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Psychosis and synthetic cannabinoids

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ABSTRACT

Synthetic cannabinoid (SC) products have gained popularity as abused drugs over the past decade in many countries. The SCs broadly impact psychological state (e.g., mood, suicidal thoughts and psychosis) and physiological functions (e.g., cardiovascular, gastrointestinal and urinary). This review is about the effects of SCs on psychotic symptoms in clinical settings and the potentially relevant chemistry and mechanisms of action for SCs. Induction of psychotic symptoms after consuming SC products were reported, including new-onset psychosis and psychotic relapses. The role of SCs in psychosis is more complex than any single chemical component might explain, and these effects may not be a simple extension of the typical effects of cannabis or natural cannabinoids.

1. Introduction

Synthetic cannabinoid (SC) products are “herbal” mixtures laced with various SCs and sold around the world under a variety of brand names such as Spice, K2, and Kush. Available in Europe since around 2004 (Advisory Council on the Misuse of Drugs, 2014), it wasn't until 2008 that the psychoactive SC, JWH-018, was first reported in the “herbal” blend Spice in the United States (The White House, 2018). These products are typically smoked or inhaled, producing a cannabis-like high; however, unlike cannabis, SCs are not detected by common drug screens (Piggee, 2009). Further, distinguishing it from cannabis are the numerous reports of adverse events associated with SC use. In response to increasing adverse event reports, many countries have imposed bans on SC products in an effort to reduce harm. For example, the United States Drug Enforcement Administration (DEA) first placed five common SCs homologues (JWH-018, JWH-073, JWH-200, CP-47,497, and CP-47,497 C8) into Schedule I controlled substances in 2011. Despite periodic additions to this list, there are over 70 known SCs that are not specifically listed as Schedule I controlled substances by the DEA. To bypass regulations, manufacturers have made minor changes to the chemical compounds to synthesize new products, making detection and use of these substances difficult to monitor, prohibit, and prevent. Thus, despite regulatory bans, SCs are the largest, most diversified and fastest growing of new psychoactive substances on the market (United Nations Office on Drugs and Crime, 2015), with North America accounting for the highest amount seized in 2014 (United Nations Office on Drugs and Crime, 2016).

Both SCs and the main psychoactive constituent of cannabis, delta-9-tetrahydrocannabinol (Δ9-THC) activate cannabinoid-1 receptors (CB1Rs), underlying their psychotomimetic effects. There has been speculation that the unpredictable and adverse effects of SCs stem from their higher affinity for and increased efficacy at CB1Rs, compared to Δ9-THC. Furthermore, the connection between Δ9-THC and psychosis has been explored for decades, while the connection between SCs and psychosis is in its infancy. What evidence is there? First, we discuss the prevalence of SC use. We then discuss factors associated with their use such as the chemistry of SCs, their mechanisms of action, and the role genetics may play in the psychoses produced by SCs. Finally, we focus on the psychotic effects of SC use.

2. Methods

PubMed and Scopus (all databases) first were searched for articles up to June 2017 to find articles that included the terms ‘synthetic cannabinoid’, ‘spice’, ‘K2’, ‘psychosis’, and ‘schizophrenia’ in the title, abstract, or keywords. The search resulted in 105 articles from PubMed and 165 articles from Scopus. The reference lists of identified studies also were cross-checked to be more comprehensive. Subsequently we excluded reviews, book chapters, irrelevant articles, studies using animal models, and articles published in languages other than English, which resulted in 42 articles (Tables 1–4). No relevant controlled clinical studies are included in this review, since to our knowledge, no

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Table 1
Case studies reporting first-onset psychosis induced by SCs in patients without previous history of psychosis.

Reference	N	Age (years); Race; Sex; Location	Psychotic history	Product used	Psychotic symptoms	Polydrug abuse	Laboratory results	Treatment
Khan et al. (2016)	1	21; African American; M; U.S.	Untreated childhood ADHD	Continuous, heavy use of Kush for the previous 18 months	Catatonia, self-talk, and inappropriate laughter	Occasional cannabis use	UDS was positive for cannabis	Hospitalization; discharged on Aripiprazole Maintena Depot
	1	17; Caucasian; M; U.S.	None	A 2-week Spice binge	Catatonia, delusions	Smoking cannabis periodically for 1 year prior	UDS was negative	Hospitalization; discharged on valproic acid, lorazepam, and olanzapine
Ozer et al. (2016)	1	17; NA; M; Turkey	None	Inhaled "bonsai", a SC product, nearly daily for 10 days before admission	Capgras syndrome, persecutory delusions and AH	Tried volatile substances a couple of times previously	Metabolites of substances which could not be diagnosed in the urine other than SC were negative	Hospitalization; Olanzapine
Roberto et al. (2016)	1	18; African American; M; U.S.	None	K2 and Spice daily for 3–4 weeks	Delusions and disorganized behavior.	Alcohol and cannabis	Blood alcohol was negative; urine toxicology was positive for cannabinoids	Hospitalization; discharged on risperidone
Sönmez and Kösger (2016)	1	31; NA; M; Turkey	None	2 gs of "Bonsai" 3 times a week for 6 months, followed by 6 gs almost daily in the last 6 months	Anger, insomnia, and delusions	None	urine and blood tests results were negative	Hospitalization; discharged on olanzapine
Durand et al. (2015)	1	23; NA; M; U.S.	None	"Mr. Nice Guy", an SC product, sporadically for 6 months. Used it almost daily two weeks before the admission	Visibly psychotic as evidenced by persecutory delusions	Cannabis	UDS was positive for cannabinoids only	Hospitalization (15 days); Haloperidol, valproic acid, and lorazepam
Schwartz et al. (2015)	7	16–30; NA; 3 M & 4 F; U.S.	None	"Crazy Clown", a synthetic incense containing SC	Delirium, psychosis, and aggressive behaviors	Hx of cocaine use (N = 1)	Formula matches to ADB-PINACA or its N-pentanoic acid metabolite were detected in the samples	ICU; intubation (N = 3); No treatment (N = 3); normal saline (N = 1)
Ustundag et al. (2015)	1	18; NA; M; Turkey	None	SC for 6 months	Self-talking and laughing, delusions, and manic symptoms	Volatile substances had begun 4 years before	No remarkable findings	Discharged on Olanzapine, valproic acid, and quetiapine
Haro et al. (2014)	1	18; NA; F; Spain	NA	Spice for at least 6 months	VH and soliloquy	Hx of hashish use	Laboratory analysis of sample substances showed JWH-081, JWH-250, JWH-203, and JWH-019	Aripiprazole, lorazepam, and biperiden
Meijer et al. (2014)	1	26; M; NA; U.S.	ADHD stable with lisdexamfetamine	Smoked "Black Diamond", an SC product	Paranoid delusions	NA	NA	Amputation
Rahmani et al. (2014)	2	17; Caucasian; M; U.S.	Strong family Hx	Spice	Delusions, VH	Cannabis for at least 3 years; recently started LSD, psilocybin, mushrooms, bath salts, & oxycodone	NA	Hospitalization (120 days); discharged on clozapine and metoprolol
		17; Caucasian; M; U.S.	Strong family Hx	Smoked spice frequently and had done so a few nights prior to presentation	Paranoia and disorganized thought process and behaviors	Hx of cannabis, LSD, ecstasy and benzodiazepines	NA	Hospitalization; discharged on clozapine
Smith and Roberts (2014)	1	17; NA; M; U.S.	None	2 to 3 g of K2 daily for 2 months prior to admission	AVH, catatonia and disorganized thought process	NA	UDS positive for cannabinoids	Hospitalization; lorazepam, olanzapine and ECT
Berry–Cabán et al. (2013)	1	20; Hispanic; M; U.S.	None	Spice	Uncommunicative, unable to follow commands, and combative and physical restraints were applied	Alcohol, "plant feeders"	No remarkable findings	Hospitalization (9 days); Risperidone
Chan et al. (2013)	1	21; NA; M; UK	None	6-APB, metabolites of both tetrahydrocannabinol and JWH-122	Agitation and paranoid behavior	6-APB	UDS detected 6-APB and metabolites of the SC receptor agonist JWH-122 and tetrahydrocannabinol	Hospitalization

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