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Review

The behavioral profile of spice and synthetic cannabinoids in humans

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ABSTRACT

The use of synthetic cannabinoids (spice) is increasing. The number of descriptions of (new) clinical side effects is also increasing.

We screened relevant publications for articles about spice with a focus on the clinical manifestations of the use of this drug.

Spice creates diffuse psychiatric and somatic effects that are only partially similar to those of natural cannabinoids. Most of the observed effects are related to sympathomimetic-cardiac effects and neuropsychiatric manifestations.

Clinical treatment is primarily based on intensive apparative and laboratory monitoring and supportive therapy.

Because the exact active ingredients of spice are often difficult to determine with standard specific toxicology testing, the assessment and analysis of consumed substances by specialized laboratories is recommended.

Contents

1. Introduction

The use of new psychoactive drugs (NPS) is increasing across Europe. Prominent among these new substances are synthetic cathinones, amphetamine-like substances, such as ketamine, and synthetic cannabinoids, which are the most frequently used across Europe. Misuse of these synthetic cannabinoids is rapidly increasing. Initial descriptions and examinations of the clinical side effects of these substances are occurring in parallel (Jaenicke et al., 2014; Seely et al., 2011; Underwood, 2015; Mobius et al., 2014). In 2012, the lifetime prevalence of spice consumption was 7% among persons aged 15–18, and the 30-day prevalence was 2% (Barratt et al., 2015; Gurdal et al., 2013; Mills et al., 2015).

Names within the drug scene associated with this inhomogeneous group of substances include: spice, spice gold, diamond-spice, chill X, abyss, Pandora's box, exodus, annihilation, fire, smoke, sence, chillX, chillys, highdi's, earth impact, and many more (Kemp et al., 2015). Here, we summarize all of the different names that are most frequently used in the scene under the name spice. To evade legal restrictions, spice is consciously mislabeled as a research chemical, herbal incense or a legal high. Moreover, spice is often labeled with explicit warnings that state that it is not for human consumption and that it is distributed via websites under names such as "garden friends" or herbal cooking websites (Mobius et al., 2014; WHO, 2015; Hall and Degenhardt, 2015; Torjesen, 2015; Di Forti et al., 2014, 2009; Forrester et al., 2012).

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Table 1
Overview of documented clinical side-effects of *spice* (in descending appearance). The five most common symptoms are underlined.

Cardiovascular	Neurological	Neuropsychiatric	Metabolic	Renal	Gastrointestinal	Pulmonary	Muscular	Cutaneous	Ocular
Tachycardia with/ without ECG changesa	Dizziness/ somnolence	Agitation/aggressive behavior/non-compliance regarding treatment	Hyperglycemia	Elevated creatinine	Nausea/vomiting	Dyspnea (unspecific)	CK elevation	Xerostomia	Conjunctival hyperemia
Arterial hypertensiona	Muscle cramps/fasciculation	Hallucinations, psychosis (all senses, ongoing, short)	Hypokalemia	Renal failure	Elevated liver enzymes	Hyperventilation	Myalgia	Diaphoresis	Mydriasis
Bradycardia	Seizures (partial, generalized)	Anxiety/panic attacks	Fever/hyperthermia	Dehydration	Gastritis	–	–	Photosensitivity	–
Cardiac ischemia[a]	Unspecific headache	Suicidal ideations	–	–	–	–	–	–	–
Syncope	Ataxia, tremor, paresthesia	Suicide[a]	–	–	–	–	–	–	–
Chest pain	Stroke (ischemic)	Confusion, delusions	–	–	–	–	–	–	–
Hypotension	Amnesia (anterograde)	–	–	–	–	–	–	–	–

[a] Fatal courses documented.

2. Methods

A keyword-based search of the PubMed database was performed. In addition to the drug-scene associated names, we searched for all content that included: spice, synthetic cannabinoids, legal highs, NPS, spice/drug, herbal highs. A keyword search containing the receptor profile and chemical detection of spice was also conducted. We collected all abstracts and publications related to spice and read them, focusing on the pharmacology, epidemiology, and, in particular, clinical manifestations and side effects of this drug. The references of these publications were also examined for important sources that were not identified by the PubMed search. Overall, 205 publications were screened for use in the preparation of this study on the behavioral profile of spice.

3. Mode of action/receptor profile of spice

Research on the cannabinoid system has revealed several hundred agonists, each displaying varying affinities for cannabinoid (CB-R)-type receptors (CB-1R and CB-2R) and varying potentials for abuse. The active compound of spice was first described in 2009, following the detection of formerly non-declared, synthetic agonists (Auwarter et al., 2009). In addition to the classical CB-R agonist cannabinoids, such as the most common CB-R agonist delta-9-tetrahydrocannabinol (THC) from the Cannabis sativa plant, other synthetic substances that closely resemble THC, such as the approved anti-emetic nabilone and 6aR,7,10,10aR-tetrahydro-1-hydroxy-6,6-dimethyl-6Hdibenzo[b,d]pyran-9-methanol (HU210 cannabinoids), are known.

Among the spice aminoalkylindoles, the JWH series, which was first synthesized by the chemist J.W. Huffmann, contains many CB ligands. Spice itself is subdivided into aminoalkylindoles (including different sub-substances such as JWH-018, JWH-073, JWH-019, and JWH-250) and cyclohexylphenols (including the sub-substances CP-47,497-C6, CP-47,497, and CP-47,497-C8). The above agonists are lipid-soluble and non-polar, typically contain 20–26 carbon atoms, and are fairly volatile. However, these compounds represent only a small selection of synthetic cannabinoids, and some of these compounds have been banned (e.g., JWH-018, JWH-073, and JWH-019) following documentation of their harmful effects on human health (Table 1) (Wiley et al., 2012; Hermanns-Clausen et al., 2013).

The reporting of a new substance and its subsequent characterization and legal regulation requires time; thus, many substances are not yet prohibited, and the consumption of these substances is often semi-legal. Therefore, the substances are not prohibited at the time of consumption because their negative effects on health first have to be documented, which is then followed by extensive characterization procedures before the substance can be covered by legal bans. However, there are at least 100 chemically related substances that are estimated as being similarly psychotropic. These chemically related representatives are not yet restricted by any bans (Forrester et al., 2012; Gunderson, 2013). All known substances are potent, can compete with the cannabinoid CB-R receptor agonists and have receptor affinities that can be 30 (e.g., CP-47,497 and (C8)-CP-47,497) to 500 times stronger (e.g., HU-210) than those of the classical, natural cannabis component Δ9-THC. These compounds all elicit dose-dependent CB-1R activations in the central and peripheral neurons, which create diffuse somatic and psychological effects that are only partially similar to those of cannabis (Gunderson, 2013; Grigoryev et al., 2013, 2012, 2011). In addition to specific cerebral processes, the endocannabinoid system participates in the regulation of the physiological regulation processes, such as caloric balance and the control of arterial smooth muscle tone, and it also regulates immune processes. CB-R1 receptors are primarily found in the nervous system, whereas