

“Spice” and “K2” Herbal Highs: A Case Series and Systematic Review of the Clinical Effects and Biopsychosocial Implications of Synthetic Cannabinoid Use in Humans

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Cannabis, the most commonly used illicit substance, exerts its primary psychoactive effect via delta-9 tetrahydrocannabinol (Δ^9 -THC) agonism of cannabinoid receptor type 1 (CB1). Some users develop a cannabis use disorder and physical dependence manifested by withdrawal symptoms during abstinence. Hence, there is growing public health concern about increasing use of a new generation of synthetic cannabinoid (SC) agonists (eg, JWH-018, CP 47,497) marketed as natural herbal incense mixtures under brand names such as “Spice” and “K2.” Anecdotal reports suggest overlapping effects with marijuana when the mixtures are smoked, however, systematic evaluation of SC-related psychoactive properties and adverse effects is lacking. We conducted a systematic review of published reports on SC clinical effects in humans. Most highlight potential toxicity such as acute anxiety and psychosis. In addition, we carefully document three cases in which experienced marijuana users meeting criteria for cannabis dependence with physiologic dependence smoked SC products regularly. The SC mixture effects were reportedly similar to marijuana and well tolerated. The individuals all reported that SC product use effectively alleviated cannabis withdrawal. Biopsychosocial factors associated with SC initiation and usage by the cases help to shed light on psychopharmacologic, clinical, and public health aspects of SC product consumption. (Am J Addict 2012;21:320–326)

INTRODUCTION

Cannabis is the most commonly used illicit substance in the world.¹ Initiation often occurs among young individuals (ie, < 18 years old), and although most users do not develop problems related to their use, a substantial minority meet criteria for a cannabis use disorder.² In some cases, these disorders are associated with an abstinence syndrome upon cessation of drug use (for review, see Budney et al. 2004).³ Cannabis withdrawal symptoms such as irritability, anxiety, sleep disruptions, aches and pains, among others can be quite unpleasant.³ A growing database demonstrates that administration of delta-9 tetrahydrocannabinol (Δ^9 -THC), the major psychoactive component of cannabis, attenuates cannabis withdrawal symptoms.⁴ This observation underscores the pharmacological specificity of the cannabis abstinence syndrome.⁴

Recently, a new generation of synthetic cannabinoid (SC) agonists has been reported to be used recreationally, especially by teens and young adults.^{5,6} The products are marketed as natural herbal incense or potpourri under various brand names such as “Spice” or “K2,” and have been sold legally in “head shops,” convenience stores, and through the Internet to those seeking the “cannabis high.” The poorly labeled contents have been found to include a mixture of psychoactively inert herbs and aromatic extracts sprayed with SC compounds.^{7–9} The compound that has generated the most interest, JWH-018, was developed by chemist John W. Huffman (JWH) at Clemson University, USA.⁷ Other cannabinomimetic compounds detected in Spice-type products in the United States, Europe, and Japan include SCs developed for research purposes

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such as CP 47,497 and cannabicyclohexanol, which were originally synthesized by Pfizer, as well as JWH-073, JWH-250, HU-210, and the fatty acid, oleamide.^{5,9–14}

Although anecdotal reports indicate that smoked inhalation of SC-containing mixtures produces psychoactive effects overlapping with those of cannabis,^{7,10,15} SC compounds have not been systematically studied in humans. Thus, the veracity of these claims is uncertain. Indeed, there is concern that SCs may exert deleterious effects on human health. Relative to Δ^9 -THC, the synthetic compounds are more potent and efficacious agonists,^{5,16} which could lead to greater cannabinomimetic toxicity.⁷ Marijuana, the most frequently used cannabis agent, contains over 60 identified natural cannabinoids that may modulate Δ^9 -THC-related effects, including negative ones.^{16,17} Anecdotal case reports and increasing calls to poison control centers suggest potential adverse effects of SC exposure such as anxiety, tachycardia, and psychosis, which coupled with the abuse potential of the substances, recently led to Drug Enforcement Agency (DEA) control of several SCs under the Controlled Substances Act.¹⁸ However, to date no systematic epidemiologic surveillance or comprehensive pharmacological assessment has taken place in humans to inform questions about the pharmacological effects and tolerability of these compounds.

In this report, we present the cases of three SC users who came to our attention during clinical care or participation in a human laboratory study examining medication development for cannabis use disorders. All patients met criteria for cannabis dependence and reported that SC use alleviated symptoms of cannabis withdrawal. To our knowledge, this is the first report to provide suggestive evidence that SC can mitigate symptoms associated with the cannabis abstinence syndrome and further demonstrate the pharmacological specificity of cannabis withdrawal. In addition, given the emerging public health issue of SCs, we systematically reviewed the existing literature on SC agonist-containing herbal blends to examine potential clinical effects and biopsychosocial correlates of initiation and usage. These issues are discussed in the context of the cases to shed light on clinical and public health concerns regarding use of SC products.

METHODS

The three consecutive cases were identified between August 2010 and September 2010 at the University of Virginia (UVA) in Charlottesville. Case 1 was evaluated in primary care and Cases 2 and Case 3 were assessed during participation in an inpatient residential laboratory study examining medication development for cannabis dependence (NCT01204723). All three patients underwent a clinical interview by a physician (EWG) and were determined to meet DSM-IV-TR criteria for cannabis dependence (with physiological dependence). The findings are reported using an

age estimate and without identifying information to protect case identity.

In conducting the literature review, English language studies were identified from the MEDLINE (PubMed) and PsychINFO databases through May 14, 2011 using medical subject headings “cannabinoids,” “humans,” and “Receptor, Cannabinoid, CB1/agonists.” Additional text words were also searched including, “Spice cannabinoid,” “K2,” “synthetic,” “JWH-018,” “CP 47,497,” “JWH-250,” and “JWH-073.” Only peer-reviewed publications that involved SC product or compound administration in humans were considered for the review. Two reviewers (EWG and ASJ) conducted an initial review of titles and abstracts of the electronic searches followed by more detailed assessment of relevant articles and examination of bibliographies of related reviews to find other sources. For studies presenting findings with the same or overlapping cohort, the most comprehensive sample was selected so as not to present duplicate data. The available studies presenting clinical effects of SC compounds were summarized qualitatively and findings discussed in the context of the current case series. Given the lack of peer-reviewed published information on this topic, an Internet search with Google was performed using similar terms to obtain governmental, poison control, health system, and media news releases and reports. The UVA Institutional Review Board exempted the case series from review.

RESULTS

Nine articles (summarized in Table 1) reported SC effects in humans, including five case reports of toxicity,^{19–23} a semistructured patient interview among inpatients on a forensic and rehabilitative psychiatric unit,²⁴ and three human toxicology laboratory studies evaluating SC detection in serum and urine samples.^{10,25,26} Although two of the three laboratory studies administered commercial SC product samples in a laboratory setting,^{10,25} they did not systematically report clinical effects with subjective psychoactive or psychomotor/cognitive performance measurements. Four studies confirmed specific SC compound ingestion through either testing of the commercial product that was smoked or through detection in serum/urine samples.^{10,23,25,26} JWH-018 was in all four samples, along with CP 47,497 (two samples), and JWH-073 (one sample).

The nine studies suggest a cannabis-like effect after smoking SC products, including alteration in mood, perception, conjunctival injection, xerostomia, and increased pulse. Use may be complicated by more severe adverse effects including acute anxiety and psychotic reactions, particularly in those with an underlying biologic vulnerability.^{19–21,24} Other associated effects reported in these studies, as well as in calls to Poison Control Centers^{27,28} and National Drug Intelligence Center surveillance,⁶ include hypertension, hyperventilation, diaphoresis, numbness and

TABLE 1. A systematic review of published studies reporting clinical effects of synthetic cannabinoids in humans

Reference	N	Product (SC)	Amount smoked	Study type	Patient characteristic	Effects
Zimmerman et al., 2009 ¹⁸	1	Spice Gold (JWH-018, CP 47,497)	3 g/day (chronic use)	Case report	20 M with untreated ADHD	DSM-IV/ICD-10 dependence with tolerance and withdrawal that started on Day 2 of abstinence with: cognitive impairment; craving; diaphoresis; nausea; diarrhea; tremor; headache; internal unrest; insomnia; nightmares; depressed mood; palpitations; mild sustained hypertension and tachycardia (blood pressure 140/85–90 and pulse 95–100). Psychosis with paranoid and imperative voice hallucinations; anxiety.
Müller et al., 2010 ²⁰	1	Spice (JWH-018, CP 47,497)	3 g	Case report	25 M prior cannabis-induced psychosis	
Müller et al., 2010 ²¹	1	Spice (JWH-018, CP 47,497)	400 m	Case report	21 M with treated ADHD	Panic attack; anxiety; blurred vision; unsteady gait; fear; diaphoresis; irritability; weakness; palpitations; tachycardia. The panic attack lasted approximately 2 hours. Persistent anxiety resolved after lorazepam.
Vearrier and Osterhoudt, 2010 ²²	1	JWH-018 “Pure” product purchased online	One “bong hit”	Case report	17 F	Agitation; visual hallucinations; anxiety; tachycardia (pulse 120), mild blood pressure increase (135/85); occasional muscle fasciculations; hypokalemia (2.9 mEq/L). Given lorazepam and effects resolved after 2 hours.
Schneir et al., 2011 ²³	2	Banana Cream Nuke (JWH-018, JWH-073)*	0.5 g	Case report	20F, 22F	Anxiety; disoriented; injected conjunctiva; tachycardia (pulse 126 in one case); palpitations and a few beats of lateral gaze nystagmus (one case.) Effects resolved after 2 hours.
Every-Palmer, 2011 ²⁴	15	Aroma (JWH-018; oleamide)	Not reported	Semistructured interview	Mean age 34 years, all male with prior psychotic illness	All used as a cannabis substitute. Adverse effects included: psychosis (69%); anxiety (15%); tolerance (23%). None reported physical dependence. Acute effects lasted about 2 hours, with the psychotic reaction lasting 2 days to several weeks.

(Continued)

TABLE 1. Continued

Reference	N	Product (SC)	Amount smoked	Study type	Patient characteristic	Effects
Auwarter et al., ²⁰⁰⁹ ¹⁰	2	Spice Diamond (JWH-018; CP 47,497 derivative)*	0.3 g	Human lab toxicology study	Investigator self-experiment	Performance and subjective effects measurements not reported, however, noted effects were: altered mood/perception; injected conjunctiva; increased pulse; xerostomia. Acute effects lasted about 6 hours, with mild, nonspecified residual next-day effects.
Teske et al.; ²⁰¹⁰ ²⁵	2	Smoke (JWH-018, 2.9% potency)*	100–150 g (50 µg per kg)	Human lab toxicology study	33 F, 47 M	Sedation; "sickness," xerostomia; hot flushes; burning eyes; "thought disruption;" increased pulse, no change in BP followed by residual tiredness lasting 6–12 hours.
Sobolevsky et al., ²⁰¹⁰ ²⁶	3	Tropical Synergy (JWH-018, CP 49,497)*	1 g	Human lab toxicology study [†]	Mean age 22 ± 1 year (2 male, 1 female)	Anxiety; paranoia; hallucinations; short-term memory defect; impaired sense of time; injected conjunctiva; tachycardia.

SC = synthetic cannabinoid(s) confirmed or suspected of being in the brand name product based on regional product testing. *Confirmed SC compound based on direct testing of the product consumed or by urine/serum analysis. [†]Uncontrolled administration outside of the laboratory. †Primary metabolites were assessed in forensic samples seized by police during acute drug intoxication.

tingling, nausea, vomiting, tremors, muscle twitching, and seizures. Most acute effects dissipate approximately 2 hours postingestion; however, it remains unclear whether there are more prolonged residual effects of consumption.

CASE PRESENTATIONS

Case 1 is an approximately 30-year-old male with a 10-year history of marijuana use. He reported numerous unsuccessful attempts to discontinue marijuana use in the past year, in part, because of physical dependence. On the initial day of abstinence, he experienced typical withdrawal symptoms including irritability, dysphoria, poor sleep, and anxiety.²⁹ He reported smoking approximately 1–2 g/day of low-grade, seeded marijuana with an approximate street price of \$25 per 7 g. He initiated Spice in June 2010 to find a replacement for marijuana given concern about possible court-mandated drug testing. He had heard anecdotes and read online that Spice use resulted in a marijuana-like high but was undetected by commercially available urine toxicological screens. He was also motivated to avoid marijuana abstinence symptoms. During initial use, he purchased a 3 g bag of Spice, which he mixed in a 50:50 ratio with marijuana. For approximately 3–4 days, he smoked the mixture, and then transitioned to pure Spice. With this approach, he did not experience any marijuana withdrawal symptoms and also noted that Spice-only use resulted in similar psychoactive effects as marijuana. Other SC brands included Spice Diamond, XXX, K2, K2-Blond, Black Box, and Smoke 'n' Skulls (price range \$30–40 per 3g).

Despite ongoing concern about court-mandated toxicology testing, he continued marijuana use because of excessive cost of the SC products relative to marijuana, which for him at the time was free and unlimited in supply. Between July 2010 and August 2010, he smoked approximately 3 g of SC products every other week. He no longer used the 50:50 crossover approach and started abruptly transitioning between marijuana and SC products. Three grams of SC products would last approximately 3–4 days, then he would switch back to marijuana. He did not report withdrawal symptoms during abrupt transition between marijuana and SC products. Around September 2010, he lost access to free unlimited marijuana and subsequently increased SC product use to 3 g or more per week. He only smoked SC products in a "bowl" and described the psychotropic effects as similar to marijuana regarding onset and duration of action. However, he felt that the SC mixtures were twice as potent by weight compared to the low quality marijuana he usually smoked. The only adverse effect he reported from SC use was a productive cough that did not occur with marijuana. He denied constitutional complaints and pulmonary exam was clear.

Case 2 is an approximately 25-year-old male with an 8-year history of marijuana use. His typically smoked blunts (a mixture of marijuana and tobacco), consuming an ounce

per week of mid-grade marijuana with few seeds and costing approximately \$50 per 7g. If he did not smoke marijuana, he experienced a withdrawal syndrome beginning on the initial day of abstinence that primarily manifested as irritability. Unlike Case 1, he was not attempting to decrease or stop marijuana use. He initiated SC product use in May 2010 seeking a novel high. He initially smoked various SC products during consecutive weekends (\$40/3 g over 2–3 days). Brands included Spice Gold, Zombie, 2010, Bee Stinger, and Black Mamba. He smoked only by flavored blunt either alone or combined with marijuana. He noted no irritability of marijuana withdrawal during days in which he smoked only SC products without concurrent marijuana use. He described the “same feeling” as marijuana, with equally rapid onset, possibly shorter duration, but an “extreme high” that he likened to high quality marijuana. He reported no adverse effects other than dislike of SC product taste, which was the reason for smoking by flavored blunt. Initially, he used Spice regularly for 2–3 months to “try all the kinds,” noting that the herbal products are marketed like a drug dealer markets numerous marijuana strains. In July 2010, he decreased regular use to 3 g every 2–3 months as the novelty wore off and as he became concerned about nonspecific anecdotes of potential harm.

Case 3 is an approximately 20-year-old male with a 4-year history of marijuana use. He typically smoked at least 7 g/week (\$50) of mid-grade marijuana via blunt or bowl. He was not attempting to decrease or stop marijuana use and experienced a withdrawal syndrome beginning on the initial day of abstinence that included irritability and cravings. He initiated SC product use in May 2010. During the initial months, he smoked SC products primarily mixed with marijuana to get a “combined effect,” noting greater “elevation” compared to either substance alone. He had only smoked SC products in a blunt. From May–August 2010 he spent approximately \$25–30 every 2 days on SC products but cut back in September solely because of cost. Brands included those mentioned above and also Blueberry (\$30–40/3 g). Around October it became more difficult to obtain marijuana because of lack of marijuana selling contacts in his new rural residence. He noted that SC product use alleviated the irritability and cravings of marijuana abstinence. Avoidance of marijuana withdrawal became the primary motivator for current use of SC products, which were readily available. In addition, when smoking SC products alone, he described similar high quality as marijuana but of shorter duration of action and faster onset. He did not report any adverse effects of SC product use.

DISCUSSION

The case series illustrates several pharmacological, clinical, and public health issues surrounding recent increased usage of SC-containing herbal products. All patients were

regular marijuana smokers meeting DSM-IV-TR cannabis dependence criteria. Use of SC products alone or in combination with marijuana resulted in similar subjective effects as marijuana alone (eg, euphoria). Variation between cases in the degree, onset, and duration of high from SC products could reflect differences in baseline tolerance and also varying amounts and types of SC compounds in the herbal preparations.^{9,13} Notably, all three individuals reported physical dependence on marijuana and experienced an attenuation or a lack of marijuana-related withdrawal by smoking SC preparations, which is consistent with evidence demonstrating Δ^9 -THC administration substantially assuages withdrawal symptoms.^{29,30} To our knowledge, these are the first reported cases suggesting cross-tolerance in which SC products substitute for marijuana to relieve withdrawal. Given the pharmacological specificity of marijuana withdrawal and that THC mediates its effect by CB1 neuronal activation, the cases provide novel *in vivo* suggestion of SC bioactivity via CB1 receptor agonism in humans. Of course, given the uncontrolled nature of case reports, carefully controlled studies of SC in humans are needed to confirm these results and further characterize the psychopharmacological effects.

Given the considerable overlapping effects of SC products and marijuana observed in this case series here, an important implication is that clinicians who treat cannabis use disorders should also assess patients for use of SC products. Development of urine toxicology assays for SC metabolites is under way,²⁶ but unfortunately routine laboratory testing for SCs is not readily available. Because of a distinct molecular structure that is different from THC metabolites, SC use will be undetected by laboratory assays for marijuana use even in heavy users.^{10,19} Case 1 initiated SC use because of concern that court-mandated toxicology testing would detect his marijuana use. Such rationale for SC usage is reported among other populations in the United States⁶ and Europe⁵ and raises concern about clinical monitoring.

Demographically, the cases are young adults with recent SC product initiation, which reflects the burgeoning US trend indicated by an alarming rise in calls to poison control centers nationally²⁷ and observation by law enforcement officials.⁶ Although a detailed review of poison control cases and adverse effects has yet to be published, there were 2,304 calls from 49 states and the District of Columbia as of November 22, 2010 according to the American Association of Poison Control Centers' National Poison Data System (NPDS).²⁷ In contrast, only 13 calls were received for all of 2009.³¹ This represents a nearly 200-fold increase in calls to poison control from 2009 to 2010, potentially reflecting growing use. In comparison, there were 4,009 case mentions of marijuana during calls to poison control centers in 2008, of which 1,020 were single exposures to marijuana alone.³² Unfortunately, the lack of prevalence data on SC product use precludes speculation about relative toxicity compared to marijuana.

SC product use was psychoactively well tolerated by the three cases in contrast to anecdotal reports collated in Table 1 suggesting potential acute anxiety reactions, agitation, psychosis, paranoia, and cognitive impairment.^{6,15,19,20,22,24,27,28} Other reported associated effects have included nausea, hyperventilation, diaphoresis, pallor, headache, numbness, seizures, muscle twitching, and autonomic hyperactivity. Some of these adverse effects are incongruent with those typically associated with acute effects of Δ^9 -THC (eg, hypertension, hyperventilation, nausea, vomiting, seizures) and rather than a direct result of SC agonism, could be secondary to an acute anxiety reaction or cross contamination from concomitant use of other drugs as well. The only reported adverse effect among our cases was medical in nature and included acute onset of productive cough during periods of SC product use. Similar pulmonary complaints are associated with chronic marijuana use.³³ However, the pulmonary risk of SC inhalation along with burned unidentified plant materials in the herbal mixtures remains unknown. This has led to recommendation for vaporization as a preferable delivery method of the volatile SCs without concomitant burned plant material.^{34,35} Although numerous “legal weed” vaporizers are listed for sale online, vaporization of SC preparations has not been tested in a controlled research environment. Further study remains needed to examine potential adverse health effects of SC use.

The cases provide insight into potential biopsychosocial correlates of initiation and persistent use, such as the use of SC products concurrently with marijuana by Case 3 to maximize the high, whereas Case 2 decreased use over time because of concern about health risk. Case 2 also noted the impact of marketing that drew him in initially to try numerous brands. The herbal product marketing approach includes conspicuous packaging with psychedelic art, catchy names, and diverse branding. Cost and accessibility of SC product and marijuana were a common consideration for all cases. Specific brand-name products (eg, Spice) and SC compounds have undergone increased prohibition during the last 2 years across much of Europe where the Spice phenomenon began several years earlier than the United States. In the United States, approximately 15 states enacted prohibitory policy regarding either brand-name products or specific SC ingredients. In addition, the DEA recently placed five SCs under temporary control on March 1, 2011 (JWH-018, JWH-073, JWH-200, CP 47,497, and cannabicyclohexanol), which will federally prohibit sale and possession for at least 1 year.¹⁸

Efforts to control SC consumption in Europe and the United States are understandable given our lack of empirical knowledge about the effects of these products in humans. Yet the products remain accessible in Europe via the Internet where they are sold without age restriction and with limited or no control.³⁶⁻³⁹ In addition, with over a hundred potential SCs to choose from,⁵ manufacturers have already demonstrated remarkable flexibility to alter

the psychoactive components to evade regulation.^{11,13} Importantly the DEA and US Department of Health and Human Services are mandated to study whether SCs merit permanent control,¹⁸ which hopefully will generate epidemiologic and public health data on usage and access. Because available evidence on SC effects remains largely anecdotal, further study is also clearly needed to understand the psychopharmacology and health effects.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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