

Commentary on Hermanns-Clausen *et al.* (2013): Spicing things up – the emerging phenomenon of synthetic cannabinoid use

There is growing concern about the use and abuse of synthetic cannabinoids, referred to collectively as 'Spice'. Even though the first reports of the recreational use of Spice emerged in 2006 [1,2], it was not until 2008 that the first synthetic cannabinoid, JWH-018, was identified as a component of Spice [3]. The existing information about Spice is limited to retrospective reports of acute intoxication [4–6]. At present clinicians, emergency responders, law-enforcement and legislators must rely completely on these uncontrolled data [6], while some fairly basic information about Spice is not known. For example, what is the dose–response? What is the temporal profile of effects? Who is more vulnerable to negative effects? What are the differences between the combinations of synthetic cannabinoids present in Spice? What is the relationship between blood or urine levels of these drugs and their effects? What are the effects of these drugs on physical and laboratory parameters?

Hermanns-Clausen and colleagues [6] report on a retrospective study of 29 patients who were hospitalized for Spice-related toxicity. Individuals presented with agitation, hallucinations, acute psychosis, vomiting, tachycardia and hypertension and even seizures. These cases involved nine synthetic cannabinoids belonging to different classes. They observed that the cannabinoids present in Spice changed over time.

While this paper adds to a growing body of retrospective reports, it also highlights the need for controlled studies with carefully characterized subjects using well-validated measures to keep abreast with the ever-changing nature of Spice and other modern recreational drug use. Adolescents and young adults continue to expose themselves to unknown risks, while efforts to obtain controlled data on Spice remain stalled largely because regulatory requirements make such studies challenging to conduct in humans. The typical process of characterizing the effects of a drug in humans involves extensive toxicology testing in animals followed by slow, dose-escalation first-in-human studies. The promise of commercial viability usually underwrites the expense of toxicology testing. However, manufacturers of Spice have no incentive to conduct toxicology testing for products that they market as 'not for human consumption' [5], and neither do the young adult consumers. Whether governmental funding agencies are going to conduct toxicology testing for these drugs of abuse remains an open question.

One alternative is to conduct quasi-experimental studies in which the effects of Spice can be characterized

carefully in people who already use it, in the safety of a laboratory, attended by trained medical and psychiatric personnel. Studying the effects of synthetic cannabinoids in people who already use them recreationally does not expose them to any additional risk. In fact, conducting such studies in the safety of a medical facility with psychiatric and medical oversight will reduce the risks, as the individuals who would be smoking Spice anyway would do so in a safe environment instead of in their home or at a party. Another alternative might be to characterize the effects of synthetic cannabinoids in non-human primates. However, the active constituents of Spice change over time in response to legislation in a perpetual 'cat-and-mouse game' [6,7]. Thus, studying a specific synthetic cannabinoid present in Spice today may be irrelevant a year from now, when the active constituents have changed.

The existence and evolution of Spice illustrates some unintended consequences of current drug policy. Manufacturers are replacing banned compounds with related compounds for which there is little safety information, and potentially more harm. As suggested by Hermanns-Clausen and colleagues [6], these full-agonist high-affinity synthetic cannabinoids are potentially more harmful than the partial-agonist low-affinity naturally occurring delta-9-tetrahydrocannabinol (THC). One of the reasons for the growth in Spice use is because users are trying to avoid the legal consequences of using cannabis [3]. It remains to be seen whether the decriminalization/legalization of cannabis will be associated with a reduction in the use of Spice.

Controlled data on the acute pharmacology and toxicology of Spice in animals and humans is needed so that evidence-based treatments of Spice-induced side effects can be developed. It would be incorrect to assume that knowledge about the effects of cannabis and/or THC can be extrapolated to understand the pharmacology of the highly potent, full agonist, synthetic cannabinoids present in Spice. The behavioral, subjective, cognitive and physiological effects of Spice need to be characterized under controlled conditions. The relationship between effects and the blood/urine levels of parent cannabinoids and their metabolites needs to be established. Urine drug tests for synthetic cannabinoids need to become more widely available. Epidemiological studies are necessary in order to track the long-term impact of legislation. Finally, the acute and long-term effects of Spice use need to be compared to cannabis use. Studying the consequences of Spice use also has the potential of shedding further light on the association between cannabinoids and psychosis,

given that synthetic cannabinoids are high-efficacy full agonists. Furthermore, the higher potency of synthetic cannabinoids might also permit better characterization of a tolerance to cannabinoids and a cannabinoid withdrawal syndrome. Clearly, a more innovative strategy needs to be employed to anticipate rather than react to emerging drugs.

Declarations of interest

None.

Keywords: Abuse, cannabis, Spice, synthetic cannabinoids.

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