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Selected Topics: Toxicology

CURRENT "LEGAL HIGHS"

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□ **Abstract—Background: A growing number of novel substances have been abused as recreational drugs by young people in the United States (US), Europe, and Australia. Called "legal highs," these substances range from plant-based to completely synthetic compounds. Spice, Salvia, mephedrone, methylenedioxypyrovalerone (MDPV), and other cathinone derivatives have psychotropic effects and are marketed for recreational use through exploitation of inadequacies in existing controlled substance laws. Objectives: This article reviews available literature on the most common "legal highs" as well as discussing the scientific basis for the legal difficulties in controlling trafficking in these novel substances. Conclusions: "Legal highs" continue to increase in use in the US, Europe, and Australia. These substances are powerful, can mimic effects of more traditional drugs of abuse, and are intentionally manufactured to circumvent existing controlled substance laws. As controlled substance legislation may be inadequate in the face of the quickly evolving legal highs, physicians are likely to see an increase in the prevalence of legal highs. Published by Elsevier Inc.**

□ **Keywords—mephedrone; bath salts; Spice; synthetic cannabinoids; herbal high; Salvia; Salvinorin A; cathinone derivatives; MDPV; naphyrone; Vanilla Sky; plant food**

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INTRODUCTION

Over the past decade, a growing number of substances have been abused as recreational drugs, primarily by young people, in the United States (US), Europe, and Australia. So-called "legal highs" are substances with psychotropic effects that are intentionally marketed and distributed for recreational use by exploiting inadequacies of existing controlled substance legislation. The speed at which novel compounds are being introduced and subsequently modified by drug designers to avoid detection or legal scrutiny, has left scientific and legislative communities participating in a cat-and-mouse legislative and public health game that seems to have no foreseeable resolution. As compared to traditional psychotropics of abuse (e.g., cocaine, phencyclidine, opiates), little information exists in the medical literature concerning this rapidly emerging class of recreational drugs. The sheer number of substances marketed as legal highs, as well as the speed at which they are developed and modified by drug designers, complicates a truly comprehensive review of currently circulating compounds. This review instead focuses on the most widely used and high-media-profile legal highs that have appeared

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in popular culture and in Emergency Departments (EDs) over the past several years.

DISCUSSION

Spice and Synthetic Cannabinoids

"Spice" is the generic term used to encompass a variety of herbal products (SPICE, K2, Genie, Yucatan Fire) with purported marijuana-like effects marketed online and in specialty "head shops" since 2004 (1). Most Spice products contain synthetic cannabinoids intentionally added to the herbal mixture; they, rather than the constituent herbal blend itself, are responsible for the psychotropic effects (2,3). SPICE quickly became the most popular and recognizable of these herbal products, and the term "Spice" is now generally applied to all products containing synthetic cannabinoids regardless of branding. A large number of psychoactive compounds found in Spice are the result of the abuse of work performed by Dr. John William Huffman, whose research group developed over 400 synthetic cannabinoids (4). Until December 2010, many of these synthetic cannabinoids circumvented scheduling by the US Drug Enforcement Administration (DEA), and Spice products were legal to purchase, possess, and distribute (5). The name "SPICE," and the product's logo of a stylized, exotic open eye, are believed to be references to the fictional substance "Melange" described in Frank Herbert's 1965 science fiction classic *Dune* (1).

Spice use in the US dramatically increased in 2010 (6,7). In 2009, Poison Control Centers from 41 states reported a total of 13 calls related to Spice; in 2010 a total of 2906 calls were received; and in 2011 the number increased to 6959 (8). EDs have reported similar increases in cases over the same time period (7). Observations of Internet forums and online gaming communities identify adolescents and young adults as composing the majority of Spice users (3). A 2011 Office of Drug Control Policy publication reported the 1-year prevalence of Spice use by 12th graders at 11.4%, making Spice the second-most used illicit substance by 12th graders behind marijuana (9). A desire to get "high" as well as the inability of commercial drug tests to identify Spice are most often cited by individuals as motivations for use (3). Although there exists commercially available testing to detect metabolites of some cannabinoids previously reported in Spice, current formulations are unlikely to contain these specific cannabinoids, rendering such testing obsolete (10). As a result of these testing difficulties, Spice has particularly appealed to illicit users in law enforcement, fire fighting, the Armed Forces, and other communities that are subject to regular drug testing (11).

The synthetic cannabinoids found in Spice likely evoke a physiologic response similar to tetrahydrocannabinol (THC), the psychoactive substance in marijuana (12). Pharmacodynamic testing of compounds similar to those found in some Spice blends demonstrates cannabinoid receptor affinity ranging from several multiples to several orders of magnitude greater than the affinity of THC found in natural growing marijuana (13).

Inhalation is the most common method of Spice intake. Effects as described by users suggest a state of intoxication comparable to that achieved with marijuana use (5). Within 10 min of inhaling a 0.3-g dose, users demonstrate mild to moderate cognitive impairment, as well as changes in perception and mood (14). Objective findings after inhalation include scleral injection, tachycardia, xerostomia, and increased appetite (14). Effects gradually diminish over 6 h (14). Spice is relatively inexpensive, as products retail for approximately 10–20 US dollars per gram (4,6). Little to no toxicology information pertaining to the particular synthetic cannabinoids found in Spice exists in the literature, and to date, in vivo testing has been limited to metabolite detection. Case reports have documented such adverse effects as Spice dependence, Spice withdrawal, Spice-induced cannabis psychosis, and Spice-associated seizures (15–17). Recently, a case series of myocardial infarctions after Spice use was reported in three teenaged boys (18).

Germany led the international community in initial research on Spice, as well as criminalization efforts. In January 2009, Germany banned the production, sale, acquisition, and possession of the two specific psychoactive synthetic chemicals found in Spice (CP 47,497-C8 and JWH-018) (1). Remarkably, a mere 4 weeks after criminalization, samples of Spice obtained throughout Germany demonstrated replacement of recently banned compounds with JWH-073, an unregulated chemical homologue (1). Such findings support the belief that the drug designers of Spice intentionally searched for a family of unregulated psychoactive compounds that could be easily replaced with equally effective homologues for the purpose of avoiding criminalization (1).

Until December 2010, only one of the psychoactive ingredients reported in Spice, HU-210, was categorized as a Schedule I substance according to the DEA (19). HU-210 has a chemical structure substantially similar to THC, which allows it to be classified as a controlled substance under the Federal Analog Act (19). Other synthetic cannabinoids found in Spice have structures that varied substantially enough to avoid automatic classification.

There are presently multiple formulations of Spice circulating worldwide; the exact synthetic cannabinoids contained in each blend change quickly over time as drug designers demonstrate skillful alterations of their