Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2012 December 3; 39(2): 234–243. doi:10.1016/j.pnpbp.2012.04.017.

Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids

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Abstract

"K2" and "Spice" drugs (collectively hereafter referred to as Spice) represent a relatively new class of designer drugs that have recently emerged as popular alternatives to marijuana, otherwise characterized as "legal highs". These drugs are readily available on the Internet and sold in many head shops and convenience stores under the disguise of innocuous products like herbal blends, incense, or air fresheners. Although package labels indicate "not for human consumption", the number of intoxicated people presenting to emergency departments is dramatically increasing. The lack of validated and standardized human testing procedures and an endless supply of potential drugs of abuse are primary reasons why researchers find it difficult to fully characterize clinical consequences associated with Spice. While the exact chemical composition and toxicology of Spice remains to be determined, there is mounting evidence identifying several synthetic cannabinoids as causative agents responsible for psychoactive and adverse physical effects. This review provides updates of the legal status of common synthetic cannabinoids detected in Spice and analytical procedures used to test Spice products and human specimens collected under a variety of clinical circumstances. The pharmacological and toxicological consequences of synthetic cannabinoid abuse are also reviewed to provide a future perspective on potential short- and long-term implications.

Keywords

synthetic cannabinoid; Spice; K2; 'legal highs'; intoxication; marijuana alternative

Marijuana has a long history of medicinal and recreational use, and is today the most widely produced and consumed illicit substance worldwide (UNODC, 2011). The psychoactive effects of marijuana are mainly due to delta-9-tetrahydrocannabinol (Δ^9-THC), which exhibits partial agonistic activity at CB1 cannabinoid receptors, found primarily in the central nervous system, and CB2 receptors in the periphery (Ameri, 1999). Since the discovery of Δ^9-THC, cannabinoids have been synthesized for biomedical research purposes because synthetic cannabinoids capable of selectively activating cannabinoid receptors hold great promise as new therapeutic agents (Seely et al., 2011). Until recently, these synthetic derivatives were almost exclusively designed to pharmacologically evaluate the potential of

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novel therapeutics or designed to probe specific mechanisms of action and related health effects of marijuana and hashish (Di Marzo and Petrocellis, 2006; Gerra et al., 2010).

Starting around 2004, “street chemists” began producing smokable herbal “K2” or “Spice” products (collectively hereafter referred to as Spice) as legal alternatives to marijuana (Figure 1). The manufacture, distribution and/or use of these herbal products were neither controlled nor illegal, even though they were laced with synthetic cannabinoids characterized as full agonists with high affinity at human CB1 receptors. Although package labels clearly indicate “not for human consumption”, “incense”, or “for aromatherapy use only”, clinical toxicologists understand these products are commonly used to obtain Δ^9-THC-like psychological effects (Penn et al., 2011). Further concerning to public health officials is that the popularity of Spice appears to be growing (EMCDDA, 2009). In Europe, there has been a surge of interest related to Spice compounds (Jack, 2009), which are available for both online and open sale (Marzouk, 2009). According to statistics available through the American Association of Poison Control Centers (AAPCC National Poison Data System (NPDS), there has been exponential increase in informational calls received in the US regarding Spice since 2008. The promise of a more intense high than cannabis, affordability, easy access, and avoidance of detection in standardized drug tests likely contributes to the growing use of Spice (Fattore and Fratta, 2011).

Synthetic cannabinoids available on the market

Spice represents a relatively new type of “designer drug” that has recently emerged on the recreational drug use market and is often sold via the Internet, gas stations, convenience stores, and head shops without age restrictions (Nakajima et al., 2011; Psychonaut Web Mapping Research Group, 2010; Zawilska, 2011). It has been suggested that some Spice may have been manufactured in China (EMCDDA, 2009; Jack, 2009), but it remains unclear where and how the production of these herbal mixtures actually takes place.

Limited knowledge of the exact chemical composition and toxicology of Spice ingredients is available. Package information typically lists vegetable ingredients considered inert (white and blue water lily, blue and pink lotus, etc), and less frequently lists plants that naturally contain potentially psychoactive alkaloids, like aporphines (Dresen et al., 2010). However, due to lack of regulation, safety information and a list of active pharmacological agents are not typically provided. Product testing has determined there are countless formulations available for Spice, ranging from powders and liquids, to smoking mixtures (Verster, 2010). Analytical tests also reveal that cannabinoid constituents and dosages can vary greatly between products, lots, and within the same package (EMCDDA 2009; Hillebrand et al., 2010). Variations observed within the same package are often referred to as “hot spots”.

Some of the first synthetic cannabinoids detected in Spice were synthesized and named after John W. Huffman, a medicinal chemist at Clemson University who was part of a NIDA-funded research project to evaluate the therapeutic potential of many synthetic cannabinoids (Huffman et al., 1994). The “JWH” series of synthetic cannabinoids evolved from a computational melding of the chemical structural features of Δ^9-THC with previously developed aminoalkylindoles (Huffman et al., 1994). Today, the JWH series of cannabinoids are arguably the dominant cannabinoids detected in Spice (Carroll et al., 2012; Uchiyama et al., 2011a). JWH-018 (1-penthyl-3-(1-napthoyl)indole) was one of the first compounds to be abused and probably selected because the compound is easily synthesized and has high pharmacological activity (Huffman, 2009; Huffman et al., 1994). To date, more than 40 studies have been published examining the *in vitro* and *in vivo* effects of JWH-018 (source: http://www.ncbi.nlm.nih.gov/pubmed). The chemical structure of JWH-018 is based upon

that of WIN 55,212–2, the prototypic aminoalkylindole cannabinoid (Atwood et al., 2010; D'Ambra et al., 1992; Eissenstat et al., 1995).

In addition to the JWH compounds, other synthetic cannabinoids detected in Spice include the classical cannabinoid HU-210 developed by Raphael Mechoulam at the Hebrew University in the 1960s and the cyclohexylphenol ("CP") non-classical cannabinoids developed by Pfizer in the 1970's. HU-210 is structurally very similar, but more potent than Δ^9-THC. However, HU-210 is difficult to synthesize. CP-47,497 is easier to synthesize and is thought to be highly popular because it retains full agonistic activity at CB1 receptors, like its prototypical derivative CP-55,940. Other indole-derived cannabinoids synthesized by Alexandros Makriyannis (the "AM" compounds) have also been detected in many Spice products (Hudson and Ramsey, 2011; Makriyannis and Deng, 2001).

One unique characteristic of Spice is its ever changing composition. The first Spice products commonly contained JWH-018 and JWH-073, but as these aminoalkylindoles and other bicyclic non-classical compounds like CP-47,497 and its C8 homolog became regulated, there has been an emergence of new derivatives like JWH-081, JWH-122, JWH-210, and AM-2201, presumably in an attempt to continue to avoid regulations. Despite slight chemical structure modifications, all of the synthetic cannabinoids are lipid-soluble, non-polar, and highly volatilized compounds that mimic the actions of Δ^9-THC.

Other substances identified in Spice include fatty acids and their esters (linoleic acid, palmitic acid), amide fatty acids (oleamide, palmitoylethanolamide), plant-derived substances (eugenol, thymol, and flavours like acetyl vanillin), preservatives (benzyl benzoate) and additives (alpha-tocopherol) (Uchiyama et al., 2010; Zuba et al., 2011). Spice products may also contain high quantities of vitamin E and are often contaminated with the β2–adrenergic agonist clenbuterol (Dresen et al., 2010), thus providing a basis for sympathomimetic-like effects (tremor, tachycardia, anxiety) often described in intoxicated patients presenting to emergency departments (Simmons et al., 2011a, 2011b).

Legislation

The emergence of aminoalkylindoles and cyclohexylphenols in packages labelled as "incense" and "not for human consumption" initially posed several interesting legal questions. Although individuals were injuring themselves after reportedly using Spice, structural dissimilarities between these emerging drugs and natural cannabinoids prevented classification of these drugs as Δ^9-THC analogs under existing designer drug regulatory policies (Moran, 2011). Such regulatory issues may partly explain the delay in controlling abuse and distribution of synthetic cannabinoid compounds and argue that regulatory efforts should not be based exclusively on chemical structure comparisons (Wiley et al., 2011).

In Europe, starting from 2009, some countries (Austria, Germany, France, Luxembourg, Poland, Lithuania, Sweden, UK and Estonia) subjected all products containing synthetic cannabinoid compounds to the Narcotics Law, so that they were no longer accessible in head shops and online stores (UK Statutory Instrument, 2009). Since then, several local communities began the regulatory process for these new agents, either administratively or through enacted legislation, by adopting specific ordinances aimed to ban substances that have chemical structures or effects similar to synthetic cannabinoids or used with the intention to achieve similar effects (Brown, 2011). However, some ordinances were vague and inconsistent across jurisdictional boundaries. These inconsistencies, along with mounting evidence demonstrating the toxic nature of these potential drugs of abuse (Lapoint et al., 2011), support the need for consistent legislation. As of March 2011, the most widely abused synthetic cannabinoids (JWH-018, JWH-073, JWH-200, CP-47,497, and (C8)-CP-47,497) were scheduled by the US Department of Justice and placed on the Schedule 1

list under 21 U.S.C.811(h) of the Controlled Substances Act (DEA, 2011). Several individual states have also taken action under existing statutes or emergency scheduling rules. Despite these efforts, legal confusion remains as new cannabinoids emerge within products shipped with certificates of analyses and labelling indicating the absence of regulated substances (Figure 1). Moreover, Spice drugs are still readily available on the Internet with manufacturers continually making slight structural modifications to continue circumventing legal actions. Broad legislation may seem like a feasible solution, but care must be taken to prevent unintended consequences. A primary concern is the possibility that overregulation might slow new drug development or inadvertent regulation of common over-the-counter medications. Since cannabinoids are promising novel therapeutic agents (Chang et al., 2012; Engeli, 2012; Mackie, 2006), overregulation could be particularly troublesome for this class of compounds.

Detection and identification of Spice in human samples

Before clinical consequences and public health impacts of Spice can be adequately characterized, development of standardized forensic procedures is necessary to delineate the specific synthetic cannabinoids contained in Spice. Standardized human tests are also necessary to confirm drug exposures and to further pharmacokinetic and pharmacodynamic testing of these compounds. Without testing to confirm a positive drug screening assay, researchers cannot identify the causative agents and, more importantly, link specific drug use and routes of administration with pharmacological effects. As technology develops it is anticipated that affordable clinical assays will become widely available.

The ever changing composition of Spice poses significant burdens on forensic and public health laboratories charged with characterizing these new potential drugs of abuse (Moran, 2011). Over the past few years, great effort has been given to developing testing strategies capable of identifying and quantifying synthetic cannabinoids used within Spice herbal products, including liquid chromatography tandem mass spectrometry (LC-MS/MS) (Teske et al., 2010) and high mass resolution techniques like matrix-assisted laser desorption/ ionization-time of flight mass spectrometry (MALDI-TOF) (Gottardo et al., 2012). All of these techniques meet specificity, accuracy, sensitivity, and precision requirements posed by forensic laboratories even when concealing agents, like glycerine or fatty acid amides, are added. All analytical testing strategies require detection of low concentrations of the psychoactive compounds typically found in Spice herbal products (0.1–1.0% of weight). Recently, such techniques were used by Hudson and colleagues to detect reported and previously unreported cannabinoid compounds in Spice. Results from these studies importantly provide a detailed database of over 140 chemicals associated with “legal highs” (Hudson and Ramsey, 2011; Hudson et al., 2010b).

Most of the cannabinoids detected to date can be generally characterized as aminoalkylindoles originally synthesized by John W. Huffman or Alexander Makriyannis (i.e. JWH-018, JWH-122, AM-2201, etc), cyclohexylphenols originally made by Pfizer (i.e. CP-47,497 and its C8 homolog), benzoylindoles currently produced by Research Chemical Suppliers (i.e. RCS-4 and RCS-8), or classical synthetic cannabinoids originally produced at Hebrew University (HU-210).

Detection of parent compounds and/or metabolites in bodily fluids by commonly used bioanalytical methods is essential for forensic, scientific and medical purposes. Until recently, detection of synthetic cannabinoids in urine drug screens was difficult due to only slight differences between the chemical structures present in Spice and the lack of appropriate reference metabolic standards and laboratory capacity (Moran, 2011). JWH-018 and other synthetic cannabinoids are most often measured in human serum by LC-MS/MS

(Hudson et al., 2010b; Teske et al., 2010) as are downstream metabolites of several synthetic cannabinoids (Chimalakonda et al., 2011a, 2011b; Dresen et al., 2010, 2011; ElSohly et al., 2011; Grigoryev et al., 2011a, 2011b; Möller et al., 2011; Moran et al., 2011; Sobolevsky et al., 2010). Validation of testing procedures in oral fluid is also being pursued by using the Quantisal™ device, which incorporates the use of solid-phase extraction and LC-MS (Coulter et al., 2011). Oral fluid analysis can provide information on recent drug consumption and is becoming more popular as a method for the detection of drugs both in the workplace and by law enforcement. The analytical procedure described by Coulter and colleagues allowed the detection of JWH-018 following a single smoking session of two different herbal product brands, namely “Blueberry Posh” and “Black Mamba” (Coulter et al., 2011).

Pharmacology & Toxicology

Cannabinoid receptors are part of the complex endocannabinoid system that is not fully understood. Cannabinoid receptors are G-protein coupled receptors (GPCRs) for which activation results in presynaptic hyperpolarization through changes in calcium influx and potassium efflux, ultimately resulting in neuronal hyperpolarization and a decrease in neurotransmitter release (Ameri, 1999). Cannabinoid CB1 receptors are among the most abundant GPCRs expressed in the brain and play a significant role in the modulation of GABA and glutamate neurotransmission (Hájos and Freund, 2002). Cannabinoid CB2 receptors are predominantly expressed on immune cells and are thought to mediate immunosuppression by inducing apoptosis, inhibition of proliferation, and suppression of cytokine and chemokine production (Rieder et al., 2010). Cannabinoid receptors are also commonly complexed as heterodimers with other receptors (Hoio et al., 2008). As such, the interplay between cannabinoid and opioid receptors is a target of pharmaceutical strategies aimed at new, effective pain control in humans (Desroches and Beaulieu, 2010), but the combined effects of opioid/Spice are unknown.

The potential harm of Spice constitutes a significant public health concern since exposures and anecdotal reports of human fatalities following synthetic cannabinoid exposure are increasing (Fattore and Fratta, 2011). The American Association of Poison Control Centres reported the call volume of K2 exposure increased exponentially from 53 calls in 2009 to over 6,000 in 2011 (AAPCC, 2011). Users may mistakenly equate the safety and dosing profile of marijuana to that of an herbal blend containing synthetic cannabinoid agonists. Although the plant material is most likely only an inert vessel for the active synthetic cannabinoids, the pharmacology and toxicology of the plant material used in these incense blends is also unknown.

Even though Spice effects are described as marijuana-like after smoking or ingestion, the health implications are not entirely characterized. Data available indicate that these compounds produce a collection of effects resembling Δ^9-THC intoxication, although structure-activity relationship analyses reveal that some compounds may exhibit higher potency and affinity for cannabinoid receptors (Huffman and Padgett, 2005). In addition to higher potency, some synthetic cannabinoids have long half-lives and/or result in the production of active metabolites (Brents et al., 2011, 2012), that may induce tachyphylaxis (Wells and Ott, 2011).

While policy-makers and law enforcement agencies struggle to bring the Spice phenomenon under control, researchers, scientists, and clinicians must begin characterizing the pharmacokinetic and pharmacodynamic properties of these toxic substances in humans. Without this basic information it is difficult to fully characterize both the short- and long-term effects of these compounds. Below is a summary of information available for each

major area, and Figure 2 is a schematic summary of biological information available for JWH-018, one of the most well characterized synthetic cannabinoids.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic and pharmacodynamic profiles of most synthetic cannabinoids in humans are largely unknown. Case reports indicate oral and inhalational bioavailability, but the degree of bioavailability is not entirely known. Currently, no cases of parenteral or rectal routes of administration have been published. JWH-018 has a short half-life in human blood following smoking (Teske et al., 2010); however, specific metabolic pathways leading to detoxification (and/or activation) and excretion remain to be determined. It is generally thought that hepatic cytochrome P450 oxidation is followed by glucuronic acid conjugation and renal excretion (Gronewold and Skopp, 2011). Specific cytochrome P450 isozymes responsible for synthetic cannabinoid metabolism have not been identified, but Chimalakonda et al. (2011a) reported UGT1A1, UGT1A3, UGT1A9, UGT1A10 and UGT2B7 as major UDP-glucuronosyltransferases responsible for conjugation (Figure 2).

Unlike Δ^9-THC metabolites, synthetic cannabinoid metabolites retain varying amounts of biologic activity and can act as agonists, neutral antagonists, or inverse agonists at CB1 receptors (Figure 2). Some oxidized products of JWH-018 have affinity for CB1 receptors similar to the parent drug, while other products have been found to exhibit affinity similar to Δ^9-THC (Brents et al., 2011). The same authors also demonstrated that mono-hydroxylated derivatives of JWH-073, another synthetic cannabinoid often found in Spice products, retain intermediate to high affinity for CB1 receptors, acting as partial agonists or neutral antagonists (Brents et al., 2012).Seely et al. (2012) has also shown that the glucuronic acid conjugate of an omega-hydroxyl metabolite of JWH-018 retains reasonable affinity for CB1 receptors and can act as a neutral antagonist (Figure 2). The diverse metabolite activity profile of aminoalkylindole metabolites may partially explain the mixed effects of these drugs and highlight potential safety concerns.

Importantly, some synthetic cannabinoids such as JWH-015 and JWH-133 show affinity not only for the CB1, but also for the CB2 receptors (Huffman, 2005; Uchiyama et al., 2011b) which are highly expressed on the marginal zone of the spleen, tonsils and immune cells, especially on macrophages, B cells, natural killer cells, monocytes, T-lymphocytes, polymorphonuclear neutrophils and astrocytes (Ameri, 1999). Thus, it can be anticipated that Spice drugs containing synthetic cannabinoids with affinity for the CB2 receptor may also affect the immune system by modulating chemotaxis of T lymphocytes (Ghosh et al., 2006), or inducing thymic atrophy and apoptosis (Lombard et al., 2007). Accordingly, synthetic cannabinoid receptor agonists may inhibit tumor growth and metastasis of breast cancer (Qamri et al., 2009) and human tumour prostate PC-3 cell growth (Olea-Herrero et al., 2009), and interact with chemokine receptor CXCR4 in modulating breast cancer growth and invasion (Nasser et al., 2011). In addition, the presence of CB2 receptors in neurons and glial cells in the brain (Onaivi et al., 2006) supports the idea that JWH-015 and JWH-133 might also affect basic neural cell processes like cell proliferation and survival (Fernández-Ruiz et al., 2007). Notably, chronic exposure of mice to JWH-015 has been associated with increased vulnerability to drug abuse and depression (Onaivi et al., 2008a, 2008b), while intra-accumbens administration of JWH-133 has been found to dose-dependently decrease the rewarding and locomotor-stimulating effects of cocaine in mice, likely by a dopamine-dependent mechanism (Xi et al., 2011).

Although no studies have been published, Spice compounds may interact with non-cannabinoid receptor targets by directly binding non-cannabinoid receptors, such as the vanilloid type 1 receptor (TRPV1), a non-selective cation channel gated also by capsaicin, protons and heat (Di Marzo et al., 2002), or through the formation of heterodimers between

CB1 receptors and D2 dopamine, μ-opioid, or orexin-1 receptors (Hudson et al., 2010a; Milligan and Smith, 2007). Several cannabinoids have previously been shown to directly bind or modulate in an orthosteric or allosteric manner the deorphanized G-protein coupled receptor GPR55, opioid (μ- and δ-opioid) and acetylcholine (muscarinic and nicotinic) receptors, serotonin (5-HT3) and glutamatergic (NMDA) receptors, and nuclear (PPARα) receptors (reviewed in Pertwee et al, 2010). However, pharmacological implications of non-cannabinoid receptor target activation by synthetic cannabinoids commonly found in Spice remains to be determined.

Acute Effects

JWH-018 is characterized as a full agonist at CB1 receptors with an E_{max}= 0.29 pmol/mg drug (compared to the E_{max}= 0.06 pmol/mg of Δ^9-THC and E_{max}= 0.28 pmol/mg of CP-55,940, a well characterized full agonist at CB1 receptors) (Brents et al., 2011). Several other synthetic cannabinoids have also been characterized using both *in vitro* and *in vivo* models (Brents et al., 2011; Järbe et al., 2011; Vann et al., 2009; Wiley et al., 1995, 1998); however, most behavioural research is relatively limited. Remarkably, there are no controlled studies in humans, but Auwärter et al. (2009) did report the duration of action for JWH-018 and CP 47,497 was 1–2 and 6–8 hours, respectively. Further, human data concerning the induction and duration of adverse effects remains limited. The lack of available reliable detections assays and the dynamic, unpredictable nature of these substances prevent consistent, quality case reporting of Spice abuse in the literature. Below is a summary of information available on the acute psychoactive and physical effects associated with synthetic cannabinoid use. The most common reported adverse clinical effects are summarized in Table 1.

Psychoactive effects—Single case reports in adults describe an assortment of psychoactive effects ranging from pleasant, desirable euphoria to anxiety, psychosis, and alterations in cognitive abilities (Auwärter et al., 2009; Castellanos et al., 2011; Müller et al., 2010; Vardakou et al., 2010). Observations in humans have been supported with animal models using *in vivo* drug discrimination procedures. Drug discrimination procedures are widely utilized in animal studies to investigate abuse-related effects of a psychoactive drug by establishing the interoceptive effects of a training drug (i.e. Δ^9-THC), as a cue for performing a specific operant response (i.e. food-reinforced lever-pressing) (Solinas et al., 2006). Contrary to other drugs, Δ^9-THC discrimination has been shown to possess great pharmacological specificity for psychoactive cannabinoid compounds (Barrett et al., 1995), in that it shares discriminative stimulus effects exclusively with compounds that bind to the cannabinoid CB1 receptor (Wiley et al., 1995). Notably, THC generalization/substitution is highly predictive of cannabinoid receptor agonism in humans (Balster and Prescott, 1992). In mice trained to discriminate Δ^9-THC, JWH compounds have discriminative stimulus effects similar to Δ^9-THC, in comparison to the binding affinity of Δ^9-THC for CB1 receptors (Vann et al., 2009). In other words, compounds with the highest CB1 affinity (JWH-204) substituted for Δ^9-THC with high potency, while compounds with the poorest CB1 affinity (JWH-205) produced less potent Δ^9-THC-like effects. Very recently, JWH-018 and JWH-073 have been shown to exert Δ^9-THC-like discriminative stimulus effects in monkeys and dose-dependently attenuate a discriminative stimulus induced by a CB1 receptor antagonist (i.e., withdrawal) (Ginsburg et al., 2012). Furthermore, development of tolerance and physical abstinence syndrome has been described after protracted use of high Spice doses (Zimmermann et al., 2009).

Physical effects—Clinical case reports describe a variety of physical effects ranging in severity from nausea to more serious sympathomimetic-like symptoms such as psychomotor agitation, diaphoresis, and palpitations (Castellanos et al., 2011; Every-Palmer et al., 2010,

2011; Schneir et al., 2011; Zimmermann et al., 2009). Although infrequently associated with marijuana smoking, generalized convulsions have been described in a healthy young boy who smoked a spice product called “Happy Tiger Incense” that was later confirmed to contain the 4 different synthetic cannabinoids JWH-018, JWH-081, JWH-250 and AM-2201 (Schneir and Baumbacher, 2011).

Subjective and physiologic effects of Spice can also vary greatly (Schifano et al., 2006; Vardakou et al., 2010). For example, after consumption of “Smoke”, “Spice Gold” or other Spice products, some users report sedation while others relate agitation, sickness, hot flushes, burning eyes and xerostomia along with mydriasis and tachycardia (Auwärter et al., 2009; Teske et al., 2010). Tremors and palpitations have also been described after consumption of “Banana Cream Nuke”, a spice blend containing JWH-018 and JWH-073 (Schneir et al., 2011).

Recently, the first cases of acute myocardial infarction have been reported in healthy adolescents (16 year old boys) after using Spice (Mir et al., 2011), but the lack of confirmed cannabinoid exposure (synthetic or otherwise) limits clinical application. Despite the recent availability of specific techniques for the quantitative measurement of synthetic cannabinoids and their metabolites in urine (Chimalakonda et al., 2011a, 2011b; Moran et al., 2011), these patients were only tested for Δ^9-THC, which did not address whether other active, non-cannabinoid contaminants induced myocardial infarction.

Severe toxicity following synthetic cannabinoid exposure has been recently described (Lapoint et al., 2011; Simmons et al., 2011b). In one case report, symptoms included generalized seizures within 30-min of pure JWH-018 ingestion, and laboratory analyses confirmed the presence of a primary JWH-018 metabolite in the patient’s urine (Lapoint et al., 2011). Another patient presented with emesis, agitation, mydriasis, mild tachycardia and seizure activity one hour after smoking SpicyXXX (Simmons et al., 2011b).

Importantly, in NG 108-15 cells, a cell line expressing functional cannabinoid receptors (Ho and Zhao, 1996; Matsuda et al., 1990), the synthetic cannabinoids CP-55,940, CP-47,497 and CP-47,497-C8 have been recently found to be cytotoxic, as they induced apoptosis in a dose-dependent manner likely activating the capsase cascade and involving CB1 receptors, but not CB2 receptors (Tomiyama and Funada, 2011).

Long Term Effects

While the acute adverse effects of synthetic cannabinoids are recognized and documented, there is no information about the chronic use and toxicity of synthetic cannabinoids. However, speculations can be proposed based on the long-term effects of heavy marijuana use. Prolonged cannabis use has been associated with an increased risk of psychosis (McGrath et al., 2010) in younger, heavy users in an age- and dose-dependent manner (Arseneault et al., 2002; D’Souza et al., 2009). Consumption of the Spice product known as “Aroma” (containing JWH-018) is associated with psychosis relapse (Every-Palmer, 2010, 2011) while a different product called “Spice” was found to trigger psychotic symptoms in a patient with a history of recurrent psychotic episodes (Müller et al., 2010). Recently, new-onset psychosis has been described in ten otherwise healthy men who smoked synthetic cannabinoids more than once (from 4 times over 3 weeks up to daily use over 1.5 year) (Hurst et al., 2011). This case report described a constellation of psychotic symptoms, ranging from auditory and visual hallucinations to paranoid delusions, from thought blocking to disorganized speech, from anxiety and insomnia to stupor and suicidal ideation (Hurst et al., 2011). These and other similar clinical reports led to the suggestion that synthetic cannabinoids could precipitate psychosis in vulnerable individuals, similarly to marijuana.

Long-term heavy cannabis use has also been associated with reduced brain volume, where the hippocampus and the amygdala are the cerebral regions significantly changed, roughly −12% and −7% respectively (Yücel et al., 2008). The hippocampus and the amygdala are brain regions involved, respectively, in memory and the pathophysiology of schizophrenia (Tamminga et al., 2010) and emotion processing (Phelps and LeDoux, 2005). Interestingly, long-term Spice users often experience psychotic episodes as well as irritability and anxiety (Castellanos et al., 2011; Every-Palmer, 2010, 2011; Schneir et al., 2011).

Cannabinoids have important effects on a broad spectrum of physiological processes known to strongly influence emotional processing, sensory perception, and elaboration of incoming sensory information (Akirav, 2011; Ashton and Moore, 2011). Cannabinoids modulate prefrontal cortex neural functioning by decreasing the release of GABA and increasing extracellular glutamate and dopamine levels (Ferraro et al., 2001a, 2001b; Pistis et al., 2002). Given this evidence, one can hypothesize that prolonged use of Spice may induce significant alterations in emotional processing and cognitive functioning.

In addition to direct modulation of serotonin release by GABA, serotonin levels can also be affected indirectly by endocannabinoid control of GABA and glutamate release. For example, administration of the potent 5HT-2a and 5HT-2c agonist (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) with concurrent chronic administration of the CB1 receptor agonist HU-210 resulted in potentiation of DOI-induced hyperthermia (Hill, 2006). Furthermore, high doses of THC and other cannabinoids are inhibitors of monoamine oxidase (MAO) (Fišar, 2010, 2012). However, the prevalent abuse of Δ^9-THC and the lack of significant toxicity resulting from MAO inhibition with cannabis indicates this mechanism is unlikely to cause adverse effects reported with Spice use.

Notably, the first withdrawal syndrome with Spice use was described in a 20-year old male who smoked “Spice Gold” daily over an 8-month period. He found Spice relaxing, sedative and with cannabis-like psychoactive effects, but requested medical treatment after experiencing internal unrest, profuse sweating, drug craving, nocturnal nightmares, tremor, and headache after a period of abstinence (Zimmermann et al., 2009).

User profile

In a recent “Monitoring the Future” survey, about 11 percent of US high school seniors (aged 17 to 18 years of age) admitted using Spice (Vandrey et al., 2012), and it appears that male adolescents are at greater risk for using Spice (Castellanos et al., 2011; Forrester et al., 2011). Spice abusers can be grouped in three main categories based upon previous drug use: 1) marijuana smokers, 2) occasional drug users seeking to avoid legal complications, and 3) drug-naïve, curious experimenters. The European Monitoring Centre for Drugs and Drug Addiction collected information on patterns of use of spice mostly through Internet fora, where users typically share experiences (EMCDDA, 2009). It was found that spice products are smoked, often in association with marijuana, or consumed orally as an infusion, and that while in Spain users recommend using pipes, in Slovakia they prefer inhaling the fumes of the burning mixture (EMCDDA, 2009).

Most clinical cases report intoxication and serious medical consequences after Spice consumption in male teenagers and, to a lesser extent, in young women (Bryner, 2010; Mir et al., 2011; Schneir et al., 2011; Young et al., 2011; Zimmermann et al., 2009). Other studies have investigated the prevalence of Spice use in college students and concomitant use with other drugs of abuse such as nicotine and marijuana (Hu et al., 2011). Results show that 8% of college students surveyed used Spice, where the majority of college users were first or second year male students. Concurrent use with hookah tobacco (88%), marijuana (91%) or cigarettes (77%) was also prevalent among college students. Also, co-abuse of

Spice and alcohol was observed in 10 out of 11 adolescents (15 – 19 years old) evaluated at the South Miami Hospital Addiction Treatment Center in Miami–Dade County, Florida (Castellanos et al., 2011).

Conclusions and Future Perspectives

Spice drugs have been referred to as “new designer drugs” (Mustata et al., 2009), “a never ending story” (Lindigkeit et al., 2009), “a new trend” (Vardakou et al., 2010), “a case study” (Griffiths et al., 2010), “legal highs” (Zawilska, 2011), and “the new marijuana” (Wells and Ott, 2011). Whatever the name, synthetic cannabinoids are currently among the main players in the recreational drug market and represent a major challenge for health-care professionals as well as public health and law enforcement officials. Internet accessibility of Spice is counteracting the work of law enforcement personnel, while difficulties in discerning the exact composition of each herbal blend and predicting drug effects and toxicity remain a formidable task. Clandestine chemists continually modify chemical structures to create high affinity, potent hybrids that purposely avoid detection and legal consequences (Jankovics et al., 2012; Westphal et al., 2012). Appropriate legislation is necessary to assist in limiting availability as well as efforts to educate local communities, physicians, and those working within the judicial system. Misinformation regarding the use and toxicity of these compounds has led to a generalized belief that synthetic cannabinoids are marijuana-like and safe for consumption; however current data clearly demonstrate the toxic nature of these new drugs of abuse.

The pace at which quasi-legal synthetic cannabinoids are being produced is unprecedented. Since about 2004, products marketed under brand names like K2 or Spice are continually being reformulated with pharmacologically active cannabinoids that avoid regulation and detection in standardized drug tests. Sadly, morbidity and mortality reports continue to increase as these new drugs gain popularity worldwide. The biomedical research response has rapidly achieved several technological advances and is now answering questions regarding safety. This information is leading to better protection of public health, but comprehensive legislation with better educational, deterrent, and monitoring programs are still lacking.

Since most synthetic cannabinoids are not currently found using routine toxicology screening tests, health care providers, especially those working in emergency care settings, should be constantly on alert for K2 drug-induced toxicity despite negative drug-screening results. Limited data are currently available on the pharmacodynamics and pharmacokinetics of synthetic cannabinoids. While it is widely known that most Spice drugs are potent CB1 agonists, exact molecular mechanisms underlying their toxic effects remain to be determined. These compounds and their metabolites have been found to possess higher binding affinity for cannabinoid receptors than marijuana, which implies greater potency, greater adverse effects, and perhaps a longer duration of action. Clearly, Spice is not a safe alternative to marijuana. The wide abuse of Spice highlights the urgent need for further evaluating the synthetic cannabinoids effects *in vivo* to: (1) improve our understanding of how these compounds interact with cannabinoid and non-cannabinoid receptors in both the brain and periphery, (2) better characterize the pharmacology and toxicology, (3) properly delineate drug scheduling and legislation, (4) develop treatments for intoxication, and (5) implement effective deterrents like workplace and athletic monitoring programs.

Acknowledgments

This work was supported by the Association of Public Health Laboratories [Grant Innovations in Quality Public health Laboratory Practice] (JHM), the Centers for Disease Control [Contract 200-2007-21729] (JHM), and an

award from the University of Arkansas for Medical Sciences Translational Research Institute, which is funded by the National Center for Research Resources [1 UL 1RR029884, Curtis Lowery, PI].

The authors would like to thank Gregory Endres and Tracey Barraco from Cayman Chemical Company (Ann Arbor, Michigan) for assisting in the development of graphics. Technical reviews provided by Drs. Paul Prather and Nathaniel Smith are also greatly appreciated.

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Figure 1.
Representative packaging and herbal material typically found within (A) Spice and (B) K2 products. (C) An example of deceptive language typically used on Spice labels to indicate 'not for human consumption' and the absence of controlled synthetic cannabinoids.

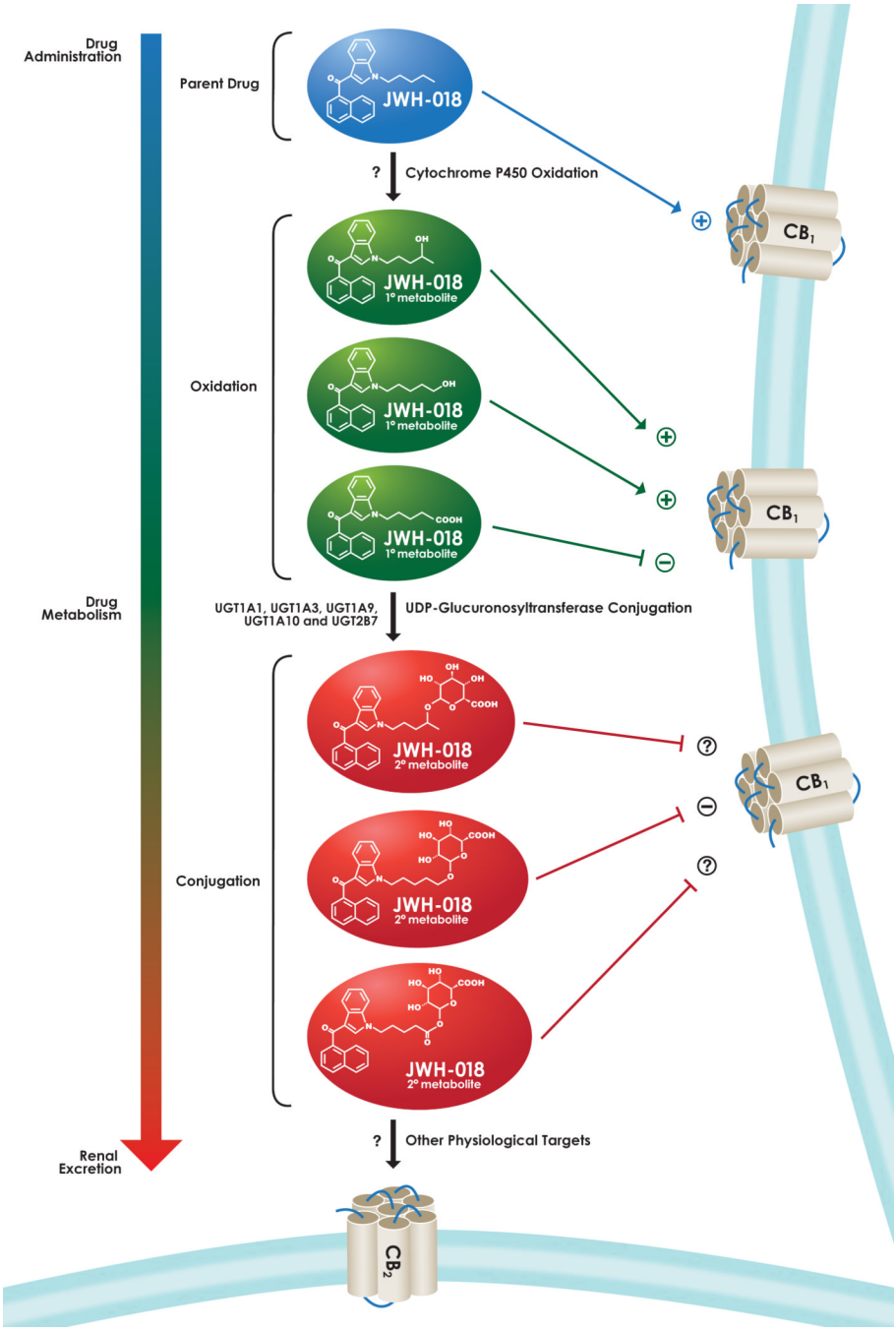

Figure 2.

A schematic representation that summarizes what is known about JWH-018 metabolism, excretion and potential downstream interactions with CB1 receptors and other physiological targets, like CB2 receptors. “+” indicates agonism, “−” indicates antagonism, “X” indicates no binding affinity, “?” indicates not known.

Table 1

Spice Induced Adverse Clinical Effects

CENTRAL EFFECTS	
Psychosis	Acute exacerbation of cannabis-induced recurrent psychotic episodes *(Müller et al., 2010)* Enhanced risk of psychosis relapse in vulnerable individuals (*Every-Palmer, 2010, 2011)* New-onset psychosis in otherwise healthy young men (*Hurst et al., 2011)*
Seizures	Seizure activity approximately 1h after smoking "SpicyXXX" (*Simmons et al., 2011)* Generalized seizure in a healthy 48 years old man within 30min after ingesting a spice mixture purchased from the Internet (*Lapoint et al., 2011)* Witnessed generalized convulsions *(Schneir & Baumbacher, 2012)*
Anxiety	Occurrence of anxiety shortly after smoking "Banana Cream Nuke" *(Schneir et al., 2010)* Frequent anxiety in 15–19 years old boys consuming synthetic cannabinoids *(Castellanos et al., 2011)* Self-reports of users experiencing anxiety after injection of "Aroma" (*Every-Palmer, 2010, 2011)*
Agitation	Reported to Texas poison centers by 20–23 years old patients following exposure to synthetic cannabinoids (*Forrester et al., 2011)*
Irritability	Reported to South Miami Hospital Addiction Treatment Center by 15–19 years old individuals who smoked Spice or K2 *(Castellanos et al., 2011)*
Memory changes	Reported by all smokers evaluated at the South Miami Hospital Addiction Treatment Center *(Castellanos et al., 2011)*
Sedation	Detected in a 21 yrs old man an unknown time after smoking spice *(Simmons et al., 2011)*
Confusion	Detected in a 27 yrs old man 1h after smoking SpicyXXX *(Simmons et al., 2011)*
CARDIOVASCULAR EFFECTS	
Tachycardia	A common clinical feature in 21–27 yrs old patients smoking SpicyXXX and other spice products *(Forrester et al., 2011; Simmons et al., 2011)*
Tachyarrhythmia	Detected in a healthy 48 years old man 30min after ingesting an ethanol mixture containing a white powder he purchased from the Internet *(Lapoint et al., 2011)*
Cardiotoxicity	Chest pain, tachycardia, and bradycardia occurred in a 17 years old boy after smoking K9 *(Young et al., 2011)*
Chest pain	Three 16 years old boys complained of chest pain within days after using K2 *(Mir et al., 2011)*
GASTROINTESTINAL EFFECTS	
Nausea	Along with agitation, tachycardia, drowsiness, vomiting, and hallucinations, nausea was frequently reported after synthetic cannabinoid exposure *(Forrester et al., 2011)*
Vomiting	Described in a 19 years old healthy boy along with a generalized 1–2min convulsion while smoking "Happy Tiger Incense" *(Schneir & Baumbacher, 2012)*
OTHER EFFECTS	
Somnolence, Dilated Pupils, Brisk Reflexes, Emesis	All common clinical features in 21–27 years old patients smoking SpicyXXX *(Simmons et al., 2011)*
Appetite Changes	Opposite changes have been reported, patients reporting both decreased and increased appetite *(Castellanos et al., 2011)*
Tolerance, Withdrawal & Drug Dependence	Tolerance developed in a 20 years old boy after smoking "Spice Gold" daily for 8 months; during abstinence, he reported inner unrest, craving, nocturnal nightmares, copious sweating, headache, nausea, and tremor *(Zimmermann et al., 2009)*