported to have CB_1 and CB_2 agonist activities (Wiley et al., 2013a).

CB_1 receptors activated by JWH-018, JWH-073 and CP 47,497 inhibited release of neurotransmitters in autaptic neurons (isolated cultured neurons that form synapses onto themselves) and inhibition was reversed by rimonabant treatment (Atwood et al., 2011). Table 5 summarizes SC CB_1 and CB_2 intrinsic activity.

SC intrinsic activities appear to have full or partial agonist properties similar to that of THC; though SC produce *in vivo* pharmacodynamic effects at lower median effective dose (ED_{50}), which is the drug dose required to produce measurable response in 50% of the test population.

In summary, SC binding affinities to CB_1 and CB_2 receptors had varying intrinsic values when measured by in vitro functional assays, but Ki values were not necessarily equivalent to ED_{50} in animals. The majority of SC found in seized materials have unknown intrinsic

values. In vivo evaluation of intrinsic activities could assist clinical treatment development for SC-related symptoms.

4. CONCLUSION

4.1 Summary

SC consumption has become widespread, despite law enforcement and regulatory control measures. Epidemiological data suggest that the majority of SC users are young adults who perceive SC as safer than non-cannabinoid illicit drugs and a favorable cannabis alternative eliciting cannabis-like “high” while avoiding detection by standard drug screens. However, data suggest that many SC users prefer cannabis over SC due to the drugs’ negative effects. SC are readily accessible, sold under several names and packaging with smoking as the most common route of administration. Most SC smokers are men from 13–59 years old, many with a history of polydrug use such as cannabis, alcohol, and nicotine.

SC were investigated in animals to characterize THC effects and evaluate their therapeutic benefits. Acute SC administration in rodents produced the cannabinoid tetrad of effects with dose-dependent anxiolytic and anxiogenic properties. Chronic SC administration was anxiogenic and produced more pronounced behavioral deficits in rodents exposed during adolescence, but no significant physiological effects in animals exposed *in utero*. SC substituted for THC in animal (rats and monkeys) discrimination studies, and also attenuated antagonist-elicited withdrawal in monkeys previously exposed to THC.

Recreational SC intake arose in the 2000’s and many adverse effects were reported. Acute SC intoxication can lead to ED presentation and hospitalization, requiring supportive care, benzodiazepines, and fluids. While most such patients were released within 24h of admission, severe adverse effects such as cardiotoxicity, AKI, and psychosis resulted in hospitalization for as long as 2 weeks. Deaths directly linked to SC use were quite rare. Some chronic SC users experienced withdrawal symptoms when they stopped drug intake.

Most SC have greater binding affinity to CB_1 receptors than does THC, suggesting a possible mechanism for the severity of acute clinical reactions that result in ED presentation. However, SC intrinsic activity data are limited, with few direct comparisons to THC, making it premature to draw any conclusions about mechanisms.

4.2 Knowledge Gaps and Limitations

SC epidemiology data are limited and derived mostly from cross-sectional surveys of small, self-selected convenience samples. Community-based epidemiological surveys with large, nationally representative samples are needed to better understand SC epidemiology.

Although hundreds of animal studies were conducted with SC, the majority focused on CP55,940, HU-210, and WIN55-212-2. Newer SC identified in herbal products and human clinical samples need further investigation.

Human controlled SC administration studies and systematic *in vitro* and *in vivo* pharmacokinetic studies are needed to fill in important gaps in our knowledge of SC

pharmacokinetics, tissue/organ distribution, elimination, metabolite biological activity, and drug-drug interactions. Human studies will be difficult to conduct in the US, as they must go through a rigorous multi-agency approval process (i.e., Drug Enforcement Administration, Food and Drug Administration, and Institutional Review Board) before they can be conducted; the preclinical safety and pharmacokinetic data to support such applications are lacking.

Analytical laboratories are challenged with SC identification in biological matrices due to structural diversity and similarity. Unidentified SC in a patient's sample, makes it difficult to definitively evaluate SC clinical effects or develop specific treatments. Medical treatment must often remain symptomatic. To address the increasing safety and public health issues associated with SC intake, future studies are needed to evaluate SC abuse liability, *in utero* and long-term effects, which are part of developing withdrawal and addiction treatment similar to the effects elicited by cannabis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Ms. Anne White-Olson and Ms. Barbara Brandys, NIH Library, Bethesda, MD for their invaluable assistance with the electronic literature search.

Role of funding source

This work was funded by an interagency agreement between the Department of Defense Counter Narcotics Program and Chemistry and Drug Metabolism Section, IRP, National Institute on Drug Abuse, NIH.

REFERENCES

Abalo R, Cabezos PA, Vera G, Lopez-Miranda V, Herradon E, Martin-Fontelles MI. Cannabinoid-induced delayed gastricv emptying is selectively increased upon intermittent administration in the rat: role of CB1 receptors. Neurogastroenterol. Motil. 2011; 23:457–467. [PubMed: 21303434]

Acheson SK, Moore NL, Kuhn CM, Wilson WA, Swartzwelder HS. The synthetic cannabinoid WIN 55212-2 differentially modulates thigmotaxis but not spatial learning in adolescent and adult animals. Neurosci. Lett. 2011; 487:411–414. [PubMed: 21055447]

Alhadi S, Tiwari A, Vohra R, Gerona R, Acharya J, Bilello K. High times, low sats: diffuse pulmonary infiltrates associated with chronic synthetic cannabinoid use. J. Med. Toxicol. 2013; 9:199–206. [PubMed: 23539384]

American Association of Poison Control Centers. [Accessed on January 30, 2014] Synthetic Marijuana Data. 2013. http://www.aapcc.org/alerts/synthetic-marijuana/

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th Ed.. APA; Washington, DC: 2013.

Anaraki DK, Sianati S, Sadeghi M, Ghasemi M, Javadi P, Mehr SE, Dehpour AR. Modulation by female sex hormones of the cannabinoid-induced catalepsy and analgesia in ovariectomized mice. Eur. J. Pharmacol. 2008; 586:189–196. [PubMed: 18371951]

Arevalo-Martin A, Vela JM, Molina-Holgado E, Borrell J, Guaza C. Therapeutic action of cannabinoids in a murine model of multiple sclerosis. J. Neurosci. 2003; 23:2511–2516. [PubMed: 12684434]

Army Center for Substance Abuse Program. [Accessed on December 30, 2013] Expansion of Synthetic Cannabinoids To Military Urinalysis Testing. 2013. http://acsap.army.mil/Pdf/ALARACT%20310-2013.pdf

Arnold JC, Dielenberg RA, McGregor IS. Cannabinoids increase conditioned ultrasonic vocalisations and cat odour avoidance in rats: strain differences in drug-induced anxiety. Life Sci. 2010; 87:572–578. [PubMed: 20875432]

Ashton JC, Friberg D, Darlington CL, Smith PF. Expression of the cannabinoid CB2 receptor in the rat cerebellum: an immunohistochemical study. Neurosci. Lett. 2006; 396:113–116. [PubMed: 16356641]

Atwood BK, Lee D, Straiker A, Widlanski TS, Mackie K. CP47,497-C8 and JWH073, commonly found in 'Spice' herbal blends, are potent and efficacious CB(1) cannabinoid receptor agonists. Eur. J. Pharmacol. 2011; 659:139–145. [PubMed: 21333643]

Aung MM, Griffin G, Huffman JW, Wu M-J, Keel C, Yang B, Showalter VM, Abood ME, Martin BR. Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB1 and CB2 receptor binding. Drug Alcohol Depend. 2000; 60:133–140. [PubMed: 10940540]

Auwärter V, Dresen S, Weinmann W, Müller M, Pütz M, Ferreirós N. "Spice' and other herbal blends: harmless incense or cannabinoid designer drugs? J. Mass Spectrom. 2009; 44:832–837. [PubMed: 19189348]

Balistreri E, Garcia-Gonzalez E, Selvi E, Akhmetshina A, Palumbo K, Lorenzini S, Maggio R, Lucattelli M, Galeazzi M, Distler JWH. The cannabinoid WIN55,212-2 abrogates dermal fibrosis in scleroderma bleomycin model. Ann. Rheum. Dis. 2011; 70:695–699. [PubMed: 21177293]

Banerji S, Deutsch C, Bronstein A. Spice aint so nice. Clin. Toxicol. (Phila.). 2010; 48:632.

Banister SD, Wilkinson SM, Longworth M, Stuart J, Apetz N, English K, Brooker L, Goebel C, Hibbs DE, Glass M, Connor M, McGregor IS, Kassiou M. The synthesis and pharmacological evaluation of adamantane-derived indoles: cannabimimetic drugs of abuse. ACS Chem. Neurosci. 2013; 4:1081–1092. [PubMed: 23551277]

Barlas, F.; Higgins, W.; Plfieger, J.; Diecker, K. [Accessed on March 1, 2013] 2011 Department of Defense Health Related Behaviors Survey of Active Duty Military Personnel. 2013. http://www.murray.senate.gov/public/_cache/files/889efd07-2475-40ee-b3b0-508947957a0f/final-2011-hrb-active-duty-survey-report.pdf

Barratt MJ, Cakic V, Lenton S. Patterns of synthetic cannabinoid use in Australia. Drug Alcohol Rev. 2013; 32:141–146. [PubMed: 23043552]

Basavarajappa BS, Subbanna S. CB1 receptor-mediated signaling underlies the hippocampal synaptic, learning and memory deficits following treatment with JWH-081, a new component of spice/K2 preparations. Hippocampus. 2013; 24:178–88. [PubMed: 24123667]

Bebarta VS, Ramirez S, Varney SM. Spice: a new "legal" herbal mixture abused by young active duty military personnel. Subst. Abuse. 2012; 33:191–194.

Bell MR, D'Ambra TE, Kumar V, Eissenstat MA, Herrmann JL Jr. Wetzel JR, Rosi D, Philion RE, Daum SJ, Hlasta DJ, et al. Antinociceptive (aminoalkyl)indoles. J. Med. Chem. 1991; 34:1099–1110. [PubMed: 1900533]

Benagiano V, Lorusso L, Flace P, Girolamo F, Rizzi A, Sabatini R, Auteri P, Bosco L, Cagiano R, Ambrosi G. Effects of prenatal exposure to the CB-1 receptor agonist WIN 55212-2 or CO on the GABAergic neuronal systems of rat cerebellar cortex. Neuroscience. 2007; 149:592–601. [PubMed: 17916407]

Benford DM, Caplan JP. Psychiatric sequelae of Spice, K2, and synthetic cannabinoid receptor agonists. Psychosomatics. 2011; 52:295. [PubMed: 21565605]

Bernson-Leung ME, Leung LY, Kumar S. Synthetic cannabis and acute ischemic stroke. J. Stroke Cerebrovasc. Dis. 2013; 23:1239–1241. [PubMed: 24119618]

Berry-Caban CS, Ee J, Ingram V, Berry CE, Kim E. Synthetic cannabinoid overdose in a 20-year-old male US soldier. Subst. Abuse. 2013; 34:70–72.

Bhanushali GK, Jain G, Fatima H, Leisch LJ, Thornley-Brown D. AKI associated with synthetic cannabinoids: a case series. Clin. J. Am. Soc. Nephrol. 2013; 8:523–526. [PubMed: 23243266]

Biscaia M, Fernández B, Higuera-Matas A, Miguéns M, Viveros M-P, García-Lecumberri C, Ambrosio E. Sex-dependent effects of periadolescent exposure to the cannabinoid agonist

CP-55,940 on morphine self-administration behaviour and the endogenous opioid system. Neuropharmacology. 2008; 54:863–873. [PubMed: 18329053]

Bosier B, Muccioli GG, Mertens B, Sarre S, Michotte Y, Lambert DM, Hermans E. Differential modulations of striatal tyrosine hydroxylase and dopamine metabolism by cannabinoid agonists as evidence for functional selectivity in vivo. Neuropharmacology. 2012; 62:2328–2336. [PubMed: 22365976]

Boucher AA, Hunt GE, Micheau J, Huang XF, McGregor IS, Karl T, Arnold JC. The schizophrenia susceptibility gene neuregulin 1 modulates tolerance to the effects of cannabinoids. Int. J. Neuropsychopharmacol. 2011; 14:631–643. [PubMed: 20701826]

Brantley, C. Spice, bath salts, salvia divinorum, and huffing: a judge advocate's guide to disposing of designer drugs cases in the military. 2012. p. 15-37.Army Lawyer DA PAM 27-50-467

Breivogel CS, Griffin G, Di Marzo V, Martin BR. Evidence for a new G protein-coupled cannabinoid receptor in mouse brain. Mol. Pharmacol. 2001; 60:155–163. [PubMed: 11408610]

Breivogel CS, Sim LJ, Childers SR. Regional differences in cannabinoid receptor/G-protein coupling in rat brain. J. Pharmacol. Exp. Ther. 1997; 282:1632–1642. [PubMed: 9316881]

Brents LK, Reichard EE, Zimmerman SM, Moran JH, Fantegrossi WE, Prather PL. Phase I hydroxylated metabolites of the K2 synthetic cannabinoid JWH -018 retain in vitro and in vivo cannabinoid 1 receptor affinity and activity. PLoS One. 2011; 6:e21917. [PubMed: 21755008]

Brents LK, Zimmerman SM, Saffell AR, Prather PL, Fantegrossi WE. Differential drug-drug interactions of the synthetic Cannabinoids JWH-018 and JWH-073: implications for drug abuse liability and pain therapy. J. Pharmacol. Exp. Ther. 2013; 346:350–361. [PubMed: 23801678]

Bronstein AC, Spyker DA, Cantilena LR Jr. Rumack BH, Dart RC. 2011 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report. Clin. Toxicol. (Phila.). 2012; 50:911–1164. [PubMed: 23272763]

Buchler, I.; Hayes, M.; Hedge, S.; Hockerman, S.; Eugene, D.; Kortum, S.; Rico, J.; Tenbrink, R.; Wu, K. Patent, U. (Ed.), CA 2714573 A1. United States: 2009. Indazole derivatives; p. 1-283.

Burgos E, Pascual D, Martin MI, Goicoechea C. Antinociceptive effect of the cannabinoid agonist, WIN 55,212-2, in the orofacial and temporomandibular formalin tests. Eur. J. Pain. 2010; 14:40–48. [PubMed: 19318283]

Canning J, Ruha A-M, Pierce R, Torrey M, Reinhart S. Severe GI distress after smoking JWH-018. Clin. Toxicol. (Phila.). 2010; 48:618.

Castaldo P, Magi S, Gaetani S, Cassano T, Ferraro L, Antonelli T, Amoroso S, Cuomo V. Prenatal exposure to the cannabinoid receptor agonist WIN 55,212-2 increases glutamate uptake through overexpression of GLT1 and EAAC1 glutamate transporter subtypes in rat frontal cerebral cortex. Neuropharmacology. 2007; 53:369–378. [PubMed: 17631920]

Castellanos D, Singh S, Thornton G, Avila M, Moreno A. Synthetic cannabinoid use: a case series of adolescents. J. Adolesc. Health. 2011; 49:347–349. [PubMed: 21939863]

Centers for Disease Control and Prevention. Acute kidney injury associated with synthetic cannabinoid use - multiple states, 2012. MMWR Morb. Mortal. Wkly. Rep. 2013a:62.

Centers for Disease Control and Prevention. Notes from the field: severe illness associated with reported use of synthetic marijuana - Colorado, august-september 2013. MMWR Morb. Mortal. Wkly. Rep. 2013b; 62:1016–1017. [PubMed: 24336136]

Centers for Disease Control and Prevention. Notes from the field: severe illness associated with synthetic cannabinoid use - Brunswick, Georgia, 2013. MMWR Morb. Mortal. Wkly. Rep. 2013c; 62:939. [PubMed: 24257204]

Chen B, Bromley-Brits K, He G, Cai F, Zhang X, Song W. Effect of synthetic cannabinoid HU210 on memory deficits and neuropathology in Alzheimer's disease mouse model. Curr. Alzheimer Res. 2010; 7:255–261. [PubMed: 20043809]

Chopda GR, Vemuri VK, Sharma R, Thakur GA, Makriyannis A, Paronis CA. Diuretic effects of cannabinoid agonists in mice. Eur. J. Pharmacol. 2013; 721:64–69. [PubMed: 24099963]

Cohen J, Morrison S, Greenberg J, Saidinejad M. Clinical presentation of intoxication due to synthetic cannabinoids. Pediatrics. 2012; 129:e1064–1067. [PubMed: 22430444]

Cole, W. [Accessed on September 15, 2011] “Spice” traps troops: new synthetic substance not found by most tests have become a problem on post, the military says. 2011. http://www.staradvertiser.com/news/hawaiinews/20110425__Spice__traps_troops.html

Craft RM, Wakley AA, Tsutsui KT, Laggart JD. Sex differences in cannabinoid 1 vs. cannabinoid 2 receptor-selective antagonism of antinociception produced by delta9-tetrahydrocannabinol and CP55,940 in the rat. J. Pharmacol. Exp. Ther. 2012; 340:787–800. [PubMed: 22182934]

Croxford JL, Miller SD. Immunoregulation of a viral model of multiple sclerosis using the synthetic cannabinoid R+WIN55,212. J. Clin. Invest. 2003; 111:1231–1240. [PubMed: 12697742]

Dableh LJ, Yashpal K, Henry JL. Physiological evidence of a postsynaptic inhibition of the tail flick reflex by a cannabinoid receptor agonist. Eur. J. Pharmacol. 2009; 602:36–40. [PubMed: 19027734]

Dagon Y, Avraham Y, Link G, Zolotarev O, Mechoulam R, Berry EM. The synthetic cannabinoid HU-210 attenuates neural damage in diabetic mice and hyperglycemic pheochromocytoma PC12 cells. Neurobiol. Dis. 2007; 27:174–181. [PubMed: 17604177]

Dalton V, Wang H, Zavitsanou K. HU210-induced downregulation in cannabinoid CB1 receptor binding strongly correlates with body weight loss in the adult rat. Neurochem. Res. 2009; 34:1343–1353. [PubMed: 19169813]

Dalton VS, Zavitsanou K. Cannabinoid effects on CB1 receptor density in the adolescent brain: an autoradiographic study using the synthetic cannabinoid HU210. Synapse. 2010a; 64:845–854. [PubMed: 20842718]

Dalton VS, Zavitsanou K. Differential treatment regimen-related effects of cannabinoids on D1 and D2 receptors in adolescent and adult rat brain. J. Chem. Neuroanat. 2010b; 40:272–280. [PubMed: 20673846]

De Vries TJ, Shaham Y, Homberg JR, Crombag H, Schuurman K, Dieben J, Vanderschuren LJMJ, Schoffelmeer ANM. A cannabinoid mechanism in relapse to cocaine seeking. Nat. Med. 2001; 7:1151–1154. [PubMed: 11590440]

del Arco I, Munoz R, Rodriguez De Fonseca F, Escudero L, Martin-Calderon JL, Navarro M, Villanua MA. Maternal exposure to the synthetic cannabinoid HU-210: effects on the endocrine and immune systems of the adult male offspring. Neuroimmunomodulation. 2000; 7:16–26. [PubMed: 10601815]

Deng H, Gifford AN, Zvonok AM, Cui G, Li X, Fan P, Deschamps JR, Flippen-Anderson JL, Gatley SJ, Makriyannis A. Potent cannabinergic indole analogues as radioiodinatable brain imaging agents for the CB1 cannabinoid receptor. J. Med. Chem. 2005; 48:6386–6392. [PubMed: 16190764]

Derungs A, Schwaninger A, Mansella G, Bingisser R, Kraemer T, Liechti M. Symptoms, toxicities, and analytical results for a patient after smoking herbs containing the novel synthetic cannabinoid MAM-2201. Forensic Toxicol. 2013; 31:164–171.

Desai RI, Thakur GA, Vemuri VK, Bajaj S, Makriyannis A, Bergman J. Analysis of tolerance and behavioral/physical dependence during chronic CB1 agonist treatment: effects of CB1 agonists, antagonists, and noncannabinoid drugs. J. Pharmacol. Exp. Ther. 2013; 344:319–328. [PubMed: 23197773]

Devane WA, Breuer A, Sheskin T, Jaerbe TUC, Eisen MS, Mechoulam R. A novel probe for the cannabinoid receptor. J. Med. Chem. 1992; 35:2065–2069. [PubMed: 1317925]

Dill JA, Howlett AC. Regulation of adenylate cyclase by chronic exposure to cannabimimetic drugs. J. Pharmacol. Exp. Ther. 1988; 244:1157–1163. [PubMed: 2855242]

Effron, L. [accessed on September 2, 2013] “Bath Salts,” “Spice and US Military: Are Service Members Abusing Synthetic Drugs?. 2013. http://abcnews.go.com/US/bath-salts-spice-us-military-service-members-abusing/story?id=19621742

Every-Palmer S. Synthetic cannabinoid JWH -018 and psychosis: an explorative study. Drug Alcohol Depend. 2011; 117:152–157. [PubMed: 21316162]

Faircloth J, Khandheria B, Shum S. Case report: adverse reaction to synthetic marijuana. Am. J. Addict. 2012; 21:289–290. [PubMed: 22494237]

Felder CC, Joyce KE, Briley EM, Mansouri J, Mackie K, Blond O, Lai Y, Ma AL, Mitchell RL. Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. Mol. Pharmacol. 1995; 48:443–450. [PubMed: 7565624]

Felder CC, Veluz JS, Williams HL, Briley EM, Matsuda LA. Cannabinoid agonists stimulate both receptor-mediated and nonreceptor-mediated signal transduction pathways in cells transfected with and expressing cannabinoid receptor clones. Mol. Pharmacol. 1992; 42:838–845. [PubMed: 1331766]

Forrester MB, Kleinschmidt K, Schwarz E, Young A. Synthetic cannabinoid and marijuana exposures reported to poison centers. Hum. Exp. Toxicol. 2012; 31:1006–1011. [PubMed: 22859662]

Franklin JM, Carrasco GA. Cannabinoid receptor agonists upregulate and enhance serotonin 2A (5-HT(2A)) receptor activity via ERK1/2 signaling. Synapse. 2013; 67:145–159. [PubMed: 23151877]

Franklin JM, Mathew M, Carrasco GA. Cannabinoid-induced upregulation of serotonin 2A receptors in the hypothalamic paraventricular nucleus and anxiety-like behaviors in rats. Neurosci. Lett. 2013; 548:165–169. [PubMed: 23721787]

Freeman MJ, Rose DZ, Myers MA, Gooch CL, Bozeman AC, Burgin WS. Ischemic stroke after use of the synthetic marijuana “spice”. Neurology. 2013; 81:2090–2093. [PubMed: 24212384]

Friedman LK, Rudenko V. WIN55, 212 attenuates NMDA but not kainate intra-hippocampal seizures via mglur1(alpha) and cb1 receptors in development. Epilepsy Curr. 2013; 13:478.

Ginsburg BC, Schulze DR, Hruba L, McMahon LR. JWH-018 and JWH-073: Delta-9-THC like discriminative stimulus effects in monkeys. J. Pharmacol. Exp. Ther. 2011; 340:38.

Glue P, Al-Shaqsi S, Hancock D, Gale C, Strong B, Schep L. Hospitalisation associated with use of the synthetic cannabinoid K2. N. Z. Med. J. 2013; 126:18–23. [PubMed: 23831873]

Gonzalez C, Herradon E, Abalo R, Vera G, Perez-Nievas BG, Leza JC, Martin MI, Lopez-Miranda V. Cannabinoid /agonist WIN 55,212-2 reduces cardiac ischaemia - reperfusion injury in Zucker diabetic fatty rats: role of CB2 receptors and iNOS/eNOS. Diabetes Metab. Res. Rev. 2011; 27:331–340. [PubMed: 21309057]

Goonawardena AV, Plano A, Robinson L, Platt B, Hampson RE, Riedel G. A pilot study into the effects of the CB1 cannabinoid receptor agonist WIN55,212-2 or the antagonist/inverse agonist AM251 on sleep in rats. Sleep Disord. 2011; 2011:178469. [PubMed: 23471192]

Gould, J. [Accessed on September 1, 2011] Legal High Becomes Horrible Dream. 2010. http://www.armytimes.com/article/20101002/NEWS/10020307/Legal-high-becomes-8216-horrible-dream-

Gould, J. [Accessed on October 2, 2013] Spice crackdown: Commanders get police powers. 2013. http://www.armytimes.com/article/20130527/NEWS/305270010/

Grey J, Terry P, Higgs S. Contrasting effects of different cannabinoid receptor ligands on mouse ingestive behaviour. Behav. Pharmacol. 2012; 23:551–559. [PubMed: 22772336]

Grigoryev A, Kavanagh P, Melnik A. The detection of the urinary metabolites of 1-[(5-fluoropentyl)-1H-indol-3-yl]-(2-iodophenyl)methanone (AM-694), a high affinity cannabimimetic, by gas chromatography - mass spectrometry. Drug Test Anal. 2012a; 5:110–115. [PubMed: 22522907]

Grigoryev A, Kavanagh P, Melnik A. The detection of the urinary metabolites of 3-[(adamantan-1-yl)carbonyl]-1-pentylindole (AB-001), a novel cannabimimetic, by gas chromatography-mass spectrometry. Drug Test Anal. 2012b; 4:519–524. [PubMed: 22102533]

Gunderson EW, Haughey HM, Ait-Daoud N, Joshi AS, Hart CL. “Spice” and “K2” herbal highs: a case series and systematic review of the clinical effects and biopsychosocial implications of synthetic cannabinoid use in humans. Am. J. Addict. 2012; 21:320–326. [PubMed: 22691010]

Harris CR, Brown A. Synthetic cannabinoid intoxication: a case series and review. J. Emerg. Med. 2012; 44:360–366. [PubMed: 22989695]

Heath TS, Burroughs Z, Thompson AJ, Tecklenburg FW. Acute intoxication caused by a synthetic cannabinoid in two adolescents. J. Pediatr. Pharmacol. Ther. 2012; 17:177–181. [PubMed: 23118671]

Hermanns-Clausen M, Kneisel S, Auwarter V. New drugs of abuse: acute intoxication by smoking herbal products containing synthetic cannabinoids. Clin. Toxicol. (Phila.). 2011; 49:199–199.

Hermanns-Clausen M, Kneisel S, Hutter M, Szabo B, Auwärter V. Acute intoxication by synthetic cannabinoids - four case reports. Drug Test Anal. 2013a; 5:790–794. [PubMed: 23696237]

Hermanns-Clausen M, Kneisel S, Szabo B, Auwärter V. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. Addiction. 2013b; 108:534–544. [PubMed: 22971158]

Higuera-Matas A, Soto-Montenegro ML, Montoya GL, Garcia-Vazquez V, Pascau J, Miguens M, Del Olmo N, Vaquero JJ, Garcia-Lecumberri C, Desco M, Ambrosio E. Chronic cannabinoid administration to periadolescent rats modulates the metabolic response to acute cocaine in the adult brain. Mol. Imaging Biol. 2011; 13:411–415. [PubMed: 20680479]

Hill MN, Gorzalka BB. Pharmacological enhancement of cannabinoid CB1 receptor activity elicits an antidepressant-like response in the rat forced swim test. Eur. Neuropsychopharmacol. 2005; 15:593–599. [PubMed: 15916883]

Hill MN, Gorzalka BB. Increased sensitivity to restraint stress and novelty-induced emotionality following long-term, high dose cannabinoid exposure. Psychoneuroendocrinology. 2006; 31:526–536. [PubMed: 16442741]

Hill MN, Sun JC, Tse MT, Gorzalka BB. Altered responsiveness of serotonin receptor subtypes following long-term cannabinoid treatment. Int. J. Neuropsychopharmacol. 2006; 9:277–286. [PubMed: 15967059]

Hopkins CY, Gilchrist BL. A case of cannabinoid hyperemesis syndrome caused by synthetic cannabinoids. J. Emerg. Med. 2013; 45:544–546. [PubMed: 23890687]

Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie K, Martin BR, Mechoulam R, Pertwee RG. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol. Rev. 2002; 54:161–202. [PubMed: 12037135]

Howlett AC, Berglund B, Melvin LS. Cannabinoid receptor agonists and antagonists. Curr. Pharm. Des. 1995; 1:343–354.

Howlett AC, Johnson MR, Melvin LS, Milne GM. Nonclassical cannabinoid analgetics inhibit adenylate cyclase: development of a cannabinoid receptor model. Mol. Pharmacol. 1988; 33:297–302. [PubMed: 3352594]

Hoyer F, Steinmetz M, Zimmer S, Zimmer A, Nickenig G. Modulation of atherosclerosis via cannabinoid receptor-2 in mice. Eur. Heart J. 2011; 32:516–517.

Hu X, Primack BA, Barnett TE, Cook RL. College students and use of K2: an emerging drug of abuse in young persons. Subst. Abuse Treat. Prev. Policy. 2011; 6:16. [PubMed: 21745369]

Huffman JW, Dai D. Design, synthesis and pharmacology of cannabimimetic indoles. Bioorg. Med. Chem. Lett. 1994; 4:563–566.

Huffman JW, Mabon R, Wu M-J, Lu J, Hart R, Hurst DP, Reggio PH, Wiley JL, Martin BR. 3-Indolyl-1-naphthylmethanes: new cannabimimetic indoles provide evidence for aromatic stacking interactions with the CB1 cannabinoid receptor. Biorg. Med. Chem. 2003; 11:539–549.

Huffman JW, Szklennik PV, Almond A, Bushell K, Selley DE, He H, Cassidy MP, Wiley JL, Martin BR. 1-Pentyl-3-phenylacetylindoles, a new class of cannabimimetic indoles. Bioorg. Med. Chem. Lett. 2005a; 15:4110–4113. [PubMed: 16005223]

Huffman JW, Zengin G, Wu M-J, Lu J, Hynd G, Bushell K, Thompson ALS, Bushell S, Tartal C, Hurst DP, Reggio PH, Selley DE, Cassidy MP, Wiley JL, Martin BR. Structure-activity relationships for 1-alkyl-3-(1-naphthoyl)indoles at the cannabinoid CB1 and CB2 receptors: steric and electronic effects of naphthoyl substituents. New highly selective CB2 receptor agonists. Biorg. Med. Chem. 2005b; 13:89–112.

Humbert-Claude M, Larrat B, Tanter M, Lenkei Z. Chronic cannabinoid treatment induces connectivity alterations in the juvenile rat brain evidenced by diffusion tensor imaging. Eur. Neuropsychopharmacol. 2013; 23:S275–S276.

Hurst D, Loeffler G, McLay R. Psychosis associated with synthetic cannabinoid agonists: a case series. Am. J. Psychiatry. 2011; 168:1119. [PubMed: 21969050]

Hutter M, Moosmann B, Kneisel S, Auwärter V. Characteristics of the designer drug and synthetic cannabinoid receptor agonist AM-2201 regarding its chemistry and metabolism. J. Mass Spectrom. 2013; 48:885–894. [PubMed: 23832945]

Hyatt WS, Zimmerman SM, Fantegrossi WE. Conditioned taste aversion elicited by synthetic cannabinoid JWH-018 in mice is attenuated by pretreatment with phytocannabinoid Delta-9-THC. FASEB J. 2012:26.

Järbe T, Tai S, LeMay B, Nikas S, Shukla V, Zvonok A, Makriyannis A. AM2389, a high-affinity, in vivo potent CB₁-receptor-selective cannabinergic ligand as evidenced by drug discrimination in rats and hypothermia testing in mice. Psychopharmacology (Berl.). 2011a; 220:417–426. [PubMed: 21989802]

Järbe TU, LeMay BJ, Halikhedkar A, Wood J, Vadivel SK, Zvonok A, Makriyannis A. Differentiation between low- and high-efficacy CB1 receptor agonists using a drug discrimination protocol for rats. Psychopharmacology. 2014; 231:489–500. [PubMed: 24005529]

Järbe TU, Ross T, DiPatrizio NV, Pandarinathan L, Makriyannis A. Effects of the CB1R agonist WIN-55,212-2 and the CB1R antagonists SR-141716 and AM-1387: open-field examination in rats. Pharmacol. Biochem. Behav. 2006; 85:243–252. [PubMed: 16996123]

Jarbe TU, Tai S, LeMay BJ, Nikas SP, Shukla VG, Zvonok A, Makriyannis A. AM2389, a high-affinity, in vivo potent CB1-receptor-selective cannabinergic ligand as evidenced by drug discrimination in rats and hypothermia testing in mice. Psychopharmacology. 2012; 220:417–426. [PubMed: 21989802]

Järbe TUC, Deng H, Vadivel SK, Makriyannis A. Cannabinergic aminoalkylindoles, including AM678=JWH018 found in “Spice’, examined using drug (Δ9-tetrahydrocannabinol) discrimination for rats. Behav. Pharmacol. 2011b; 22:498–507. [PubMed: 21836461]

Jiang W, Zhang Y, Xiao L, Van Cleemput J, Ji S-P, Bai G, Zhang X. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. J. Clin. Invest. 2005; 115:3104–3116. [PubMed: 16224541]

Jinwala FN, Gupta M. Synthetic cannabis and respiratory depression. J. Child Adolesc. Psychopharmacol. 2012; 22:459–462. [PubMed: 23234589]

Johnson LA, Johnson RL, Alfonzo C. Spice: a legal marijuana equivalent. Mil. Med. 2011; 176:718–720. [PubMed: 21702397]

Johnson, MR.; LS, M. The discovery of nonclassical cannabinoid analgesics. In: Mechoulam, R., editor. Cannabinoids as Therapeutic Agents. CRC Press; Boca Raton: 1986. p. 121-145.

Kang S, Kim CH, Lee H, Kim DY, Han JI, Chung RK, Lee GY. Antinociceptive synergy between the cannabinoid receptor agonist WIN 55,212-2 and bupivacaine in the rat formalin test. Anesth. Analg. 2007; 104:719–725. [PubMed: 17312233]

Kelai S, Hanoun N, Aufrere G, Beauge F, Hamon M, Lanfumey L. Cannabinoid-serotonin interactions in alcohol-preferring vs. alcohol-avoiding mice. J. Neurochem. 2006; 99:308–320. [PubMed: 16987253]

Kelly BC, Wells BE, Pawson M, Leclair A, Parsons JT, Golub SA. Novel psychoactive drug use among younger adults involved in US nightlife scenes. Drug Alcohol Rev. 2013; 32:588–593. [PubMed: 23795887]

Korya D, Kapoor A, Labiner D. Ischemic stroke in a 28-year-old woman after smoking synthetic THC. Neurology. 2013:80. Meeting Abstracts 1.

Kronstrand R, Roman M, Andersson M, Eklund A. Toxicological findings of synthetic cannabinoids in recreational users. J. Anal. Toxicol. 2013; 37:534–541. [PubMed: 23970540]

Kwilasz AJ, Negus SS. Dissociable effects of the cannabinoid receptor agonists Delta9-tetrahydrocannabinol and CP55940 on pain-stimulated versus pain-depressed behavior in rats. J. Pharmacol. Exp. Ther. 2012; 343:389–400. [PubMed: 22892341]

Lapoint J, Le V, Lackey F, Radominska-Pandya A, Moran C, James LP, Nelson LS, Hoffman RS, Moran JH. Seizures following ingestion of the synthetic cannabinoid JWH-018. Clin. Toxicol. (Phila.). 2011; 49:213–214.

Lax P, Altavilla C, Esquiva G, Cuenca N. The synthetic cannabinoid HU210 slows retinal degeneration in p23h rats. Ophthalmic Res. 2013; 50:42.

Lee MK, Choi BY, Yang GY, Jeon HJ, Kyung HM, Kwon OW, Park HS, Bae YC, Mokha SS, Ahn DK. Low doses of cannabinoids enhance the antinociceptive effects of intracisternally administered mGluRs groups II and III agonists in formalin-induced TMJ nociception in rats. Pain. 2008; 139:367–375. [PubMed: 18565658]

Levin KH, Copersino ML, Heishman SJ, Liu F, Kelly DL, Boggs DL, Gorelick DA. Cannabis withdrawal symptoms in non-treament-seeking adults cannabis smokers. Drug Alcohol Depend. 2010; 111:120–127. [PubMed: 20510550]

Leweke FM, Schneider M. Chronic pubertal cannabinoid treatment as a behavioural model for aspects of schizophrenia: effects of the atypical antipsychotic quetiapine. Int. J. Neuropsychopharmacol. 2011; 14:43–51. [PubMed: 20678304]

Lewis SE, Paro R, Borriello L, Simon L, Robinson L, Dincer Z, Riedel G, Battista N, Maccarrone M. Long-term use of HU210 adversely affects spermatogenesis in rats by modulating the endocannabinoid system. Int. J. Androl. 2012; 35:731–740. [PubMed: 22435752]

Liang YC, Huang CC, Hsu KS. The synthetic cannabinoids attenuate allodynia and hyperalgesia in a rat model of trigeminal neuropathic pain. Neuropharmacology. 2007; 53:169–177. [PubMed: 17572451]

Linsenbardt DN, Boehm SL 2nd. Agonism of the endocannabinoid system modulates binge-like alcohol intake in male C57BL/6J mice: involvement of the posterior ventral tegmental area. Neuroscience. 2009; 164:424–434. [PubMed: 19665522]

Liu C, Walker JM. Effects of a cannabinoid agonist on spinal nociceptive neurons in a rodent model of neuropathic pain. J. Neurophysiol. 2006; 96:2984–2994. [PubMed: 16943316]

Live, H. Spice Scandal Hits. U.S. Naval Academy; 2011. http://www.huffingtonpost.com/2011/02/01/spice-scandal-hits-us-_n_817009.html [Accessed on July 30, 2011]

Locatelli CA, Lonati D, Giampreti A, Petrolini V, Vecchio S, Rognoni C, Bigi S, Buscaglia E, Mazzoleni M, Manzo L, Papa P, Valli A, Rimondo C, Serpelloni G. New synthetic cannabinoids intoxications in Italy: clinical identification and analytical confirmation of cases. Eur. J. Emerg. Med. 2011; 18:309.

Loeffler, G. [Accessed on July 31, 2011] Naval Medical Center San Diego Treats Sailors following Spice Use. 2011. H.D.http://www.navy.mil/submit/display.asp?story_id=59964

Logan, BK.; Reinhold, LE.; Kacinko, SL. K2 and Beyond: A Synthetic Cannabinoid Primer (K43). American Academy of Forensic Sciences; Chicago, IL: 2011.

Logico, M. [Accessed on July 7, 2012] Confessions of Navy Spice Users: Two Sailors Reveal How Spice Ended Their Careers. 2012. http://www.navy.mil/submit/display.asp?story_id=66260

Lopez HH, Zappia K, Cushman CL, Chadwick B. Acute cannabinoid administration attenuates female socio-sexual motivation. Pharmacol. Biochem. Behav. 2010; 94:482–487. [PubMed: 19931303]

Luszczki JJ, Florek-Luszczki M. Synergistic interaction of pregabalin with the synthetic cannabinoid WIN 55,212-2 mesylate in the hot-plate test in mice: An isobolographic analysis. Pharmacol. Rep. 2012; 64:723–732. [PubMed: 22814025]

Luszczki JJ, Misiuta-Krzesinska M, Florek M, Tutka P, Czuczwar SJ. Synthetic cannabinoid WIN 55,212-2 mesylate enhances the protective action of four classical antiepileptic drugs against maximal electroshock-induced seizures in mice. Pharmacol. Biochem. Behav. 2011; 98:261–267. [PubMed: 21238473]

Macri S, Lanuzza L, Merola G, Ceci C, Gentili S, Valli A, Macchia T, Laviola G. Behavioral responses to acute and sub-chronic administration of the synthetic cannabinoid JWH-018 in adult mice prenatally exposed to corticosterone. Neurotox. Res. 2013; 24:15–28. [PubMed: 23296549]

Maguire DR, Yang W, France CP. Interactions between mu-opioid receptor agonists and cannabinoid receptor agonists in rhesus monkeys: antinociception, drug discrimination, and drug self-administration. J. Pharmacol. Exp. Ther. 2013; 345:354–362. [PubMed: 23536317]

Maguma H, Thayne K, Taylor DA. Characteristics of tolerance in the guinea pig ileum produced by chronic in vivo exposure to opioid versus cannabinoid agonists. Biochem. Pharmacol. 2010; 80:522–532. [PubMed: 20478271]

Makriyannis, A.; Deng, H. Cannabimimetic Indole Derivatives. US Patent Office; Washington, DC: 2000.

Makriyannis, A.; Deng, H. Receptor Selective Cannabimimetic Aminoalkylindoles. US Patent Office; Washington, DC: 2007.

Manzanedo C, Rodriguez-Arias M, Daza-Losada M, Maldonado C, Aguilar MA, Minarro J. Effect of the CB1 cannabinoid agonist WIN 55212-2 on the acquisition and reinstatement of MDMA-induced conditioned place preference in mice. Behav. Brain Funct. 2010 Epub ahead of print.

McCain KR, Moran JH, James LP, Foster HR. Adverse effects and confirmatory testing of JWH-018 and JWH-073 following synthetic cannabinoid use. Clin. Toxicol. (Phila.). 2011; 49:519.

McGuiness TM, Newell D. Risky recreation: synthetic cannabinoids have dangerous effects. J. Psychosoc. Nurs. Ment. Health Serv. 2012; 50:16–18.

McLaughlin PJ, Lu D, Winston KM, Thakur G, Swezey LA, Makriyannis A, Salamone JD. Behavioral effects of the novel cannabinoid full agonist AM 411. Pharmacol. Biochem. Behav. 2005; 81:78–88. [PubMed: 15894067]

McMahon LR, Ginsburg BC, Lamb RJ. Cannabinoid agonists differentially substitute for the discriminative stimulus effects of .DELTA.9-tetrahydrocannabinol in C57BL/6J mice. Psychopharmacology. 2008; 198:487–495. [PubMed: 17673980]

McQuade D, Hudson S, Dargan PI, Wood DM. First European case of convulsions related to analytically confirmed use of the synthetic cannabinoid receptor agonist AM-2201. Eur. J. Clin. Pharmacol. 2012; 69:373–376. [PubMed: 22936123]

Mechoulam R, Lander N, Breuer A, Zahalka J. Synthesis of the individual, pharmacological distinct, enantiomer of a tetrahydrocannabinol derivative. Tetrahedron Asymmetry. 1990; 1:315–318.

Mechoulam R, Parker LA. The endocannabinoid system and the brain. Annu. Rev. Psychol. 2013; 64:21–47. [PubMed: 22804774]

Melvin LS, Milne GM, Johnson MR, Subramaniam B, Wilken GH, Howlett AC. Structure-activity relationships for cannabinoid receptor-binding and analgesic activity: studies of bicyclic cannabinoid analogs. Mol. Pharmacol. 1993; 44:1008–1015. [PubMed: 8246904]

Merroun I, Errami M, Hoddah H, Urbano G, Porres JM, Aranda P, Llopis J, Lopez-Jurado M. Influence of intracerebroventricular or intraperitoneal administration of cannabinoid receptor agonist (WIN 55,212-2) and inverse agonist (AM 251) on the regulation of food intake and hypothalamic serotonin levels. Br. J. Nutr. 2009; 101:1569–1578. [PubMed: 19245736]

Miller RL, Thakur GA, Stewart WN, Bow JP, Bajaj S, Makriyannis A, McLaughlin PJ. Effects of a novel CB1 agonist on visual attention in male rats: role of strategy and expectancy in task accuracy. Exp. Clin. Psychopharmacol. 2013; 21:416–425. [PubMed: 24099361]

Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. Pediatrics. 2011; 128:e1622–1627. [PubMed: 22065271]

Müller H, Huttner HB, Köhrmann M, Wielopolski JE, Kornhuber J, Sperling W. Panic attack after spice abuse in a patient with ADHD. Pharmacopsychiatry. 2010; 43:152, 153. [PubMed: 20127596]

Müller H, Sperling W, Kohrmann M, Huttner HB, Kornhuber J, Maler JM. The synthetic cannabinoid spice as a trigger for an acute exacerbation of cannabis induced recurrent psychotic episodes. Schizophr. Res. 2010; 118:309–310. [PubMed: 20056392]

Musshoff F, Madea B, Kernbach-Wighton G, Bicker W, Kneisel S, Hutter M, Auwärter V. Driving under the influence of synthetic cannabinoids (“spice”): a case series. Int. J. Legal Med. 2013; 128:59–64. [PubMed: 23636569]

Nacca N, Vatti D, Sullivan R, Sud P, Su M, Marraffa J. The synthetic cannabinoid withdrawal syndrome. J. Addict. Med. 2013; 7:296–298. [PubMed: 23609214]

Nakajima J, Takahashi M, Nonaka R, Seto T, Suzuki J, Yoshida M, Kanai C, Hamano T. Identification and quantitation of a benzoylindole (2-methoxyphenyl)(1-pentyl-1H-indol-3-yl)methanone and a naphthoylindole 1-(5-fluoropentyl-1H-indol-3-yl)-(naphthalene-1-yl)methanone (AM-2201) found in illegal products obtained via the Internet and their cannabimimetic effects evaluated by in vitro [S-35]GTP gamma S binding assays. Forensic Toxicol. 2011; 29:132–141.

Nallapaneni A, Liu J, Karanth S, Pope C. Modulation of paraoxon toxicity by the cannabinoid receptor agonist WIN 55,212-2. Toxicology. 2006; 227:173–183. [PubMed: 16956707]

Nguyen VH, Verdurand M, Dedeurwaerdere S, Wang H, Zahra D, Gregoire MC, Zavitsanou K. Increased brain metabolism after acute administration of the synthetic cannabinoid HU210: a small animal PET imaging study with 18F-FDG. Brain Res. Bull. 2012; 87:172–179. [PubMed: 22155282]

O’Malley, PM.; Miech, RA.; Bachman, JG.; Shulenberg, JE. [Accessed on December 31, 2013] Monitoring The Future: National Results On Adolescent Drug Use. Overview Of Keyfinding, 2013. 2014. http://www.monitoringthefuture.org/data/data.html

Onaivi E, Ishiguro H, Gong J, Patel S, Meozzi P, Myers L, Perchuka A, Mora Z, Tagliaferro P, Gardner E, Brusco A, Akinsola B, Hope B, Lujilde J, Inada T, Iwasaki S, Macharia D, Teasenfitz L, Arinami T, Uhl G. Brain neuronal CB2 cannabinoid receptors in drug abuse and depression: from mice to human subjects. PLoS One. 2008; 3:e1640. doi: 1610.1371/journal.pone.0001640. [PubMed: 18286196]

Ovadia H, Wohlman A, Mechoulam R, Weidenfeld J. Characterization of the hypothermic effect of the synthetic cannabinoid HU-210 in the rat. Relation to the adrenergic system and endogenous pyrogens. Neuropharmacology. 1995; 34:175–180. [PubMed: 7617143]

Page ME, Oropeza VC, Sparks SE, Qian Y, Menko AS, Van Bockstaele EJ. Repeated cannabinoid administration increases indices of noradrenergic activity in rats. Pharmacol. Biochem. Behav. 2007; 86:162–168. [PubMed: 17275893]

Pandolfo P, Pamplona FA, Prediger RD, Takahashi RN. Increased sensitivity of adolescent spontaneously hypertensive rats, an animal model of attention deficit hyperactivity disorder, to the locomotor stimulation induced by the cannabinoid receptor agonist WIN 55,212-2. Eur. J. Pharmacol. 2007; 563:141–148. [PubMed: 17374533]

Pant S, Deshmukh A, Dholaria B, Kaur V, Ramavaram S, Ukor M, Teran GA. Spicy seizure. Am. J. Med. Sci. 2012; 344:67–68. [PubMed: 22627260]

Paquette JJ, Wang H-Y, Bakshi K, Olmstead MC. Cannabinoid-induced tolerance is associated with a CB1 receptor G protein coupling switch that is prevented by ultra-low dose rimonabant. Behav. Pharmacol. 2007; 18:767–776. [PubMed: 17989514]

Patton AL, Chimalakonda KC, Moran CL, McCain KR, Radominska-Pandya A, James LP, Kokes C, Moran JH. K2 Toxicity: fatal case of psychiatric complications following AM2201 exposure. J. Forensic Sci. 2013; 58:1676–1680. [PubMed: 23822805]

Peglow S, Buchner J, Briscoe G. Synthetic cannabinoid induced psychosis in a previously nonpsychotic patient. Am. J. Addict. 2012; 21:287–288. [PubMed: 22494236]

Pertwee, R. Receptors And Pharmacodynamics: Natural And Synthetic Cannabinoids And Endocannabinoids. Pharmaceutical Press; London: 2004. p. 103-139.

Pertwee RG. Cannabinoid pharmacology: the first 66 years. Br. J. Pharmacol. 2006; 147(Suppl. 1):S163–171. [PubMed: 16402100]

Pertwee RG. Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. Curr. Med. Chem. 2010; 17:1360–1381. [PubMed: 20166927]

Pintor A, Tebano MT, Martire A, Grieco R, Galluzzo M, Scattoni ML, Pezzola A, Coccurello R, Felici F, Cuomo V, Piomelli D, Calamandrei G, Popoli P. The cannabinoid receptor agonist WIN 55,212-2 attenuates the effects induced by quinolinic acid in the rat striatum. Neuropharmacology. 2006; 51:1004–1012. [PubMed: 16895732]

Pistis M, Perra S, Pillolla G, Melis M, Muntoni AL, Gessa GL. Adolescent exposure to cannabinoids induces long-Lasting changes in the response to drugs of abuse of rat midbrain dopamine neurons. Biol. Psychiatry. 2004; 56:86–94. [PubMed: 15231440]

Qamri Z, Preet A, Nasser MW, Bass CE, Leone G, Barsky SH, Ganju RK. Synthetic cannabinoid receptor agonists inhibit tumor growth and metastasis of breast cancer. Mol. Cancer Ther. 2009; 8:3117–3129. [PubMed: 19887554]

Rahn E, Zvonok A, Makriyannis A, Hohmann A. Antinociceptive effects of racemic AM1241 and its chirally synthesized enantiomers: lack of dependence upon opioid receptor activation. AAPS J. 2010; 12:147–157. [PubMed: 20127295]

Rahn EJ, Thakur GA, Wood JAT, Zvonok AM, Makriyannis A, Hohmann AG. Pharmacological characterization of AM1710, a putative cannabinoid CB2 agonist from the cannabilactone class: Antinociception without central nervous system side-effects. Pharmacol. Biochem. Behav. 2011; 98:493–502. [PubMed: 21382397]

Renard J, Krebs M, Jay T, Le Pen G. Long-term cognitive impairments induced by chronic cannabinoid exposure during adolescence in rats: a strain comparison. Psychopharmacology (Berl.). 2013; 225:781–790. [PubMed: 22983145]

Riebe CJ, Lee TT, Hill MN, Gorzalka BB. Precipitated withdrawal counters the adverse effects of subchronic cannabinoid administration on male rat sexual behavior. Neurosci. Lett. 2010; 472:171–174. [PubMed: 20138966]

Rodgman C, Kinzie E, Leimbach E. Bad Mojo: use of the new marijuana substitute leads to more and more ED visits for acute psychosis. Am. J. Emerg. Med. 2011; 29:232. [PubMed: 21035979]

Rodriguez de Fonseca FR, Villanua MA, Munoz RM, San-Martin-Clark O, Navarro M. Differential effects of chronic treatment with either dopamine D1 or D2 receptor agonists on the acute neuroendocrine actions of the highly potent synthetic cannabinoid HU-210 in male rats. Neuroendocrinology. 1995; 61:714–721. [PubMed: 7659195]

Rodriguez JS, McMahon LR. Discriminative stimulus effects of the synthetic cannabinoid JWH-018 in rhesus monkeys. FASEB J. 2013:27.

Rominger A, Cumming P, Xiong G, Koller G, Förster S, Zwergal A, Karamatskos E, Bartenstein P, La Fougère C, Pogarell O. Effects of acute detoxification of the herbal blend 'Spice Gold' on dopamine D2/3 receptor availability: a [18F]fallypride PET study. Eur. Neuropsychopharmacol. 2013; 23:1606–1610. [PubMed: 23452563]

Saito T, Namera A, Miura N, Ohta S, Miyazaki S, Osawa M, Inokuchi S. A fatal case of MAM-2201 poisoning. Forensic Toxicol. 2013; 31:333–337.

Schneider M, Koch M. Deficient social and play behavior in juvenile and adult rats after neonatal cortical lesion: effects of chronic pubertal cannabinoid treatment. Neuropsychopharmacology. 2005; 30:944–957. [PubMed: 15592349]

Schneider M, Schoemig E, Leweke FM. Acute and chronic cannabinoid treatment differentially affects recognition memory and social behavior in pubertal and adult rats. Addict. Biol. 2008; 13:345–357. [PubMed: 18782382]

Schneir AB, Baumbacher T. Convulsions associated with the use of a synthetic cannabinoid product. J. Med. Toxicol. 2012; 8:62–64. [PubMed: 22160733]

Schneir AB, Cullen J, Ly BT. "Spice" girls: synthetic cannabinoid intoxication. J. Emerg. Med. 2011; 40:296–299. [PubMed: 21167669]

Showalter VM, Compton DR, Martin BR, Abood ME. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): identification of cannabinoid receptor subtype selective ligands. J. Pharmacol. Exp. Ther. 1996; 278:989–999. [PubMed: 8819477]

Simmons J, Cookman L, Kang C, Skinner C. Three cases of "spice" exposure. Clin. Toxicol. (Phila.). 2011; 49:431–433. [PubMed: 21740143]

Slipetz DM, O'Neill GP, Favreau L, Dufresne C, Gallant M, Gareau Y, Guay D, Labelle M, Metters KM. Activation of the human peripheral cannabinoid receptor results in inhibition of adenylyl cyclase. Mol. Pharmacol. 1995; 48:352–361. [PubMed: 7651369]

Sobolevsky T, Prasolov I, Rodchenkov G. Detection of JWH-018 metabolites in smoking mixture post-administration urine. Forensic Sci. Int. 2010; 200:141–147. [PubMed: 20430547]

Solbrig MV, Fan Y, Hermanowicz N, Morgese MG, Giuffrida A. A synthetic cannabinoid agonist promotes oligodendrogliogenesis during viral encephalitis in rats. Exp. Neurol. 2010; 226:231–241. [PubMed: 20832403]

Substance Abuse and Mental Hearlth Services Administration. [Accessed on February 1, 2013] The DAWN Report: Drug-Related Emergency Department Visits Involving Synthetic Cannabinoids. 2012. http://www.samhsa.gov/data/2k12/DAWN105/SR105-synthetic-marijuana.pdf

Sumariwalla PF, Gallily R, Tchilibon S, Fride E, Mechoulam R, Feldmann M. A novel synthetic, nonpsychoactive cannabinoid acid (HU -320) with antiinflammatory properties in murine collagen-induced arthritis. Arthritis Rheum. 2004; 50:985–998. [PubMed: 15022343]

Tarzia G, Duranti A, Tontini A, Spadoni G, Mor M, Rivara S, Vincenzo Plazzi P, Kathuria S, Piomelli D. Synthesis and structure-activity relationships of a series of pyrrole cannabinoid receptor agonists. Bioorg. Med. Chem. Lett. 2003; 11:3965–3973.

Teske J, Weller J-P, Fieguth A, Rothaemel T, Schulz Y, Troeger HD. Sensitive and rapid quantification of the cannabinoid receptor agonist naphthalen-1-yl-(1-pentylindol-3-yl)methanone (JWH -018) in human serum by liquid chromatography-tandem mass spectrometry. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 2010; 878:2659–2663.

Thomas S, Bliss S, Malik M. Suicidal ideation and self-harm following K2 use. J. Okla. State Med. Assoc. 2012; 105:430–433. [PubMed: 23304900]

Thornton SL, Wood C, Friesen MW, Gerona RR. Synthetic cannabinoid use associated with acute kidney injury. Clin. Toxicol. (Phila.). 2013; 51:189–190. [PubMed: 23473465]

Tofighi B, Lee JD. Internet highs--seizures after consumption of synthetic cannabinoids purchased online. J. Addict. Med. 2012; 6:240–241. [PubMed: 22824736]

Tung CK, Chiang TP, Lam M. Acute mental disturbance caused by synthetic cannabinoid: a potential emerging substance of abuse in Hong Kong. East Asian Arch. Psychiatry. 2012; 22:31–33. [PubMed: 22447803]

Tuv S, Krabseth H, Karinen R, Olsen K, Oiestad E, Vindenes V. Prevalence of synthetic cannabinoids in blood samples from Norwegian drivers suspected of impaired driving during a seven weeks period. Accid. Anal. Prev. 2014:62.

Uchiyama N, Kikura-Hanajiri R, Matsumoto N, Huang ZL, Goda Y, Urade Y. Effects of synthetic cannabinoids, cannabicyclohexanol and jwh-018, on electroencephalogram power spectra and locomotor activity in rats. Sleep Biol. Rhythms. 2011; 9:342.

United Nations Office on Drugs and Crime. [Accessed on September 15, 2011] Synthetic Cannabinoids in Herbal Products. 2011. http://www.unodc.org/unodc/en/scientists/synthetic-cannabinoids-in-herbal-products.html

US Drug Enforcement Administration. Schedules of Controlled Substances: Temporary Placement of Four Synthetic Cannabinoids Into Schedule I: Notice of Intent. Fed Regist. 2014; 79:7577–7582. [PubMed: 24605391]

US Drug Enforcement Administration. Establishment Of Drug Codes For 26 Substances. Final Rule. Fed Regist. 2013a; 78:664–666. [PubMed: 23289157]

US Drug Enforcement Administration. Schedules Of Controlled Substances: Temporary Placement Of Three Synthetic Cannabinoids Into Schedule I. Final Order. Fed Regist. 2013b; 78:28735–28739. [PubMed: 23678676]

Van Der Veer N, Friday J. Persistent psychosis following the use of Spice. Schizophr. Res. 2011; 130:285–286. [PubMed: 21602030]

Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, Stella N, Makriyannis A, Piomelli D, Davison JS, Marnett LJ, Di Marzo V, Pittman QJ, Patel KD, Sharkey KA. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005; 310:329–332. [PubMed: 16224028]

Vandrey R, Dunn KE, Fry JA, Girling ER. A survey study to characterize use of spice products (synthetic cannabinoids). Drug Alcohol Depend. 2012; 120:238–241. [PubMed: 21835562]

Vearrier D, Osterhoudt KC. A teenager with agitation: higher than she should have climbed. Pediatr. Emerg. Care. 2010; 26:462–465. [PubMed: 20531137]

Verdurand M, Dalton VS, Zavitsanou K. GABA(A) receptor density is altered by cannabinoid treatment in the hippocampus of adult but not adolescent rats. Brain Res. 2010; 1351:238–245. [PubMed: 20599838]

Vigano D, Rubino T, Vaccani A, Bianchessi S, Marmorato P, Castiglioni C, Parolaro D. Molecular mechanisms involved in the asymmetric interaction between cannabinoid and opioid systems. Psychopharmacology. 2005; 182:527–536. [PubMed: 16079992]

Wegener N, Koch M. Behavioural disturbances and altered Fos protein expression in adult rats after chronic pubertal cannabinoid treatment. Brain Res. 2009; 1253:81–91. [PubMed: 19094973]

Werling LL, Reed SC, Wade D, Izenwasser S. Chronic nicotine alters cannabinoid-mediated locomotor activity and receptor density in periadolescent but not adult male rats. Int. J. Dev. Neurosci. 2009; 27:263–269. [PubMed: 19167478]

Wiebelhaus JM, Poklis JL, Poklis A, Vann RE, Lichtman AH, Wise LE. Inhalation exposure to smoke from synthetic “marijuana” produces potent cannabimimetic effects in mice. Drug Alcohol Depend. 2012; 126:316–323. [PubMed: 22776442]

Wikström M, Thelander G, Dahlgren M, Kronstrand R. An accidental fatal intoxication with methoxetamine. J. Anal. Toxicol. 2013; 37:43–46. [PubMed: 23111916]

Wiley J, Marusich J, Lefever T, Grabenauer M, Moore K, Thomas B. Cannabinoids in disguise: delta-tetrahydrocannabinol-like effects of tetramethylcyclopropyl ketone indoles. Neuropharmacology. 2013a; 75:145–154. [PubMed: 23916483]

Wiley JL, Marusich JA, Huffman JW. Moving around the molecule: relationship between chemical structure and in vivo activity of synthetic cannabinoids. Life Sci. 2013b; 23:534–531.

Wiley JL, Marusich JA, Martin BR, Huffman JW. 1-Pentyl-3-phenylacetylindoles and JWH-018 share in vivo cannabinoid profiles in mice. Drug Alcohol Depend. 2012; 123:148–153. [PubMed: 22127210]

Winstock AR, Barratt MJ. Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample. Drug Alcohol Depend. 2013; 131:106–111. [PubMed: 23291209]

Winstock AR, Mitcheson LR, Deluca P, Davey Z, Corazza O, Schifano F. Mephedrone, new kid for the chop? Addiction. 2011; 106:154–161. [PubMed: 20735367]

World Anti-Doping Agency. [Accessed on January 15, 2014] The 2014 Prohibited List International Standard. 2013. http://www.wada-ama.org/Documents/World_Anti-Doping_Program/WADP-Prohibited-list/2014/WADA-prohibited-list-2014-EN.pdf

World Anti-Doping Agency. [Accessed on May 1, 2014] 2012 Anti-Doping Testing Report. 2012. http://www.wada-ama.org/Documents/Resources/Testing-Figures/WADA-2012-Anti-Doping-Testing-Figures-Report-EN.pdf

World Anti-Doping Agency. [Accessed on February 2, 2013] The 2011 Prohibited List International Standard. 2011. http://www.wada-ama.org/Documents/World_Anti-Doping_Program/WADP-Prohibited-list/WADA_Prohibited_List_2011_EN.pdf

World Anti-Doping Agency. [Accessed on February 2, 2013] The 2010 Prohibited List International Standard. 2010. http://www.wada-ama.org/Documents/World_Anti-Doping_Program/WADP-Prohibited-list/WADA_Prohibited_List_2010_EN.pdf

Yeakel JK, Logan BK. Blood synthetic cannabinoid concentrations in cases of suspected impaired driving. J. Anal. Toxicol. 2013; 37:547–551. [PubMed: 23965292]

Young AC, Schwarz E, Medina G, Obafemi A, Feng SY, Kane C, Kleinschmidt K. Cardiotoxicity associated with the synthetic cannabinoid, K9, with laboratory confirmation. Am. J. Emerg. Med. 2011 Epub ahead of print.

Zimmermann US, Winkelmann PR, Pilhatsch M, Nees JA, Spanagel R, Schulz K. Withdrawal phenomena and dependence syndrome after the consumption of “Spice Gold”. Dtsch Arztebl Int. 2009; 106:464–467. [PubMed: 19652769]

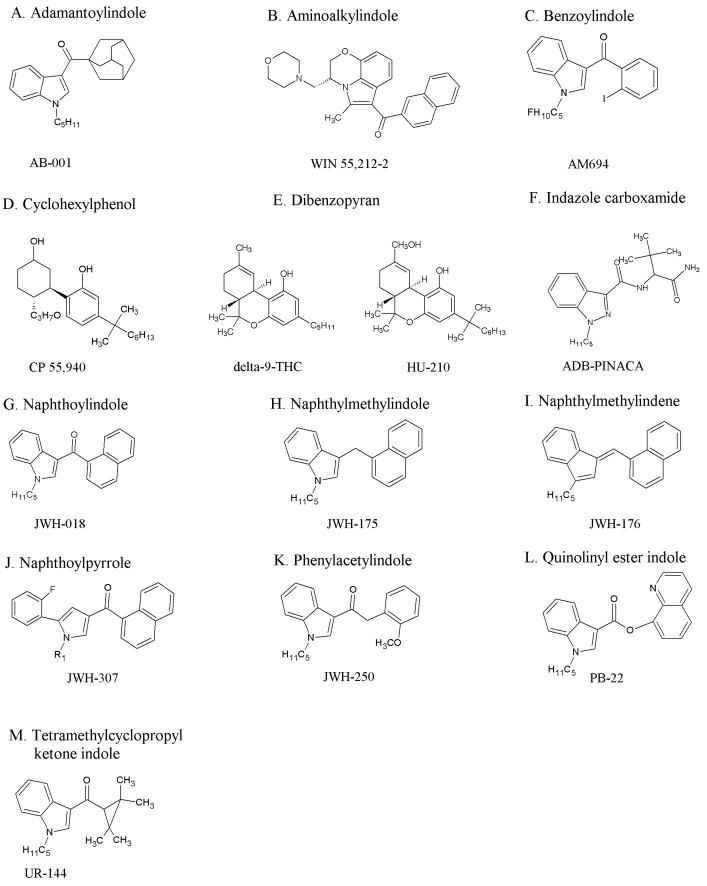

Figure 1.

Structural classes of synthetic cannabinoids. AB-001 [1-Pentyl-3-(1-adamantoyl)indole], ADB-PINACA [N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide], AM694 [1-(5-Fluoropentyl)-1H-indol-3-yl](2-iodophenyl)-methanone, delta-9-THC (delta-9-tetrahydrocannabinol), HU-210 [3-(1,1′-Dimethylheptyl)-6aR,7,10,10aR-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol], JWH-018 [(1-Pentyl-1H-indol-3-yl)-1-naphthalenylmethanone], JWH-175 [3-(1-Naphthalenylmethyl)-1-pentyl-1H-indole], JWH-176 [1-([(1E)-3-Pentylinden-1-ylidine]methyl)naphthalene], JWH-250 [(2-Methoxyphenyl)-1-(1-pentylindol-3-yl)ethanone], JWH-307 [5-(2-Fluorophenyl)-1-pentylpyrrol-3-yl)-naphthalen-1-ylmethanone], PB-22 (1-Pentyl-1H-indole-3-carboxylic acid 8-quinolinyl ester), UR-144 [(1-Pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone].

Table I

Synthetic cannabinoids (SC) pharmacodynamic evaluation and effects in animals.

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
Rat	HU-210	1,5, 25μg/kg	p.o.	Chronic	Not evaluated	Prenatal exposure	HU-210 exposure had no effect on mother's weight gain, food, & water intake. Exposed pups size & weight also did not vary from control group; however, pups exposed to 1μg/kg had higher spleen weight than other HU-210-exposed group & control.	(del Arco et al., 2000)
Rat	HU-210,RIM	4-100μg/kg	s.c.	Acute	Not evaluated	Drug relapse	HU-210 dose-dependently re-instated drug-seeking behavior in COC-exposed rats (abstained for 2 wk) which was attenuated with RIM pre-treatment	(De Vries et al., 2001)
Mouse	R(+)- & S(−) WIN55,212-2	5, 20mg/kg	i.p.	Chronic	Not evaluated	Disease treatment	High dose R(+)WIN55,212-2 on day of TMEV infection delayed onset of disease & reduced severity compared to control & S(−)WIN55,212-2.	(Croxford and Miller, 2003)
Mouse	WIN55,212-2, ACEA, JWH-015	mg/kg: 2.5-5 WIN55,212-2, 1.25-2.5 ACEA, 0.6-1.2 JWH-015	i.p.	Chronic	Not evaluated	Disease treatment	SC improved motor functions in multiple sclerosis animal model & reduced microglial activation in TMEV-infected animals	(Arevalo-Martin et al., 2003)
Rat	WIN55,212-2	2.0-8.0mg/kg	i.p.	Subchronic	Not evaluated	Drug cross-tolerance	Adolescent subchronic WIN55,212-2 exposure altered DA neurons responsivity in animals when challenged with COC, MOR or AMP compared to control or adult animals exposed under the same conditions.	(Pistis et al., 2004)
Mouse	HU-320	1, 2mg/kg	i.p.	Acute	Not evaluated	Disease treatment	HU-320 possessed anti-inflammatory & immunosuppressive properties in a rheumatoid arthritis animal model without its psychoactive effects.	(Sumariwalla et al., 2004)
Rat	HU-210, AM404, AM251, oleamide, desipramine (+ control)	5, 25μg/kg HU-210, 1& 5mg/kg AM404, 5mg/kg AM251, 10 mg/kg desipramine	i.p.	Acute	Not evaluated	Immobility	Desipramine, AM404, HU-210, & oleamide dose-dependently reduced mobility (forced swim test) in animal, which was blocked by AM251 pre-treatment.	(Hill and Gorzalka, 2005)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
Rat	HU-210	0.1mg/kg	i.p.	Chronic	Not evaluated	Immobility, Neurogenesis	Acute HU-210 decreased mobility in adult rats; chronic HU-210 exposure promoted hippocampal neurogenesis.	(Jiang et al., 2005)
Rat	AM411	0.3-5.0mg/kg	i.p.	Acute	Not evaluated	Cannabinoid tetrad	AM411 dose-dependently produced cannabinoid tetrad, impaired animal in operant lever pressing, & reduced animal's activity in open field test. Effects were attenuated by AM251, CB1 antagonist.	(McLaughlin et al., 2005)
Rat	CP55,940, MOR	mg/kg: 0.2 WIN55,212-2, 2.5 MOR	i.p.	Acute Subchronic Chronic	Not evaluated	Analgesia, Drug cross-tolerance	Acute CP55,940 & MOR exposure, when administered alone, did not significantly elicit analgesia. However, administered together significantly reduced pain in animal. Acute CP55,950 (0.2mg/kg) administration to MOR-tolerant rat produced analgesia, which was not observed in control group. Acute MOR administration to CP55,940-tolerant rat did not significantly reduced pain.	(Vigano et al., 2005)
Rat	HU-210, 8-OH-DPAT, DOI	mg/kg: 0.1 HU-210, 0.3 8-OH-DPAT, 1 DOI	i.p.	Chronic	Not evaluated	Drug cross-tolerance	Chronic HU-210 treatment increased frequency of DOI-induced wet-dog shakes compared to control (non-HU-210 exposed); Hypothermia-induced 8-OH-DPAT did not differ between HU-210 pre-treated animals & control	(Hill et al., 2006)
Rat	HU-210	5, 100μg/kg	i.p.	Chronic	Not evaluated	Increased stress hormones & response	Animals exposed to 100μg/kg HU-210 had significantly higher serum corticosterone levels, which correlated to increased stress responsivity in adult animals compared to low dose or vehicle exposed group.	(Hill and Gorzalka, 2006)
Rat	WIN55,212-2, RIM, AM1387	mg/kg: 1-5.6 WIN55,212-2 & RIM, 3 & 10 AM1387	i.p.	Acute	Not evaluated	Immobility	WIN55,212-2 dose-dependently reduced locomotor & grooming activities, which were attenuated by RIM & AM1387 pre-treatment	(Järbe et al., 2006)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
Mouse	WIN55,212-2, ETOH, 8-OH-DPAT	0-10% ETOH, 0.5mg/kg WIN55,212-2, 0.25 & 1 mg/kg 8-OH-DPAT	i.p. s.c.	Chronic	Not evaluated	Increased ETOH intake in binge-drinking model	C57BL/6 J mice progressively increased ETOH intake than DBA/2 J mice with increase body weight for both strains. Chronic WIN55,212-2 treatment did not significantly change ETOH intake while chronic 8-OH-DPAT (5HT1A receptor agonist) decreased total ETOH intake in C57BL/6 J mice. WIN 55,212-2 chronic treatment increased ETOH in DBA/2 J mice, which was not observed with 8-OH-DPAT.	(Kelai et al., 2006)
Rat	WIN55,212-2, AM251, SR144528	mg/kg: 0.06-0.25 WIN55,212-2, 1 AM251 & SR144528	i.v.	Acute	Not evaluated	Analgesia	WIN55,212-2 dose-dependently attenuated hyperalgesia in a neuropathic pain animal model, which was blocked only by AM251 (CB_1antagonist).	(Liu and Walker, 2006)
Rat	WIN55,212-2	1.5mg/kg	i.p. s.c.	Chronic	Not evaluated	Immobility, Disease treatment	WIN55,212-2 dose-dependently reduced locomotor activity & attenuated acute paraoxon-induced cholinergic toxicity; however, increased movement was observed when paraoxon was given after 7d of WIN55,212-2 daily exposure	(Nallapaneni et al., 2006)
Rat	WIN55,212-2, quinolinic acid (QA), AM251	5, 10 μM WIN55,212-2, 5 mM QA. 0.5mg/kg AM251	m.d.	Acute	Not evaluated	Disease treatment	WIN55,212-2 pre-treatment prevented extracellular level increased in the striatum induced by QA. Effect was blocked by AM251.	(Pintor et al., 2006)
Rat	WIN55,212-2	0.5mg/kg	s.c.	Chronic	Not evaluated	Prenatal exposure	Exposure to WIN55,212-2 had no effect on pre/postnatal progression & development, however, changes in GAD & GABA immunocross-reactivities in the GABAergic neuronal system were observed.	(Benagiano et al., 2007)
Rat	WIN55,212-2, THC	mg/kg: 0.5 WIN55,212-2, 5 THC	s.c.	Chronic	Not evaluated	Prenatal exposure	Prenatal WIN55,212-2 exposure reduced extracellular glutamate levels in front cerebral cortex of adolescent rats similar to THC & increased glutamate uptake by overexpression of glutamate transporter subtypes (GLT1 & EAAC1)	(Castaldo et al., 2007)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
Mouse	HU-210	0.1mg/kg	i.p.	Chronic	Not evaluated	Disease treatment	HU-210 improved performance of diabetic mice, but had no effect on hyperglycemic index or animal's weight.	(Dagon et al., 2007)
Rat	WIN55,212-2, HU-210 (+ control)	0.3-5mg/kg WIN55,212-2, 10μg/kg HU210	i.p.	Acute	3.4-7.6mg/kg WIN55,212-2 (thermal pain); 0.7-2.0mg/kg (mechanical)	Analgesia	WIN55,212-2 dose-dependently attenuated thermal & mechanical pain in trigeminal neuropathic animal pain model, which was blocked by CB_1 antagonist only.	(Liang et al., 2007)
Rat	WIN55,212-2, bupivacaine	0.3-10μg WIN 55,212-2; 1-100μg bupivacaine	i.t.	Acute	0.12-0.89μg WIN 55,212-2; 0.02-0.1μg WIN 55,212-2 + bupivacaine	Analgesia	WIN55,212-2 possess analgesic properties & effectiveness increased with co-administration of bupivacaine in rat formalin-induced pain model	(Kang et al., 2007)
Rat	WIN55,212-2	3mg/kg	i.p.	Chronic	Not evaluated	Anxiogenic	Repeated WIN55,212-2 elicited anxiogenic effects in animal that correlated with increased tyrosine hydroxylase expression in the locus coerulus.	(Page et al., 2007)
Rat	WIN55,212-2	0.25, 1.25mg/kg	i.p.	Acute	Not evaluated	Hyperactivity	WIN55,212-2 increased locomotor activity in suitable genetic ADHD animal model while it reduced in control group	(Pandolfo et al., 2007)
Rat	WIN55,212-2, RIM	60, 90μg/kg WIN55,212-2, 50pg/kg RIM	i.v.	Acute	Not evaluated	Analgesia	Co-administration of WIN55,212-2 & low dose RIM produced &extended antinociception in animal beyond 7 d. Animal exposed to WIN55,212-2 only developed tolerance by after a week.	(Paquette et al., 2007)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
Mouse	WIN55,212-2	2, 4mg/kg	i.p.	Acute	Not evaluated	Analgesia, Catalepsy	WIN55,212-2 attenuated pain in ovariectomized mice, which was blocked by 10mg/kg estrogen. Progesterone (25mg/kg) administration facilitated cataleptic effects from WIN55,212-2 (2mg/kg) administration, not estradiol.	(Anaraki et al., 2008)
Rat	CP55,940	0.4mg/kg	i.p.	Chronic	Not evaluated	Drug desensitization	CP55,940 peridolescent exposure increased morphine (1mg/kg) self-administration & changed μ-opioid receptor density in adult rats, more in male than female rats.	(Biscaia et al., 2008)
Rat	WIN55,212-2, APDC & L-AP4	3-30μg per 10μL WIN55,212-2, 100nM APDC, 30nM L-AP4	i.c.	Acute	Not evaluated	Analgesia	Intracisternal WIN55,212-2 injections at 30μg produced analgesia effects in formalin-induce TMJ-pain animal model. Co-administration of 3 μg WIN55,212-2 & 100nmol of metabotropic glutamate receptors agonists APDC & L-AP4 induced analgesic effects.	(Lee et al., 2008)
Mouse	WIN55,212-2, CP55,940, THC (+ control)	mg/kg: 0.1, 3.2 SC, 10 THC	i.p.	Acute	mg/kg: 0.00-0.06 CP55,940, 0.3 - 0.7 WIN55,212-2, 1.8-3.7 THC	Drug discrimination	SC substituted for THC in drug discrimination study with potency order: CP55,940>WIN55,212-2>THC.	(McMahon et al., 2008)
Rat	WIN55,212-2	1.2mg/kg	i.p.	Chronic	Not evaluated	Behavioral deficits from adolescent exposure	Chronic WIN55,212-2 exposure induced prominent object/social recognition & social behavioral deficits in adolescent-exposed than adult rats	(Schneider et al., 2008)
Rat	WIN55,212-2	3mg/kg	i.p. i.t.	Acute	Not evaluated	Analgesia	WIN55,212-2 acute administration attenuated induced-pain in mouse	(Dableh et al., 2009)
Mouse	WIN55,212-2, ETOH	0.5-2 mg/kg WIN55,212-2, 20% ETOH	i.p. p.o.	Acute	Not evaluated	Increased ETOH intake in binge-drinking animal model	Low WIN55,212-2 (0.5mg/kg) administration increased ETOH intake, but decreased with higher dose (1 & 2mg/kg) in a binge-drinking (C57BL6/J B6) animal model	(Linsenbardt and Boehm, 2009)
Rat	WIN55,212-2	1, 2, 5 mg/kg	i.c.v. i.p.	Acute	Not evaluated	Increased appetite	WIN55,212-2 at 1 & 2mg/kg increased rat's appetite, but reduced at 5mg/kg similar to	(Merroun et al., 2009)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
							AM251 (0.5-5mg/kg) exposure	
Mouse	WIN55,212, JWH-133, AM251, SR144528	5mg/kg	peri-tumor	Chronic	Not evaluated	Disease treatment	SC reduced tumor volume in animals injected with SC for 4 wk	(Qamri et al., 2009)
Rat	WIN55,212-2	1.2mg/kg	i.p.	Chronic	Not evaluated	Behavioral deficits from adolescent exposure	cFos protein expression in brain of adult rats altered after chronic WIN55-212-2 pubertal exposure; PPI deficits (reduced) also observed compared to control group	(Wegener and Koch, 2009)
Rat	CP55,940, THC, nicotine, AM251	mg/kg: 0.4 nicotine, 3.0 THC & AM251, 0.1-0.4 CP55,049	i.p.	Acute	Not evaluated	Immobility, Drug cross-tolerance	Subchronic nicotine treatment in adolescent rats significantly decreased locomotor activity after THC & CP55,940 administrations compared to control (vehicle) group. This was not observed in adult rats under the same conditions. Moreover, CB1 receptor binding significantly increased in the medial prefrontal cortex of adolescent rats subchronically exposed to nicotine.	(Werling et al., 2009)
Rat	CP55,940	10-50μg/kg	i.p.	Acute	Not evaluated	Anxiogenic	CP55,940 dose-dependently induced anxiety in Wistar rats & not Lewis rats	(Arnold et al., 2010)
Rat	WIN55,212-2, MOR, naloxone, indomethacin, ketamine	mg/kg: 0.5. 1 WIN55,212-2, 2-10 MOR, 1 or 2 naloxone, 2.5 or 5 indomethacin, 25, 50	i.p.	Acute	Not evaluated	Analgesia	WIN55,212-2 attenuated formalin-induced orofacial pain more potent than MOR, indomethacin, & ketamine.	(Burgos et al., 2010)
Mouse	HU-210	10, 50μg/kg	i.p.	Chronic	Not evaluated	Disease treatment	HU-210 did not improve water-maze performance in Alzheimer's disease animal model; moreover, it had no effect on amyloid β protein formation nor it enhances neurogenesis in the brain.	(Chen et al., 2010)
Rat	HU-210	25-100μg/kg	i.p.	Acute Subchronic Chronic	Not evaluated	Weight loss/gain	Weight gain was slowest with adult rats exposed 100μg/kg HU-210, but dose-dependently improved after subchronic (4 d) exposure. Acute, subchronic & chronic HU-210 treatment reduced or downregulated CB1 receptor binding, more prominent in adult than	(Dalton et al., 2009; Dalton and Zavitsanou, 2010a)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
							adolescent rat	
Rat	HU-210	25-100μg/kg	i.p.	Acute Subchronic Chronic	Not evaluated	Increased dopamine receptor density	Dopamine (D2) receptor density increased in lateral caudate putamen & olfactory tubercle brain area of adult rats after 14 day HU-210 100 μg/kg exposure.	(Dalton and Zavitsanou, 2010b)
Rat	CP55,940	20 & 40μg/kg	i.p.	Acute	Not evaluated	Altered sexual behavior	CP55,940 dose-dependently suppressed sexual motivation in female rats, previously exposed to sexual hormones	(Lopez et al., 2010)
Mouse	WIN55,212-2, MDMA	mg/kg: 1.25-5 MDMA, 0.1 & 0.5 WIN55,212-2	i.p.	Acute	Not evaluated	Drug relapse	WIN55,212-2 & MDMA induced conditioned place preference (CPP). WIN55,212-2 0.5 mg/kg reinstated MDMA-induced CPP.	(Manzanedo et al., 2010)
Guinea pig	WIN55,212-2, MOR	mg/kg: 10-80 MOR, 6 WIN55,212-2	s.c. i.p.	Chronic	Not evaluated	Hypothermia	MOR (10mg/kg) demonstrated analgesic properties from mechanical but not thermal pain. WIN55,212-2 did not produced significant analgesic effects against mechanical pain, but induced hypothermia in animals.	(Maguma et al., 2010)
Rat	R-AM1241, S-AM1241, R,S-AM1241, MOR	mg/kg: 1 AM1241, 2 MOR	i.p. s.c.	Acute	Not evaluated	Analgesia	AM1241 & its enantiomers elicited antinociception to thermal induced, but not mechanical stimulation	(Rahn et al., 2010)
Rat	HU-210	0.1mg/kg	i.p.	Acute Chronic	Not evaluated	Altered sexual behavior	HU-210 stunted sexual behavior in male rats exposed to subchronic daily doses of HU-210	(Riebe et al., 2010)
Rat	WIN55,212-2	1mg/kg	i.p.	Chronic	Not evaluated	Disease treatment	WIN55,212-2 increased survival of brain cells in viral encephalitis-infected rats & supported oligodendrocyte survival	(Solbrig et al., 2010)
Rat	HU-210	25-100μg/kg	i.p.	Acute Subchronic Chronic	Not evaluated	Brain receptor (increased GABAa binding densities)	GABAA binding densities increased in hippocampus region of adult rats after chronic 100μg/kg HU-210 exposure; in comparison, no significant changes in binding densities observed in adolescent rats under the same conditions	(Verdurand et al., 2010)
Rat	WIN55,212-2	1mg/kg	i.p.	Chronic	Not evaluated	Anxiolytic, Drug tolerance	WIN55,212-2 reduced water maze anxiety in adolescent	(Acheson et al., 2011)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
							animal during the first 2 d of administration. No effect observed in adults. No effects in adolescents on subsequent days (3-5).	
Rat	WIN55,212-2, AM251	0.5 & 5 mg/kg	i.p.	Acute Chronic	Not evaluated	Cannabinoid Tetrad, Gastroparesis	WIN55,212-2 dose-dependently invoked cannabinoid tetrad. High dose (5mg/kg) WIN55,212-2 delayed gastric emptying which progressed in chronic drug administrations. AM251 partially attenuated this effect.	(Abalo et al., 2011)
Mouse	WIN55,212-2	1mg/kg	s.c.	Chronic	Not evaluated	Disease treatment	WIN55,212 demonstrated anti-fibrosis properties in scleroderma bleomycin mouse model	(Balistreri et al., 2011)
Mouse	CP55,940	0.4mg/kg	i.p.	Chronic	Not evaluated	Hypothermia, Anxiolytic, Anxiogenic	Tolerance to CP55,940 developed more rapidly in Nrg1 heterogeneous than in wild-type mice; CP55,940 lowered WT body temperature significantly than control group. Prepulse inhibition significantly increased by CP55,940 in Nrg1 mice compared to control & WT group. CP55,940-induced anxiety significantly increased in Nrg1 mouse than WT during open field test.	(Boucher et al., 2011)
Mouse	JWH-018, JWH-018 4-hydroxyindole metabolite, THC (+ control)	mg/kg: 3 JWH-018, 10 JWH-018 4-OHindole, 30 THC	i.p.	Acute	Not evaluated	Cannabinoid tetrad	JWH-018 & JWH-018 4-hydroxyindole produced cannabinoid tetrad greater than THC	(Brents et al., 2011)
Monkey	JWH-018, JWH-073, THC (+ control), RIM	THC discrimination (mg/kg): 0.032 JWH-018, 0.1 THC; THC-treated with RIM (mg/kg): 0.32-3.2 JWH-018, 3.2-32 JWH-073, 1-10 THC	i.v.	Acute	mg/kg: 0.032-0.061 THC, 0.0091-0.019 JWH-018, 0.036-0.094 JWH-073	Drug discrimination	SC dose-dependently substituted for THC with potency order JWH-018>THC>JWH-073; ED50 dose increased in RIM-challenged animals	(Ginsburg et al., 2011)
Rat	WIN55,212-2	1 mg/kg	i.p.	Acute	Not evaluated	Disease treatment	WIN55,212-2 showed cardioprotective properties in ischemia/reperfusion injury of	(Gonzalez et al., 2011)

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Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
							diabetic rats	
Rat	WIN55,212-2, AM251	mg/kg: 1 WIN55,212-2, 2 AM251	i.p.	Acute	Not evaluated	Altered sleep pattern	WIN55,212-2 increased NREM sleep & lowered overall EEG spectral power; CB_1 inverse agonist AM251 did not prevent WIN55,212-2 sleep alterations	(Goonawardena et al., 2011)
Mouse	JWH-133	Not specified	?	Acute	Not evaluated	Disease treatment	JWH-133, a CB_2 agonist, reduced formation of artherosclerotic lesion in ApoE-deficient mice, which was not prevented in ApoE-/CB2-deficient mice.	(Hoyer et al., 2011)
Rats	CP55,940	0.4mg/kg	i.p.	Chronic	Not evaluated	Brain glucose metabolism	Acute 1mg/kg cocaine exposure of SC-periadolescent-exposed female rats lowered brain glucose metabolism in septal nuclei, no observed effects in male rats	(Higuera-Matas et al., 2011)
Rat	JWH-018 (AM678), AM5983, AM2233, WIN55,212-2, THC (+) control	mg/kg: 3THC, JWH-018, AM5983; 5.6-18 WIN55,212-2	i.p.	Acute	mg/kg: 0.9-2 WIN55,212-2, 0.1 .2 JWH-018 & AM5983, 0.3-0.8 AM2233. 1.0-1.3 THC	Drug discrimination	SC substituted for THC in the drug discrimination with potency order :AM5983>JWH-018>AM2233>WIN55,212-2>THC	(Järbe et al., 2011b)
Rat	WIN55,212-2	1.2mg/kg	i.p.	Acute	Not evaluated	Behavioral deficits from adolescent exposure	Chronic pubertal SC exposure induced social recognition deficits & interaction deficits, but were attenuated with sub-acute 7mg/kg quetiapine treatment	(Leweke and Schneider, 2011)
Mouse	WIN55,212-2	2.5-10mg/kg	i.p.	Acute	4.6-10.0mg/kg at 147.5mg/kg dose + anticonvulsant drugs	Anti-convulsant/anti-epileptic	WIN55,212-2 enhanced the anticonvulsant activity of 4 antiepileptic drugs; however, it also impaired motor coordination	(Luszczki et al., 2011)
Mouse	AM1710	0.1-10 mg/kg	i.p.	Acute	Not evaluated	Analgesia	AM1710, has CB_2 receptor selectivity over CB_1 (Ki= 17 ±10 vs 282±92 nM) dose-dependently produced analgesia in rats exposed to thermal	(Rahn et al., 2011)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
							stimulation without the effects of cannabinoid tetrad	
Rat	cannabicyclohexanol, CP47,497, JWH-018, THC (+ control)	2.5mg/kg	i.p.	Acute	Not evaluated	Catalepsy	SC increased EEG in the first 3h between 5-6.0 Hz; THC decreased EEG power between 7.0-20.0 Hz at 1h; SC reduced locomotor activity longer than THC with potency order: CCH>CP47,497>JWH-018>THC.	(Uchiyama et al., 2011)
Rat	HU-210, CP55,940	0.1 mg/kg	i.p.	Acute	Not evaluated	Locomotion, Catalepsy	CP 55,940 & HU-210 produced decreased locomotion & catalepsy	(Bosier et al., 2012)
Rat	CP55,940, THC, MOR, RIM	20-40mg/kg THC, 0.4-1.6mg/kg CP55,940	i.p.	Acute	Male (mg/kg): 0.06->200) CP55,940 0.09>200 CP55,940 + 1.0 mg/kg RIM, 0.31 103.28 CP55,940 + 10 mg/kg RIM; female, mg/kg: 0.04-0.49 CP 55,940, 0.18-1.92 CP55,940 + 1.0mg/kg RIM, 0.35-91.4 CP55,940 + 10.0 rimonabant	Analgesia	CP55,940 & THC antinociceptive effects were greater in female than male animals with or without RIM	(Craft et al., 2012)
Mouse	THC, CP 55,940, WIN55,212-2, HU-210, JW-133, methanandamide, ACEA	mg/kg: 1-6 THC, JWH-133, & methanandamide, 10-50 CP 55,940, 0.5-3 WIN55,212-2, 0.01 0.1 HU-210	i.p.	Acute	Not evaluated	Appetite increase/loss	THC, CP55,940, & WIN55,212-2 increased milk consumption, but not with HU-210, JWH-133, ACAE & methanandamide	(Grey et al., 2012)
Mouse	JWH-018, THC	3mg/kg	i.p.	Acute	Not evaluated	Appetite loss	JWH-018 exposed mice developed food aversion, but	(Hyatt et al., 2012)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
							lesser intensity & short-lived in THC pre-treated mice	
Rats	AM2389, AM5983 (+ control), THC (+ control)	Temperature (mg/kg): 0.1, 0.3 AM2389, 30 THC (temperature); drug discrimination (mg/kg): 0.18 & 0.56 AM5983 (+ control)	i.p. p.o.	Acute	0.0038-.0094mg/kg AM2389 at 1h versus 0.18 mg/kg AM5983; 0.0053-0.0090mg/kg AM2389 versus 0.56mg/kg	Hypothermia, Drug discrimination	AM2389 produced hypothermia & fully substituted for AM5983 & THC with potency order AM2389>AM5983>THC	(Jarbe et al., 2012)
Rats	CP55,940, THC	mg/kg: 0.0032-0.32 CP55,940, 0.1-10 THC	i.p.	Acute	Not evaluated	Analgesia	THC & CP55,940 dose-dependently produced analgesia in acid-induced pain stimulation than acid-induced depressed operant behavior	(Kwilasz and Negus, 2012)
Rats	HU-210	50μg/kg	i.p.	Chronic	Not evaluated	Reproductive/sexual maturity	Animal exposed to HU-210 from beginning of sexual maturity had lower body & kidney weight than control group; sperm counts also were reduced by 46% after 7 wk of HU-210 exposure	(Lewis et al., 2012)
Mouse	WIN55,212-2, pregabalin	1.28-15mg/kg WIN55,212-2, 6.25-75mg/kg pregabalin	i.p.	Acute	10.5 mg/kg (ED30); 5.7mg/kg (ED30 for 1:1 pregabalin: WIN 55,212-2)	Analgesia	WIN55,212-2 co-administered with pregabalin dose-dependently produced additive antinociceptive effect in animal thermal pain model	(Luszczki and Florek-Luszczki, 2012)
Rat	HU-210	0.1mg/kg	i.p.	Acute	Not evaluated	Glucose metabolism	Acute high dose HU-210 administration increased brain glucose metabolism by diminished after 24 h post exposure	(Nguyen et al., 2012)
Mouse	JWH-018; THC (+ control), RIM	10-50mg plant material containing 5.8% JWH-018; 200mg cannabis plant (7.4%), 3mg/kg RIM	inhale	Acute	Not evaluated	Cannabinoid tetrad	(+) cannabinoid tetrad (dose-dependent) & ptosis, hyper-reflexive response, Straub-tail; effects blocked by RIM	(Wiebelhaus et al., 2012)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
Mouse	JWH-018, 1-pentyl-3-phenylacetylindoles	see ED_{50}	i.v.	Acute	µmol/kg: 0.1-1.8 JWH-018, 1.3 13 JWH-167, 0.1-6.0 JWH-203, 0.8 2.0 JWH-204, 13 19 JWH-205, 0.9 6 JWH-251, 2.8 38 JWH-208, 1.5 3 JWH-237, 1.1-2.9 JWH-306, 0.9-2.6 THC	Cannabinoid tetrad	(+) cannabinoid tetrad	(Wiley et al., 2012)
Mouse	AB-001, AB-002, SDB-001	mg/kg: 1-10 THC, 0.3 3 JWH-018, 1-10 SDB-001, 0.3 - 30 AB-001, 3 & 30 AB-002	i.p.	Acute	Not evaluated	Hypothermia, Bradycardia	SDB-001 dose-dependently induced & prolonged hypothermia> THC & JWH-018. SDB-001, JWH-018, & THC also reduced heart-rate, but not with AB-001 or AB-002	(Banister et al., 2013)
Mouse	JWH-081, RIM	mg/kg: 0.625, 1.25 JWH-081, 3.0 RIM	i.p.	Acute	Not evaluated	Object recognition & spatial memory impairment	JWH-081 produced dose-dependent impairment in the object recognition task, spontaneous alteration & spatial recognition memory; object-recognition deficit attenuated by RIM pre-treatment	(Basavarajappa and Subbanna, 2013)
Mouse	JWH-018, JWH-073, THC (+ control)	mg/kg: 1-10 SC, 10 THC	i.p.	Acute	mg/kg: 0.6±0.2 JWH-018, 2.0±0.6 JWH-073	Cannabinoid tetrad[a], Drug discrimination	SC substituted for THC in a drug discrimination study producing synergistic effects when administered concomitantly in 1:1 & 1:3 ratios. SC also produced cannabinoid tetrad, but effects were not synergistic or additive.	(Brents et al., 2013)
Mouse	AM4054, AM7418, WIN55,212-2, THC, RIM	mg/kg: 0.01-1 AM4054, 0.03-1.0 AM7418, 1-10 THC, 0.3-10 WIN55,212-2, 1-10 RIM	s.c.	Chronic	0.06, 0.04mg/kg AM4054	Analgesia, Diuresis	SC dose-dependently elicited antinociception & produced dose-related diuresis in a 6 h period after a single administration. RIM pre-treatment did not alter urine output.	(Chopda et al., 2013)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
Monkey	AM411, AM4054, WIN55,212-2, THC (+ control), methanandamide	Acute (mg/kg): 0.32-1.0 AM411, 0.0032-0.1 AM4054, 0.32-1.0 WIN 55,212 2, 0.32-32 THC, 1.0-10 methanandamide; Chronic (mg/kg): 0.32-100 AM411, 0.1-3.2 AM4054, 1.0-32 WIN 55,212-2, 3.2 100 THC, 10-320 methanandamide	i.m.	Acute Chronic	mg/kg: 0.08-5.24 AM411, 0.01-0.07 AM4054, 0.1-1.2 WIN55,212-2, 0.33-2.11THC, methanandamide (no significant effect)	Drug tolerance	SC dose-dependently decreased response rate to stimulus shock, animal developed tolerance after chronic exposure; potency order: AM4054>AM411~ WIN55,212-2>THC> methanandamide	(Desai et al., 2013)
Rat	CP55,940	0.05mg/kg; challenged with 0.35mg/kg DOI 30 min prior to sacrifice	i.p.	Chronic	Not evaluated	Serotonin-mediated interaction	DOI-challenged rats had increased ($p<0.05$) 5-HT2A receptor-mediated prolactin & corticosterone plasma levels	(Franklin et al., 2013)
Rat	WIN55,212-2	0.5μg/kg	i.h.	Acute	Not evaluated	Catalepsy, Anti-epileptic	WIN55,212-2 produced sedation & attenuated NMDA-induced epileptic currents	(Friedman and Rudenko, 2013)
Rat	CP55,940	0.1-0.3mg/kg	i.p.	Chronic	Not evaluated	Disease treatment	CP55,940 decreased fimbria (hippocampus) fractional anisotrophy value	(Humbert-Claude et al., 2013)
Rat	HU-210	100μg/kg	i.p.	Chronic	Not evaluated	Disease treatment	Ameliorated vision loss for P23H rat model of retinitis pigmentosa	(Lax et al., 2013)
Mouse	JWH-018, WIN55,212-2	mg/kg: 0.03-0.3 JWH-018, 2 WIN55,212-2	i.p.	Acute	Not evaluated	Cannabinoid tetrad	(+) cannabinoid tetrad; reduced sedative effects of JWH-018 & WIN55,212-2 in adult mouse, prenatally exposed to corticosterone	(Macri et al., 2013)
Monkey	WIN55-212, CP55,940, Heroin, RIM	mg/kg: 0.01-0.32 CP55,940, 0.1-1.0 WIN55,212-2; 3.2 MOR , & 0.32-10μg/kg/infusion heroin, 1 RIM	i.v. & s.c.	Acute	Not evaluated	Analgesia, Drug discrimination/ cross tolerance	SC & MOR dose-dependently elicited analgesic effects; SC dose-dependently reduced frequency of heroin self-administration; effects attenuated by RIM pre-treatment	(Maguire et al., 2013)
Rat	AM4054	0.01-0.16mg/kg	i.p.	Acute	Not evaluated	Impairment	AM4054 dose-dependent impairment in animal for both two-choice operant experiments	(Miller et al., 2013)
Rat	CP55,940	0.15-0.3mg/kg	i.p.	Chronic	Not evaluated	Short-term & spatial memory deficits	Adolescent rats exposed to CP55,940 developed short-term & spatial memory impairment when tested as adults. In contrast, no long-term deleterious effects were	(Renard et al., 2013)

Animal	Drug	Dose	Route	Exposure Type	ED_{50}	Measured Effects	Results	Reference
							observed in CP55,940 exposed adult animals.	
Monkey	JWH-018, JWH-073, THC (+ control), CP55,940	0.01-1.0mg/kg	i.v.	Acute Subchronic Chronic	Subchronic (mg/kg):0 .046-0.13 THC, 0.005 0.006 CP55,940 , 0.024-0.042 JWH-018, 0.048 0.077 JWH-073, Chronic (mg/kg): 0.42-0.39 THC, 0.004-0.13 CP55,940 , 0.014-0.074 JWH-018, 0.08-0.32 JWH-073	Drug discrimination	Synthetic cannabinoids substituted for THC with developed cross-tolerance & decreased sensitivity after 14d. JWH-018, CP55,940 >JWH-073>THC	(Rodriguez and McMahon, 2013)
Mouse	UR-144, XLR-11, THC, RIM	mg/kg: 5.6 SC & THC, 3 RIM	i.p.	Acute	µmol/kg: 0.6-3.3 XLR-11, 0.6-2.6 UR-144, 3-15 THC	Cannabinoid tetrad, Drug discrimination	(+) cannabinoid tetrad , XLR11 =UR-144>THC; effects blocked by RIM; drug discrimination study (animal trained to discriminate THC), XLR-11 substituted for THC at 3.5umol/kg & 7.4umol/kg UR-144	(Wiley et al., 2013a)
Rat	AM5983, WIN55,212-2, THC (+ control)	mg/kg: 0.1-.56 AM5983, 0.1-0.3 THC, 0.1-1 WIN55,212-2	p.o.	Acute Subchronic	mg/kg: 0.04-0.13 AM5983, 0.15-0.84 THC, 0.13-0.32 WIN55,212-2	Drug discrimination	AM5983 dose-dependently substituted for THC; potency order: AM5983>WIN>THC	(Järbe et al., 2014)

Abbreviations: 8-OH-DPAT [7-(Dipropylamino)-5,6,7,8-tetrahydronaphthalen-1-ol], AB-001 [1-Pentyl-3-(1-adamantoyl)indole], AB-002 [2-(Adamantan-1-yl)-1-(1-pentyl-1H-indol-3 -yl)ethanone], ACEA (arachidonyl-2′ -chloroethylamide), AM251 [1 -(2,4-Dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-(1 - piperidyl)pyrazole-3-carboxamide], AM404 [(all-Z)-(4-Hydroxyphenyl)-5,8,11,14-Eicosatetraenamide], AM411 [(6aR,10aR)-3-(1-Adamantyl)-6,6,9-trimethyl-6a,7,10,10a-tetra-hydro-benzo[c]-chromen-1-ol], AM1387 [‘1-(2,4-dichlorophenyl)-4-(hydroxymethyl)-N-(piperidinyl)-5-arylphenyl-1H-pyrazole-3-carboxamide], AM1710 [3-1(1,1-Dimethylheptyl)-1-hydroxy-9-methoxy-6H-benzo[c]-chromene-6-one], AM2233 [(2-Iodophenyl)-[1-[(1-methyl-2-

piperidinyl)methyl]-1Hindol-3 -yl] methanone], AM2389 [90-hydroxy-3 -(1 -Hexyl-cyclobut-1 -yl)-hexahydrocannabinol], AM4054 [9b-(hydroxymethyl)-3 -(1-adamantyl)-Hexahydrocannabinol], AM4113 [5-(4-alkylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide], AM5983 [(1-[(1-methylpiperidin-2-yl)methyl)]-1Hindol-3-yl)(naphthalen-1-yl)methanone)], AMP (amphetamine), APDC [(2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate], CP55,940 [2-[(1R,2R,5R)-5-Hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-5-(2-methyl-octan-2yl)-phenol], COC (cocaine), DOI [1-(4-Iodo-2,5-dimethoxyphenyl)-2-propanamine], EEG (electroencephalogram), ETOH (ethanol), GABA (gamma-amino butyric acid), GAD (glutamic acid decarboxylase), i.c.v. (intracerebroventricular), HU-210[(6aR)[-trans-3 -(1,1 -Dimethylheptyl)-6a,7,10,10a-tetrahydro-1 -hydroxy-6,6-dimethyl-6Hdibenzo[b,d]pyran-9-methanol], HU-320 (3S,4S)-3-[2,6-Dihydroxy-4-(2-methyloctan-2-yl)-phenyl]-4-(prop-1-en-2-yl)cyclohex-1-ene-1-carboxylic acid], i.h. (intrahippocampal), i.m. (intramuscular), i.p. (intraperitoneal), i.t. (intrathecal), i.v. (intravenous), JWH-015 [Naphthalen-1-yl(2-methyl-1-propylindol-3-yl)methanone], JWH-018 [Naphthalen-1-yl(1-pentylindol-3 -yl)methanone], JWH-073 (1-Butylindol-3 -yl)naphthalen-1 -ylmethanone, JWH-081 [N-Pentyl-3-[1 -(4-methoxy)-naphthoyl]indole], JWH-133 [(6aR,10aR)-3-(1,1 -Dimethylbutyl)-6a,7,10,10a-tetrahydro -6,6,9-trimethyl-6H-dibenzo[b,d]pyran], JWH-167 [1-(1-Pentyl-1H-indol-3-yl)-2-phenyl-ethanone], JWH-203[1-Pentyl-3-(2-chlorophenylacetyl)indole], JWH-204 [2-(2-Chlorophenyl)-1-(2-methyl-1-pentylindol-3-yl)ethanone], JWH-205 1-(2-Methyl-1-pentyl-1H-indol-3-yl)-2-phenylethanone], JWH-208 [2-(4-Methylphenyl)-1-(1-pentylindol-3-yl)ethanone], JWH-251 [2-(2-Methylphenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone], JWH-237 [1-Pentyl-3-(3-chlorophenylacetyl)indole], JWH 306 [2-(2-Methoxyphenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone], L-AP4 [l-(+)-2-amino-4-phosphonobutyric acid], m.d. (microdialysis), MOR (morphine), NMDA (^-methyl-D-aspartate), RIM (rimonabant), s.c. (subcutaneous), SDB-001 [N-(adamtan-1-yl)-1-pentyl-1H-indole-3-carboxamide], SR144528 [N-[(1S)-endo-1,3,3-trimethylbicyclo [2.2.1]heptan2-yl]-5-(4-chloro-3-methylphenyl)-1-[(4-methylphenyl)methyl]-1H-pyrazole-3-carboxamide], TMEV (Theiler's encephalomyelitis virus), TMJ (temporomandibular joint), UR-144 [(1-(5-Chloropentyl)-1H-indol-3 -yl)(2,2,3,3-tetramethyl-cyclopropyl)-methanone], XLR11 [(1 -(5-Fluoropentyl)-1H-indol-3 -yl)(2,2,3,3-tetramethylcyclopropyl-)-methanone], WIN55,212-2 (R)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[(1,2,3.de)-1,4-benzoxazin-6-yl]-1-naphthalen-ylmethanone],WT (wild-type).

[a]Cannabinoid tetrad: hypomotility, catalepsy, hypothermia, analgesia

Table 2

Synthetic cannabinoid (SC) acute and sub-acute intoxication documented from case reports/series and retrospective case reviews.

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	11	M	13-27	Spice	UNK	tachycardia(6), anticholinergic toxidrome(4), agitation/irritability(4), tremor(4), confusion(3), pallor(2), mydriasis(2), hypertension(2)	UNK	UNK	(−)UDS(3); SC not tested for all	BDP(3), supportive care (10)	(Banerji et al., 2010)
USA	1	M	18	K2 Summit	30gm (sm)	tremors, blurred vision, nausea, vomiting, incoherent speech	30 min	4.5h	(−)UDS, 0.5μg/L JWH-018(serum)	anti-emetics, IVF	(Canning et al., 2010)
Germany	1	M	21	UNK	40mg (sm)	blurred vision, unsteady gait, excessive sweating, heart palpitations, anxiety	“within min”	<24h	(−)UDS	lorazepam (2mg, IV), IVF	(Müller et al., 2010)
Russia	3	2M 1F	22±1	Tropical Synergy	~1g each	reddened conjunctivae, tachycardia, anxiety, paranoia, hallucinations, short-term memory & sense of time impairment	UNK	UNK	(−)UDS, (+)JWH-018 metabolites (urine)	UNK	(Sobolevsky et al., 2010)
USA	1	F	17	JWH-018	UNK (sm)	“violent” & “crazy”, hallucinations, lower extremities numbness, muscle twitches, elevated pulse, dilated pupils	15 min	2h	(+)THC (urine), SC not tested	lorazepam (2mg, IV)	(Vearrier and Osterhoudt, 2010)
USA	1	M	20	Spice	UNK (sm)	anxiety, tachycardia, diaphoresis	UNK	UNK	(−)UDS, SC not tested	supportive care	(Benford and Caplan, 2011)
USA	11	10M 1F	15-19	UNK	UNK (sm)	euphoria(11), irritability(4), anxiety(3), numbness(2), anger(1), sadness(1), memory impairment(11), change of auditory(1) & visual (5) perception, paranoia(2), palpitations(3), muscle trembles(1) & weakness(1), blackouts(1), restlessness(1), stimulation(10	UNK	UNK	UNK	UNK	(Castellanos et al., 2011)

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
Germany	13	12M 1 F	14-28	Spice, Smoke, Jamaican Gold, Monkees-go bananas, Ninja	UNK (sm)	shaking, acute psychosis, seizers, muscle jerking, muscle pains, hypokalemia	UNK	UNK	(+)JWH-018(7), JWH-081(4), JWH-122(4); all serum, concentration UNK	UNK	(Hermanns-Clausen et al., 2011)
USA	10	M	21-25	UNK	UNK (sm)	auditory hallucinations(4), paranoid delusions(9), odd or flat affect(6), blocked thoughts(4), disorganized speech(6) & behavior(7), alogia(3), suicidal ideation(4), insomnia(6), psychomotor retardation(6) & agitation(3), anxiety(2)	UNK	UNK	(+)THC(4), (−)UDS(6), SC not tested	antipsychotics (7), hospitalizetion (6-10d)	(Hurst et al., 2011)
USA	1	M	23	Spice	UNK (sm)	nonsensical speech, paranoia, disorganized thoughts	<48h	<72h	(−)UDS	psychiatric referral, supportive care	(Johnson et al., 2011)
USA	1	M	48	JWH-018 (powder)	UNK (po with ETOH)	seizure, tachycardia, refractory supraventricular tachycardia (1 day later)	30min	<48h	(−)UDS, 74.3μg/L JWH-018 pentanoic (urine)	lorazepam (IV), electrocardioversion; ET intubation	(Lapoint et al., 2011)
Italy	10	UNK	14-55	Spice, N-joy, Forest Green (contained JWH-122)	UNK	agitation (7), confusion (6), hallucination (4), dyspnea (1), coma(2), seizure(1), mydriasis(2), xerostomia(2), vertical nystagmus(1), psychomotor agitation(2), vomiting (1)	UNK	<24h	(+)JWH-018 (blood), (+)JWH-250 (blood & urine); number of samples UNK	UNK	(Locatelli et al., 2011)
USA	1 1 1	M M M	16 16 16	K2 K2 K2	UNK (sm) UNK (sm) UNK (sm)	chest pain for 3d, diagnosed with elevated ST-segment & troponin (25μg/L) intermittent chest pain × 3d lasting ~30min, diagnosed with elevated ST-segment & troponin (11.6μg/L) intermittent chest pain × 3d lasting1-2h, elevated troponin (12μg/L)	1d after sm within 1 wk after sm 4d after sm	3d UNK 1 wk	(+)THC, SC not tested (−)UDS, SC not tested (+)THC, (+)JWH-018, JWH-073 metabolites (urine)	supportive care, coronary angiography supportive care, coronary angiography supportive care	(Mir et al., 2011)
USA	9	UNK	UNK	UNK	UNK	tachycardia, hypokalemia, agitation/irritability, hallucination, pallor, nausea, mydriasis	UNK	8-24h	(−)UDS, (+)JWH-018, JWH-073 metabolites (urine)	BDP, IVF, anti-emetics, potassium supplement	(McCain et al., 2011)

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	3	UNK	UNK	Bad Mojo	UNK (sm)	psychosis	UNK	>12h	UNK	supportive care	(Rodgman et al., 2011)
USA	2	F	20, 22	Banana Cream Nuke	½ packet (sm)	anxiety, palpitations/tachycardia	“shortly after smoking”	1h	(−)UDS, SC not tested	supportive care	(Schneir et al., 2011)
USA	1 1 1	M M M	25 23 19	UNK UNK UNK	UNK (sm) UNK (sm) UNK (sm)	“eyes-crossed & flailing arms”, unresponsive to verbal stimuli, dilated pupils unresponsive, muscle spasm, depressed breathing paranoia, delusions, short-term memory impairment	45min UNK 1h	3h <24h <24h	(−)UDS, (+)JWH-018 metabolites (urine) (−)UDS, (+)JWH-018, JWH-073 metabolites (urine) (−)UDS, (+)JWH-018 & JWH-073 metabolites	lorazepam (4mg, IV), IVF airway management, ICU admission, 5 mg haloperidol supportive care	(Simmons et al., 2011)
USA	1	M	17	K9 Pure Fire (contained JWH-073, JWH-018)	UNK (sm)	Hallucinations, dizziness, difficulty breathing, tachycardia, chest pressure that lasted for 3 days	10 min	<24h	(−)UDS, SC not tested	nitroglycerin, supportive care	(Young et al., 2011)
USA	1 1 1	M F M	19 19 23	Space Space Spice	UNK (sm) UNK (sm) UNK (sm)	paranoia, hallucinations, agitation, tachycardia, hyperglycemia mild drowsiness, short-term memory impairment, hyperglycemia anxiety, agitation, breathing difficulty, hyperventilation, tachycardia, injected sclera	2h UNK UNK	<6h <6h	(−)UDS, SC not tested (−)UDS, (+)APAP, (+)DXM, (+) doxylamine, (+)levorphenol, SC not tested (−)UDS, SC not tested	lorazepam (2mg, IV) supportive care lorazepam. IVF, anti-emetic	(Bebarta et al., 2012)
USA	1 1 1	F M M	16 18 16	K2 Spice Spice	UNK (sm) UNK (sm) UNK (sm)	catatonia, tachycardia, (+) vertical nystagmus headache, dizziness, profuse sweating, agitation, aggression, restlessness, tachycardia, hyperventilation disorientation, agitation, slowed speech	UNK UNK UNK	<24h <24h <24h	(−)UDS, SC not tested (−)UDS, SC not tested (−)UDS, SC not tested	diphenhydramine (50mg, IV), lorazepam (2mg IV × 2 dose) diphenhy-dramine (50mg, IV), lorazepam (2mg, IV) lorazepam (4mg IV), IVF	(Cohen et al., 2012)

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	1	M	17	K2	UNK (sm)	dizziness, confusion, lethargy, vomiting, tachycardia	“immediately after 1 inhalation”	UNK	(−)UDS, SC not tested	IVF, naloxone (2mg, IV), supportive care	(Faircloth et al., 2012)
USA	3	M	20-30	K2, XXX, K2 Blond, Black Box, Smoke n’ Skulls, Zombie, Blueberry	3g/d (sm)	similar(1) or elevated “high” than cannabis(2)	UNK	UNK	UNK	UNK	(Gunderson et al., 2012)
USA	1 1	F F	19 17	Bayou Blaster® Humboldt Gold	UNK (sm)	jerking motions of extremities, agitation, altered mental status, somnolence, tachycardia agitation, hallucinations, myoclonic jerking, aggression, tachycardia, flushed skin, dilated pupils, “inappropriate laughter”	“immediately after smoking” UNK	<3h <3h	(−)UDS, SC not tested (−)UDS, SC not tested	admitted to mental health ward; discharged after 4 days	(Harris and Brown, 2012)
USA	1 1	M M	17 15	K2 K2	UNK (sm) UNK (sm)	hypertonia, apnea, cyanosis, confused, swollen red eyes, tachycardia, chest & back pain loss of consciousness, tachycardia, headache, fatigue	UNK UNK	<12h	(−)UDS, SC not tested (−)UDS, SC not tested	adenosine (6 mg, IV), APAP IVF	(Heath et al., 2012)
Germany	29	25M 4F	14-30	Bonzai, Jamaican Gold, Lava Red, Maya, Monkees go bananas tropical car perfume, Ninja Strong, OMG, Spice, Smoke, Space,	UNK (sm)	Poisoning severity score (PSS) 1 (n=9):drowsiness, vertigo, ataxia, restlessness, paraesthesia, mild visual or auditory hallucinations mild muscular tenderness or pain, tachycardia, mild change in blood pressure, vomiting, diarrhea, abdominal pain, mild hypoglycemia, mild electrolyte imbalance, short-term hypothermia PSS2 (n=18): unconsciousness, brief apnea or slowed breathing, confusion, agitation, hallucination, delirium, seizures, visual and auditory hallucinations, dystonia, rhabdomyolysis or chest pain, sinus brady or tachycardia, irregular EKG,	1-20h	UNK	2.3μg/L CP47,497-C8 (1), <0.1-13μg/L JWH-018 (8), 0.11μg/L JWH-073(1), 1.2-42μg/L JWH-081(7), 0.17-40μg/L(11), 2.5-190μg/L JWH-210(11), 0.1-1.1 JWH-250(4), 0.2μg/L AM694; all measured in serum	Supportive care (29), BDP (8), IVF (5), anti-emetics (2), potassium supplement (5), neuroleptics (1), psychiatric care (1), ET (1)	(Hermanns-Clausen et al., 2013b)

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
						prolonged coughing, bronchospasm, difficulty breathing, vomiting, diarrhea, abdominal pain, electrolyte imbalance, moderate hypoglycemia, and prolong hypothermia					
USA	1 1	M M	19 15	Climax Silver-K2	“pinch” (sm) UNK (sm)	seizure, unresponsive, aggression, “abnormal” speech, slow & shallow breathing, loss of consciousness loss of consciousness, shallow breathing	UNK UNK	UNK UNK	(−)UDS, SC not tested (−)UDS< SC not tested	supportive care ET intubation, supportive care	(Jinwala and Gupta, 2012)
USA	1	F	18	KS	UNK (sm)	panic attack, paranoia, chest pain, hyperventilation, nausea	UNK	UNK	(−)UDS, SC not tested	supportive care	(McGuiness and Newell, 2012)
USA	1	M	20	Black Mamba	UNK (sm)	tonic-clonic seizures, dry skin, drowsiness, elevated pulse	“immediately after smoking”	<3h	(+)AM2201 metabolites (urine)	IVF, supportive care	(McQuade et al., 2012)
USA	1	M	59	Spice	1.5g/d (sm)	“flashbacks” combat-related trauma, re-admitted 3wk later for hallucinations, then 2d later, total 3 admissions	UNK	<24h /visit	(−)UDS, SC not tested	BDP, gabapentin (400mg QID), hydroxyzine (25mg TID PRN), apiprazole (10mg qD), benztropine (1mg BID), bupropion (150mg BID)	(Peglow et al., 2012)
USA	1	M	48	Spice	3g(sm)	tonic-clonic seizures, tachycardia, diaphoresis, mydriasis	UNK	<24h	(−)UDS, 140mg/dL BAC (serum), (+)JWH-018 metabolites (urine)	lorazepam (4mg IV)	(Pant et al., 2012)
USA	1	M	19	Happy Tiger (contained JWH-018, JWH-081, JWH-250, AM2201)	UNK (sm)	convulsions, vomiting	“immedi-ately after smoking”	<24h	(−)UDS, SC not tested	midazolam (5mg IV), supportive care	(Schneir and Baumbacher, 2012)

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	1	M	20	K2	UNK (sm)	agitation, confusion, suicidal ideation, self-inflicted wounds, hyperventilation, tachycardia	UNK	<24h	(−)UDS, SC not tested	supportive care	(Thomas et al., 2012)
USA	1	M	48	K2 Summit	0.3g (po with milk)	Sedated, nauseous, “detached,” flushed, loss of consciousness, tonic-clonic seizure, tachycardia, depressed breathing, hyperthermia, supraventricular tachycardia	45 min	<48h	(−)UDS, SC not tested	lorazepam (IV), electrocardioversion, ET intubation	(Tofighi and Lee, 2012)
Hong Kong	1	M	36	K2	0.5g/d (sm)	agitation, profuse sweating, tachycardia, delusion, elevated blood pressure	UNK	<24h	(−)UDS, (+)DXM, (+)ephedrine, (+)promethazine, SC not tested	midazolam (IM)	(Tung et al., 2012)
USA	1	M	21	MadHatter, Kite, Scooby Snax	UNK (sm)	fainted while driving, tachycardia, elevated blood pressure, dyspnea & hyperventilation	UNK	UNK	(+)THC (urine), 0.75μg/L AM2201, JWH-122, JWH-210 (blood), (+)AM2201 & JWH-018 metabolites (urine)	ICU admission, airway management, antibiotics, steroids	(Alhadi et al., 2013)
USA	1 1	F F	22 26	K2 Peak Extreme	UNK (sm) UNK (sm)	palpitations, dyspnea, “angor animi,” dysarthria, difficulty standing, drowsiness, inattention, left face & hemi-body weakness, & hemianesthesia, diagnosed with ischemic stroke confirmed by CT scan left facial weakness, left-sided numbness, dysfluency, hemi-anesthesia, left visual neglect, diagnosed with ischemic stroke confirmed by CT scan	“while smoking” <24h	UNK UNK	(+)THC, BDP, & salicylates (urine) (−)UDS	supportive care warfarin, supportive care	(Bernson-Leung et al., 2013)
USA	1	M	20	Spice	UNK (sm)	uncommunicative, unable to follow instruction, combatant	UNK	UNK	(−)UDS, SC not tested	IVF, lorazepam (2mg) admission, supportive care	(Berry-Caban et al., 2013)

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	1 1 1 1	M M M M	20 23 26 30	Spice Spice Spice Spice	UNK (sm) UNK (sm) UNK (sm) UNK (sm)	nausea, vomiting for 2d; history of smoking SC within the last few weeks nausea, vomiting for 2 d; history of SC within few weeks nausea, vomiting, diarrhea, lower abdominal pain × 2d; history of SC intake × 2yr, but changed “supplier” in last week nausea, vomiting, diarrhea, abdominal pain × 3d; history of SC intake × 1yr, but changed “supplier” in few wks.	48h 48h 48h 72h	UNK UNK UNK UNK	(−)UDS, SC not tested (−)UDS, SC not tested (−)UDS, SC not tested (−)UDS, SC not tested	renal biopsy, inpatient admission, supportive care renal biopsy, inpatient admission, supportive care renal biopsy, inpatient admission, supportive care inpatient admission, supportive care	(Bhanushali et al., 2013)
USA	16	15M 1 F	15-33	Blueberry, Clown Loyal, Flame 2.0, Mad Monkey, Mr. Happy, Phantom Wicked, Spice Gold	UNK (sm)	nausea(15), vomiting(15), abdominal(8) & flank(4) pain, back pain(2)	“within h or days”	UNK	42μg/L XLR-11 pentanoic acid (blood, n=1), 35-35μg/L XLR-11, 38-102μg/L XLR-11 pentanoic acid metabolite (serum, n=2), 6μg/L UR-144 (serum, n =1), 400-529μg/L XLR-11 pentanoic acid (urine, n=2); SC not tested for n=9	renal biopsy(8), hemodialysis (5), corticosteroid (4)	(Centers for Disease Control and Prevention, 2013a)

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	17	11M, 6F	13-60	Black Mamba, Crazy Monkey, Crazy Clown, Dead Man Walking, Funky Monkey, Sexy Monkey, SinX, Spice, TenX, Twilight, 3X	UNK (sm)	elevated blood pressure(81), tachycardia(73), somnolence(45), aggressive or violent behavior(40), agitation(40), confusion(32)	UNK	UNK	UNK	inpatient(7) & ICU(10) admission	(Centers for Disease Control and Prevention, 2013b)
USA	22	18M 4F	16-57	Crazy Clown (contained ADB-PINACA)	UNK	hyperglycemia(13), hypokalemia(9), acidosis(7), tachycardia(13), nausea/vomiting(8), confusion/disorientation(7), aggression(7), somnolence/unresponsiveness (7), seizures(3), pneumonia(2), rhabdomyolysis(1), myocardial infarction(1).	UNK	UNK	(+)ADB-PINACA (n=5, serum)	ICU admission (6), assistant ventilation (5)	(Centers for Disease Control and Prevention, 2013c)
Switzerland	1	M	31	Samurai King	300 mg (sm)	agitation, aggression, anxiety, confusion, panic, vomiting, dilated pupils, tachycardia, elevated blood pressure, hyperglycemic	“few min”	<3h	(−)UDS, 49μg/L MAM2201 (plasma) after 1h	supportive care	(Derungs et al., 2013)
USA	1 1	M F	26 19	Spice (contained JWH-018) Spice (contained JWH-018)	UNK (sm)	dysarthia, expressive aphasia, right face & arm weakness, incoherent speech, tachycardia loss of consciousness, vomiting, altered mental status, & jerking movements of extremities, aphasia, sensory loss, right hemiplegia, tachycardia	50 min “a few min” after sm		(+)THC (urine), SC not tested (+)THC (urine)	brain MRI revealed cerebral infarct & patient treated for stroke brain MRI revealed clot & cerebral infarct	(Freeman et al., 2013)
New Zealand	17	10M 7M	26 mean	K2	UNK	paranoia, thought disorder, disorganized behavior, anxiety, depression, suicidal ideation(3), homicidal	UNK	UNK	UNK	inpatient psychiatric unit admission	(Glue et al., 2013)

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
						ideation(1)					
Germany	1 1 1 1	M M M M	19 17 17 20	Bonzai NS Jamaican Lava	UNK (sm) UNK (sm) UNK (sm) UNK (sm)	tonic-clonic seizures, unresponsive, vomiting somnolence, tachycardia, mydriasis, unequal pupil size, retrograde amnesia nausea, mild agitation, trembling, “laugh attacks,” confusion, somnolence, mydriasis, tachycardia, hyperglycemia skin pallor, vomiting, “rolled his eyes,” tachycardia, somnolence	<24h “shortly after smoking” “few min”	<72h <12h <6h	0.4μg/L JWH-018, 230 μg/L JWH-122, 7.8μg/L JWH-210 (serum), 39μg/L THC (urine), (+) JWH-018, JWH-073, JWH-122, JWH-210 metabolites (urine) 0.2μg/L MAM2201, 0.2μg/L UR-144 (serum), (+)MAM2201, UR-144, JWH-018 metabolites (urine) 42μg/L JWH-081 (serum), (+)JWH-018, JWH-073, JWH-081 metabolites (urine) 15.0μg/L JWH-122 & metabolite, JWH-018 metabolites (serum)	midazolam, ventilation, supportive care supportive care IVF, K+ supplement, supportive care BDP, IVF, potassium supplement	(Hermanns-Clausen et al., 2013a)
USA	1	M	30	Scooby Snacks (contained JWH-018,JWH-073, JWH-122, AM2201, AM694)	UNK (sm)	abdominal pain, nausea, vomiting (intermittent); history of ED visit 3d prior for the same symptoms	UNK	UNK	(−)UDS, (+)JWH-018, JWH-073, AM2201 metabolites (urine)	IVF, ondansetron (IVF), discharged with promethazine	(Hopkins and Gilchrist, 2013)
USA	1	F	28	K2 (contained JWH-018 & JWH-122)	UNK (sm)	nausea, left-side hemiplegia & paralysis, incoherent & slurred speech, confusion	UNK	UNK	UNK	brain MRI revealed multiple embolism	(Korya et al., 2013)

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
USA	1 2 1 1 1 1 1	18 14 20 29 21 21 22	M F M M M M M	Jamaican Extreme BooM NS BooM, OMG UNK UNK UNK	UNK (sm) UNK (sm) UNK UNK UNK UNK	unable to follow instruction, slowed movement, confused & disoriented, slurred & babbling speech, slowed breathing, dilated pupils confused, slurred & babbling speech, disoriented, “blunt” mood “vestibular disorder”, impaired fine motor skills, dilated pupils, delayed reaction, “blunt” mood dilated pupils with delayed reaction to light, “dizzy mind & retarded behavior” delayed reaction & movement, anxiety, constricted pupils with no reaction to light, “dizzy mind,” depressed mood no signs of impairment except for smell of alcohol in breaths delayed movement, anxiety, lack of apathy, “inert”, delayed pupils’ reaction to light	UNK UNK UNK UNK UNK UNK UNK	UNK UNK UNK UNK UNK UNK UNK	4.6μg/L AM2201, 0.2μg/L JWH-018 (blood) 0.4 & 0.8μg/mL JWH-210, 0.3μg/ml JWH-122 (blood) 0.3μg/L AM2201, 1.7μg/L JWH-019, 7.6μg/L JWH-122, 4.4μg/L JWH-210 (blood) 1.0μg/L JWH-122, 6.2μg/L JWH-210 (blood) 0.5μg/L JWH-018, 0.3μg/L JWH-122, 0.7μg/L JWH-210 (blood) 1.74% BAC, 1.1μg/L JWH-307 (blood) 1.9μg/L JWH-018, 28μg/L JWH-122, 2.5μg/L JWH-210, <0.1μg/L for AM2201, JWH-307, MAM2201, & UR-144 (blood)	UNK, DUID case UNK, DUID case UNK, DUID case UNK, DUID case UNK, DUID case UNK, DUID case UNK, DUID case	(Musshoff et al., 2013)
USA	1 1	F M	22 20	Mr. Nice Guy Mr. Nice Guy	1g/d (sm) 3g/d(sm)	cramping in extremities, sweats & chills, cravings, headache, insomnia, vivid dreams, anorexia, anxiety, tachycardia, hyperventilation chest pain, palpitations, dyspnea, headache, diaphoresis, tremors, tachycardia	6 d prior ED visit 6 d prior ED visit	<1 wk	UNK UNK	lorazepam (2mg IV), IVF, BDP inpatient admission, BDP, hydroxyzine diphenhydramine; discharged with quetiapine	(Nacca et al., 2013)
USA	1	M	26	Mr. Happy (contained 69mg/g XLR-11, 61mg/g UR-144)	UNK (sm)	abdominal pain, nausea, vomiting, lower back pain.	<24h		(−)UDS, 529μg/L XLR-11 pentanoic acid (urine), 36μg/L XLR-11, 6μg/L UR-144, 102μg/L XLR-11 pentanoic acid (serum) initial; 34	inpatient admission for 6d	(Thornton et al., 2013)

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory results (matrix)	Treatment	Reference
									µg/L XLR-11, 3µg/L UR-144, 62µg/L XLR-11 pentanoic acid after 3.5h after initial test		
Norway	16	15 M 1F	17-41	UNK	UNK	mild to moderate impairment	UNK	UNK	<0.1µg/L THC (n=10), 0.1-1.3µg/L AM2201 (n=3), 0.1-0.5µg/L JWH-018 (n=3), 0.5-1.7µg/L JWH-122 (n=2), 0.5 µg/L JWH-250 (n=1), 1.0µg/L RCS-4 (n=1); <0.1-1.0µg/L AMP (n=4), <0.1-1.9µg/L MAMP (n=7), <0.1-2.4µg/L BDP (n=12), 0.11 ppm ETOH (n=1), <0.1 µg/L LSD (n=2), <0.1 µg/L ketamine (n=1); all analytes confirmed in whole blood samples	UNK, DUID cases	(Tuv et al., 2014)
USA	12	M	18-31			vertical nystagmus(1), tachycardia(9), elevated blood pressure(2), body & extremities tremors(6), eye tremors(5), swaying or unsteady gait(5)	UNK	UNK	0.4-4.0µg/L (n=7), 0.1-1.1µg/L JWH-018 (n=6), <0.1-0.1µg/L JWH-081, <0.1-2.5µg/L JWH-122 (n=3), <0.1-0.1µg/L JWH-210 (n=4), 0.4-2.7µg/L JWH-250 (n=2)	UNK, DUID cases	(Yeakel and Logan, 2013)

Abbreviations: ADB-PINACA [N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide], AM2201 [N-(5-Fluoropentyl)-3-(1-naphthoy)lindole], AMP (amphetamine), APAP (acetaminophen), BDP (benzodiazepines), BID (twice a day), DXR (dextromethorphan), DUID (driving under the influence of drugs), ECG (electrocardiogram), ED (emergency department), ET (endotracheal intubation), ETOH (ethanol), ICU (intensive care unit), IVF (intravenous fluids), IV (intravenous), JWH-018 [naphthalen-1-yl-(1-pentylindol-3-yl)methanone], JWH-019 [(1-Hexylindol-3-yl)naphthalene-1ylmethanone], JWH-073 [naphthalen-1-yl-(1-butylindol-3-yl)methanone], JWH-081 [4-Methoxy-1-napthalen-1-yl-(1-pentyindol-3-yl)methanone], JWH-122 [1-Pentyl-3-(1-(4-methylnaphthoyl))indole], JWH-210 [4-Ethylnaphthalen-1-yl-(1-pentylindol-3-yl)methanone], JWH-250 [1-Pentyl-3-(2-methoxyphenylacetyl)indole], JWH-307 [(5-(2-Fluorophenyl)-1-pentylpyrrol-3-yl)-1-(naphthalenylmethanone)], MAM2201 [1-(5-Fluoropentyl)-3-(4-methyl-1-napthoyl)indole], MRI (magnetic resonance imaging), qD (every day), QID (four times a day), po (oral), RCS-4 [4-

Methoxyphenyl-(1-allyl-1H-indol-3-yl)methanone], sm (smoked), THC (delta-9-tetrahydrocannabinol), TID (three times a day), UDS (urine drug screen), UNK (unknown), UR-144 [(1-Pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone], XLR-11 [(1-(5-Fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone],

Table 3

Human synthetic cannabinoid (SC) administration studies

Country	N	Sex	Age	SC Brand	Dose (Route)	Symptoms	Time Onset	Duration	Laboratory Results (matrix)	Reference
Germany	2	M	--	Spice	300mg (sm)	reddened conjunctiva, dry mouth, elevated pulse, perception & mood change, mild impairment	10min	6-24h	(+)CP47,497 (blood)	(Auwärter et al., 2009)
Germany	1 1	M F	47	Smoke	150mg (sm) 100mg (sm)	nausea, sedation, dry mouth, “hot flushes”, “burning eyes”, “thought disruption”, elevated pulse & blood pressure, slight pupil dilation, mild exhaustion	“immediate”	6-12h	(+)JWH-018 (serum) 8.1-10.2μg/L after 5min, <1μg/L after 3h	(Teske et al., 2010)
USA	6	M	--	K2 Standard (2), K2 Citron (2), K2 Summit (2)	300mg (sm) one or two puffs	reddened conjunctiva(6), burning eyes(1), xerostomia(4), tachycardia(6), anxiety(4), paranoia(2), sedation(4), mood & perception changes(5), thought disruption/loss of concentration (4), impaired sense of time(4), exhaustion(3), perceived impairment(5)	2-3min; peaked at 5-10min	NS	(+)4-5μg/L JWH-018 & JWH-073 (blood) peak; <1μg/L after 2h	(Logan et al., 2011)
Russia	1	M	47	AM694	10mg (po), 1mg (sm)	None	NS	NS	(+)AM694 hydroxylated & pentanoic metabolites (urine)	(Grigoryev et al., 2012a)
Russia	1 1	M F	47 4 3	AB-001	13mg (po) 26mg (po)	None	NS	NS	(+)AB-001 hydroxylated metabolites (urine) peaked after 5-7h	(Grigoryev et al., 2012b)
Germany	1	M	42	AM2201	5mg (po)	None	NS	NS	(+)0.6μg/L AM2201 at 1.5h (serum); <.0001μg/L at 5d; AM2201 metabolites 0.05-0.2μg/L & JWH-018 metabolites 0.7-0.3μg/L (serum) at 1.5h; metabolites in urine	(Hutter et al., 2013)

Abbreviations: AB-001 [(1-Pentyl-1H-indol-3-yl)adamantylmethanone], AM694 [1-(5-fluoropentyl)-3-(2-iodobenzoyl)indole], AM2201 [N-(5-Fluoropentyl)-3-(l-naphthoy)lindole], CP47,497 [2-[(1R, 3S)-3-hydroxycyclohexyl]- 5-(2-methyloctan-2-yl)phenol], JWH-018 [naphthalen-1-yl-(1-pentylindol-3-yl)methanone], JWH-073 [naphthalen-1-yl-(1-butylindol-3-yl)methanone], NS (not specified), po (oral administration), sm (smoked administration)

Table 4

Synthetic cannabinoid (SC) CB_1 and/or CB_2 receptor binding affinity.

Compound	Class	CB_1 K_i (nM)	CB_2K_i (nM)	THC/SC CB_1K_i [a]	Reference
AB-FUBINACA	Indazole carboxamide	0.9	--	45.6	(Buchler et al., 2009)
ADB-FUBINACA	Indazole carboxamide	0.4	--	103	(Buchler et al., 2009)
AM679	Benzoylindoles	13.5	49.5	3.0	(Makriyannis A and Deng, 2000)
AM694	Benzoylindoles	0.1	1.4	410	(Makriyannis A and Deng, 2000)
AM1220	Naphthoylindoles	3.9	73.4	10.5	(Makriyannis A and Deng, 2000)
AM1248	Adamantylindoles	11.9	4.8	3.4	(Makriyannis A and Deng, 2007)
AM2201	Naphthoylindoles	1.0	2.6	40	(Makriyannis A and Deng, 2000)
AM2232	Naphthoylindoles	0.3	1.5	136	(Makriyannis A and Deng, 2000)
AM2233	Napthoylindoles	2.8	--	14.6	(Deng et al., 2005)
(±)CP47,497	Cyclohexylphenols	2.2±0.5	--	18.6	(Melvin et al., 1993)
CP47,497(C8)	Cyclohexylphenols	0.8±0.1	--	51.3	(Melvin et al., 1993)
CP55,940	Cyclohexylphenols	1.1±0.04	--	37.3	(Melvin et al., 1993
HU-210	Dibenzopyrans	0.2	0.4±0.1	205	(Devane et al., 1992)
JWH-015	Naphthoylindoles	336±36	13.8±4.6	0.1	(Aung et al., 2000)
JWH-018	Naphthoylindoles	9.0±5.0	2.9±2.7	4.6	(Aung et al., 2000)
JWH-019	Naphthoylindoles	9.8±2.0	5.6±2.0	4.2	(Aung et al., 2000)
JWH-030	Naphthoylindoles	87.0±3.0	--	0.5	(Tarzia et al., 2003)
JWH-073	Naphthoylindoles	8.9±1.8	38.0±24.0	4.6	(Aung et al., 2000)
JWH-081	Naphthoylindoles	1.2±0.03	12.4±2.2	34.2	(Aung et al., 2000)
JWH-122	Naphthoylindoles	0.7±0.5	1.2±1.2	58.6	(Huffman et al., 2003)
JWH-200	Naphthoylindoles	42.0±5.0	--	1.0	(Huffman et al., 2003)
JWH-203	Naphthoylindoles	8.0±0.9	7.0±1.3	5.1	(Huffman et al., 2005a)
JWH-210	Naphthoylindoles	0.5±0.03	0.7±0.01	82	(Huffman et al., 2005b)
JWH-250	Phenylacetylindoles	11.0±2.0	33.0±2.0	3.7	(Huffman et al., 2005a)
JWH-251	Phenylacetylindoles	29.0±3.0	146±36.0	1.4	(Huffman et al., 2005a)
JWH-307	Naphthoylpyrroles	7.7	--	5.3	(Huffman et al., 2005a)
THC	Dibenzoypyran	41±2	36±10	1.0	(Showalter et al., 1996)
UR-144	Tetramethylcyclo-propyl indoles	29.0±0.9	4.5±1.7	1.4	(Wiley et al., 2013a)
WIN55,212-2	Aminoalkylindoles	62.3	3.3	0.7	(Felder et al., 1995)
XLR11	Tetramethylcyclo-propyl indoles	24.0±4.6	2.1±0.6	1.7	(Wiley et al., 2013a)

Abbreviations: AB-FUBINACA [N-[(2S)-1 -Amino-3-methyl-1-oxo-2-butanyl]-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide], ADB-FUBINACA [N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl-1H-indazole-3-carboxamide], AM679 [1-Pentyl-3-(2-iodo-benzoyl)indole], AM694 [1-(5-Fluoropentyl)-3-(2-iodobenzoyl)indole], AM1220 [1-((N-,Methylpiperidin-2-yl)methyl)-3-(1-naphthoyl)indole], AM1248 [1-[(1-Methyl-2-piperidin-yl)methyl]-1H-indol-3-yl]-adamantylmethanone], AM2201 [N-(5-fluoropentyl)-3-1(-napthoylindole)], AM2232 [5-(3-(1-Napthoyl)-1H-indol-1-yl)pentannitrile], AM2233 [(2-Iodophenyl)-[1-[(1-methyl-2-piperidinyl)methyl]-1H-indol-3-

yl]methanone], CP47,497 [2-[(1S,3S)-3-Hydroxycyclohexyl]-5-(2-methyloctan-2-yl)phenol], CP47,497(C8) [trans-3-(4-(1,1-Dimethyloctyl)-2-hydroxyphenyl)cyclohexanol], HU-210 [(6aR)[-trans-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6Hdibenzo[b,d]pyran-9-methanol]], JWH-015 [2-Methyl-1-propyl-3-(1-naphthoyl)indole], JWH-018 [Naphthalen-1-yl(1-pentyl-indol-3-yl)methanone], JWH-019 [N-Hexyl-3-(1-naphthoyl)indole], JWH-030 [3-(1-Naphthoyl)-1-pentylpyrrole], JWH-073 [N-Butyl-3-(1-naphthoyl)indole], JWH-081 [N-Pentyl-3-[1-(4-methoxy)-naphthoyl]indole], JWH-122 [1-Pentyl-3-(1-(4-methylnaphthoyl))indole], JWH-200 [1-(2-(Morpholin-4-yl)ethyl)-3-(1-naphthoyl)indole], JWH-203 [1-Pentyl-3-(2-chlorophenylacetyl)indole], JWH-210 [1-Pentyl-3-(1-(4-ethylnaphthoyl))indole], JWH-250 [1-Pentyl-3-(2-methoxy-phenylacetyl)indole], JWH-251 [2-(2-Methylphenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone], JWH-307 [5-[(2-Fluorophenyl)-1-pentylpyrrol-3-yl]-1 (naphthalenyl)methanone]; THC (Delta-9-tetrahydrocannabinol), UR-144 [1-Pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone], XLR11[(1-(5-Fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethyl-cyclopropyl-)-methanone]

[a] Ratio calculated between THC CB_i K_i = 41 nM and mean CB_1 K_i for each synthetic cannabinoid. Ratio >1 represents greater CB_1 binding affinity than for THC.

Drug Alcohol Depend. Author manuscript; available in PMC 2015 November 01.

Table 5

Agonist-stimulated activation of CB_1 and CB_2 receptors by synthetic cannabinoids represented as median maximum effective dose (EC_{50}) or inhibitor binding affinity (Ki) values.

Drug	Model	EC_{50} or K_i (nM)		Intrinsic activity at CB_1 receptor	Reference
		CB_1	CB_2		
AB-FUBINACA	GTPγS binding	23.2	--	Full agonist	(Buchler et al., 2009)
ADB-FUBINACA	GTPγS binding	1.0	--	Full agonist	(Buchler et al., 2009)
AM2201	GTPγS binding	24.4	--	Full agonist	(Nakajima et al., 2011)
AM694	GTPγS binding	52.8	--	Full agonist	(Nakajima et al., 2011)
CP47,497 C8	Internalization assay	4.4	--	Full agonist	(Atwood et al., 2011)
(−)CP55,940	adenylate cyclase inhibition	25	0.7±0.2	Full agonist	(Howlett et al., 1988; Slipetz et al., 1995)
CP55,940	GTPγS binding	3.4±2.4, 25±14.4	23±6.8	Full agonist	(Brents et al., 2011; Wiley et al., 2013a)
HU-210	adenylate cyclase inhibition	--	0.4±.07	--	(Slipetz et al., 1995)
HU-210	GTPγS binding	2.9	--	Full agonist	(Breivogel et al., 2001)
JWH-018	Internalization assay	10.1	--	Full agonist	(Atwood et al., 2011)
JWH-018	GTPγS binding	36, 6.8±2.5	--	Partial to full agonist	(Brents et al., 2011; Nakajima et al., 2011)
JWH-018 4-hydroxyindole	GTPγS binding	17.0±9.6	--	Partial to full agonist	(Brents et al., 2011)
JWH-019	GTPγS binding	98.9	--	Full agonist	(Nakajima et al., 2011)
JWH-073	Internalization assay	45.6	--	Full agonist	(Atwood et al., 2011)
JWH-210	GTPγS binding	20.4	--	Full agonist	(Nakajima et al., 2011)
JWH-251	GTPγS binding	29.0±5.5	8.3±0.8	Full agonist	(Huffman et al., 2005a)
JWH-302	GTPγS binding	29.3±0.8	24.4±6.9	Full agonist	(Huffman et al., 2005a)
RCS-4	GTPγS binding	199	--	Partial agonist	(Nakajima et al., 2011)
THC	adenylate cyclase inhibition	430	--	Partial agonist	(Dill and Howlett, 1988)

Drug	Model	EC_{50} or K_i (nM)		Intrinsic activity at CB_1 receptor	Reference
		CB_1	CB_2		
THC	GTPγS binding	167±4.7, 81±34	--	Partial agonist to full agonist	(Breivogel et al., 2001; Brents et al., 2011)
UR-144	GTPγS binding	95±20	334±170	Full agonist	(Wiley et al., 2013a)
XLR-11	GTPγS binding	159±38	145±73.8	Full agonist	(Wiley et al., 2013a)
WIN55,212-2	adenylate cyclase inhibition	24±3.7	0.7±0.2	Full agonist	(Felder et al., 1992; Slipetz et al., 1995)
WIN55,212-2	GTPγS binding	170±80	--	Full agonist	(Breivogel et al., 2001)

Abbreviations: AB-FUBINACA [N-[(2S)-1-Amino-3-methyl-1-oxo-2-butanyl]-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide], ADB-FUBINACA [N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl-1H-indazole-3-carboxamide], AM694 [1-(5-Fluoropentyl)-3-(2-iodobenzoyl)indole], AM2201 [N-(5-fluoropentyl)-3-1(-napthoylindole)], CP47,497(C8) [trans-3-(4-(1,1-Dimethyloctyl)-2-hydroxyphenyl)cyclohexanol], HU-210 [(6aR)[-trans-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6Hdibenzo[b,d]pyran-9-methanol]], JWH-015 [2-Methyl-1-propyl-3-(1-naphthoyl)indole], JWH-018 [Naphthalen-1-yl(1-pentyl-indol-3-yl)methanone], JWH-019 [N-Hexyl-3-(1-naphthoyl)indole], JWH-030 [3-(1-Naphthoyl)-1-pentylpyrrole], JWH-073 [N-Butyl-3-(1-naphthoyl)indole], JWH-081 [N-Pentyl-3-[1-(4-methoxy)-naphthoyl]indole], JWH-122 [1-Pentyl-3-(1-(4-methylnaphthoyl))indole], JWH-200 [1-(2-(Morpholin-4-yl)ethyl)-3-(1-naphthoyl)indole], JWH-203 [1-Pentyl-3-(2-chlorophenylacetyl)indole], JWH-210 [1-Pentyl-3-(1-(4-ethylnaphthoyl))indole], JWH-250 [1-Pentyl-3-(2-methoxy-phenylacetyl)indole], JWH-251 [2-(2-Methylphenyl)-1-(1-pentyl-1H-indol-3-yl)-ethanone], JWH-307 [5-[(2-Fluorophenyl)-1-pentylpyrrol-3-yl]-1 (naphthalenyl)methanone], UR-144 [(1-Pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone], XLR11 [(1-(5-Fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethyl-cyclopropyl-)-methanone], WIN55,212-2 [(R)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[(1,2,3.de)-1,4-benzoxazin-6-yl]-1-naphthalen-ylmethanone]