Review

Biological Psychiatry

Synthetic Cannabinoids—Further Evidence Supporting the Relationship Between Cannabinoids and Psychosis

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ABSTRACT

Consumption of synthetic mind-altering compounds, also known as "new psychoactive substances," is increasing globally at an alarming rate. Synthetic cannabinoids (SCs) are among the most commonly used new psychoactive substances. They are usually purchased as marijuana-like drugs, marketed as herbal blends and perceived as risk-free by inexperienced users. Yet, contrary to Δ^9-tetrahydrocannabinol, SCs may lead to severe health consequences, including anxiety, tachycardia, hallucinations, violent behavior, and psychosis. This review focuses on the latest (2010–2015) evidence of psychotic symptoms induced by ingestion of products containing SCs. Reports suggesting that SCs may either exacerbate previously stable psychotic symptoms (in vulnerable individuals) or trigger new-onset psychosis (in individuals with no previous history of psychosis) are reviewed. Pharmacology and toxicology of these compounds are discussed, with particular reference to their psychoactive effects.

Keywords: Herbal blends, Intoxication, Novel psychoactive substances, Psychosis, Spice, Synthetic cannabinoids

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SYNTHETIC CANNABINOIDS: NOVEL PSYCHOACTIVE SUBSTANCES WITH MARIJUANA-LIKE EFFECTS

In the last decade, an increasingly high number of new psychoactive substances used as alternatives to traditional drugs of abuse emerged on the illicit drug market. Among them, synthetic cannabinoids (SCs) represent the largest, most diversified, and fastest growing group (1). Commonly known as "Spice," "K2," or "Kronic," these products are usually sprayed on herbal mixtures, wrapped in foil packets with the indication "not for human consumption" (2), and sold via the Internet as "natural legal" highs, nail polish removers, deodorizers, incense, or potpourri (3). Although marketed as marijuana-like compounds, SCs cause more frequent and severe negative effects than the natural plant they are supposed to mimic (4). The contents and effects of SCs are unpredictable because of the variety of chemicals they contain and a manufacturing process devoid of quality controls and regulations.

Owing to the lack of standardization, even ingredients of the same brand can vary over time and across countries, and the provided ingredient list (if present) is often incomplete, if not purposely misleading. Adolescents account for 40% of users (5). Men are more likely to consume SCs than women (6–9), and many first-time users are experienced marijuana smokers (10). Most users smoke SCs using a water pipe ("bong") or joint and report weekly (or more frequent) use along with the experience of side effects, such as dissociation or paranoia (6). Some individuals smoke SC-based products when unable to obtain marijuana or to alleviate irritability associated with abstinence (11).

REGULATION, CONSUMPTION MOTIVES, AND DETECTION OF SCs

Following identification of the first SCs as the main active (nondeclared) ingredients of an herbal blend called "Spice" (12,13), many countries have taken measures to control diffusion of these products (14). A particularly eventful year was 2011 in terms of legislation of synthetic products. Initially, legislative actions imposed bans on specific substances, adding such substances to the list of controlled substances. To bypass regulation, street manufacturers synthesized and marketed new compounds with minor changes to the chemical composition but with a pharmacologic activity very similar to the banned drugs. Thus, new, previously unknown SCs are constantly appearing on the market, making proliferation and use of these substances difficult to control.

In the United States, the Drug Enforcement Administration first banned SCs in 2011, and the Synthetic Drug Abuse Prevention Act permanently placed other SCs into Schedule I of the Controlled Substances Act in January 2013, as required under the Food and Drug Administration Safety and Innovation Act of 2012 (signed into law by President Barack Obama) (15). Since then, >250 new, uncontrolled compounds have been synthesized to take their place. In 2014, 177 different SCs were reported to the United Nations Office on Drugs and Crime early warning advisory from 58 different countries and territories (1).

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After the first legislative actions taken between 2011 and 2012, the European Monitoring Centre for Drugs and Drug Addiction reported the identification of >20 SCs in 2013 and another 15 in the first 9 months of 2014 (10). The European Drug Emergency Network confirmed an unprecedented growth in the number of intoxications related to the use of novel psychoactive substances, including SCs (16). In some countries, current legislation provides a broader definition of prohibited drugs, not only covering unidentified and unregulated drugs but also targeting entire classes of substances rather than specific molecules. This more general approach has been adopted in the United Kingdom, where all compounds derived from a certain chemical structure are classified as class B drugs.

First-time consumers typically report using SCs for various reasons, such as curiosity, wide availability, easy access, and lower costs compared with marijuana (2). Herbal mixtures containing SCs are described as "natural high" marijuana-like smoking blends and are traded in youth-oriented wrapping under a captivating brand name. Until recently, they were legal and easily accessible in service stations, tobacconists, and online shops, supporting the general perception of SCs being "safe drugs" or "legal marijuana substitutes." SCs are not easily detected in routine blood and urine analyses, making them particularly attractive to individuals undergoing drug testing in the workplace, a substance use treatment program, or criminal justice settings.

In the past few years, great efforts have been made to develop testing strategies able to identify and quantify SCs, including liquid chromatography tandem mass spectrometry and matrix-assisted laser desorption/ionization time of flight mass spectrometry (17–19). More recently, a new enzyme-linked immunosorbent assay urine assay was validated for screening SCs in urine targeting the JWH-018 compound and related analytes (20), whereas gas chromatography–triple quadrupole tandem mass spectrometry has been implemented with electron and chemical ionization for the qualitative identification of many SCs (21). Nonetheless, identification of SCs is still challenging for toxicology, forensic testing, and public health laboratories. To further complicate the screening process, natural agents such as vitamin E are often added to herbal blends to interfere with detection.

BEYOND Δ^9-TETRAHYDROCANNABINOL PHARMACOLOGY: WHY DO SCs INDUCE STRONGER EFFECTS THAN MARIJUANA?

Similar to phytocannabinoids, SCs are highly lipophilic and easily cross the blood-brain barrier (22). Preclinical studies demonstrated a conspicuous overlap in the effects of SCs and Δ^9-tetrahydrocannabinol (THC), including hypomotility, antinociception, catalepsy, hypothermia, and discriminative stimulus properties (23,24). However, SCs induce stronger physiologic and psychoactive effects than THC, such as seizures, collapses, cardiac toxicity, and acute kidney failure (25,26).

This potentiated effect might be due to the fact that THC is a weak, partial agonist of the cannabinoid subtype 1 receptor (CB_1R), whereas SCs act as potent, full agonists at the same receptor. Moreover, THC displays a modest affinity (K_i = 35–80 nmol) at the CB_1R, whereas SCs typically display a higher affinity (K_i = 27–29 nmol), with the highest affinity (K_i = .1 nmol) achieved by the AM-694 compound (27). Similarly, intrinsic activity (i.e., efficacy) at the CB_1R is higher for SCs than for THC (28). When two or more SCs are tested in drug discrimination protocols, the rank order of drug potency parallels affinity to CB_1Rs—that is, compounds with the highest and lowest affinity for CB_1Rs also exhibit the highest and lowest potency in inducing THC-like discriminative stimulus effects, respectively (23,29,30). These effects were antagonized by the selective CB_1R antagonist/inverse agonist rimonabant, demonstrating that the discrimination is CB_1R dependent (31). However, whether the effects of SCs in humans correlate with their binding profiles has not been investigated so far. Similarly, to date, there are no controlled data on the effect of full CB_1R agonism in humans.

Numerous SCs identified in confiscated products display a higher affinity for peripheral cannabinoid subtype 2 receptors (CB_2Rs) than central CB_1Rs (32,33). A comprehensive list of receptor binding affinity and intrinsic activity of the most common SCs at both CB_1Rs and CB_2Rs was published recently (34). Central and peripheral actions of SCs still need to be clarified; however, they were found to interact with other, noncannabinoid receptors and neurotransmission systems (Figure 1). SCs have been shown to 1) stereoselectively inhibit currents through recombinant homo-oligomeric 5-hydroxytryptamine 3 serotonin receptors (35), 2) increase 5-hydroxytryptamine 1A receptor density and messenger RNA expression in the rat hippocampus (36), 3) act as antagonists at the *N*-methyl-D-aspartate receptor (37), 4) inhibit monoamine oxidase activity (38), 5) modulate the function of strychnine-sensitive α1 glycine receptors (39), and 6) affect the functioning of the cytokine network (40). Moreover, the CB_2R agonist JWH-133 increases glutamate uptake (41), whereas MAM-2201 (a new SC recently detected in herbal products) inhibits glutamate release at Purkinje cell synapses via activation of presynaptic CB_1Rs and induces a

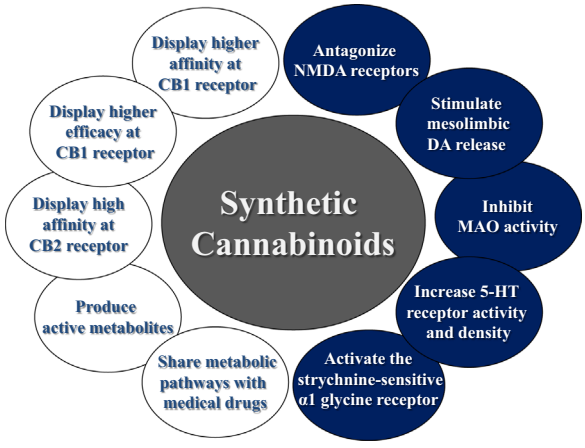

Figure 1. Factors explaining intoxication and psychotropic effects of synthetic cannabinoids with respect to Δ^9-tetrahydrocannabinol (white circles) and their interactions with other (nonendocannabinoid) neurotransmission systems (blue circles). CB1, cannabinoid subtype 1; CB2, cannabinoid subtype 2; DA, dopamine; 5-HT, 5-hydroxytryptamine (serotonin); MAO, monoamine oxidase; NMDA, *N*-methyl-D-aspartate.