“Noids” in a nutshell: everything you (don’t) want to know about synthetic cannabimimetics

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Abstract

Purpose – *“Spice” products are synthetic cannabimimetics (SC; also called “synthetic cannabinoids”)-based designer drugs used as a legal alternative to cannabis for their very strong tetrahydrocannabinol (THC)-like effects. The purpose of this paper is to provide an analysis of more recent clinical and pharmacology/toxicology findings relating to SC and describe how they could impact on health, with a particular focus on mental health.*

Design/methodology/approach – *A systematic search and descriptive analysis of the available evidence on psychopathological issues related to misuse was performed here, whilst taking into account the Pubmed/Medline databases, a range of conference proceedings and national/international agencies’ reports.*

Findings – *While THC is a partial agonist, SC are full agonists on the cannabinoid receptors (CB-rs) and the administration of multiple SC can produce additive and/or synergistic agonistic interaction effects on the endocannabinoid system. These levels of strong CB-rs’ activation may be high enough to produce severe physiological and psychological disturbances. The available evidence suggests an existing relationship between SC use and psychosis (“Spiceophrenia”). The acute SC intoxication is usually characterized by tachycardia/hypertension; visual/auditory hallucinations; mydriasis; agitation/anxiety; tachypnoea; nausea/vomiting; and seizures.*

Research limitations/implications – *The absence of clinical trials and longitudinal studies, together with the heterogeneity of SC compounds does not facilitate a precise assessment of the health risks related to their use, with long-term effects being of particular concern.*

Originality/value – *Appropriate, non-judgemental, prevention campaigns with a special focus on the differences between SC and cannabis may need to be organized on a large scale. At the same time, clinicians need to be regularly updated about novel psychoactive substances, including SC, to promptly recognize signs/symptoms of intoxication.*

Keywords *Substance misuse, Schizophrenia, Psychosis, Spice, Synthetic cannabimimetics, Synthetic cannabinoids*

Paper type *Literature review*

Introduction

“Spice” products (also referred to as “herbal incenses/blends/potpourri”, with brand names like “Spice”, “K2”, “Kronic”, “Bonzai”, and many others) are synthetic cannabimimetics (SC; also called “synthetic cannabinoids”)-based designer drugs used/sold as legal alternatives to cannabis (commonly known as “marijuana”) for their very strong tetrahydrocannabinol (THC)-like effects (Auwärter *et al.*, 2013). Spice is composed by both a dried vegetal matrix, to mimic the “grass effect” of marijuana dried inflorescences, and a mixture of SC which are sprayed on it.

SC drugs are primarily smoked, either in joints or with the help of related paraphernalia, e.g. “hookah” or “bong” water pipes (Psychonaut Web Mapping Research Group, 2010).

SC-based capsules and powder forms preparations, however, are available as well (Presley *et al.*, 2013).

"Spice" products have been on the market from early 2004 but SC were recognized as the main molecules responsible for their psychoactive effects only in late 2008 (Steup, 2008; Auwärter *et al.*, 2009). The market of these drugs is global, with Spice being found online, either as a wholesale or for retail, but also from head shops, gas stations, and from an ever expanding range of other outlets (Daly, 2013). Spice is usually labelled as "not for human consumption" to circumvent food, drug, and medicine safety laws, with the contained compounds not typically being clearly labelled in the packaging itself. A range of SC molecules are typically identified within any given Spice package (Seely *et al.*, 2012), with batches of the same brand possibly having a different composition and varying concentrations of SC in the mixture itself (Presley *et al.*, 2013). Other substances, together with SC, can be found in Spice products. This may include psychoactive herbs and plants (Ogata *et al.*, 2013); benzodiazepines/phenazepam; tryptamines (Park *et al.*, 2013; Uchiyama *et al.*, 2013a); phenethylamines/NBOMe compounds (Uchiyama *et al.*, 2014); cathinones; and opioid receptor agonists (Uchiyama *et al.*, 2013b).

Search methods and aims of the study

We aimed here at providing an analysis of more recent clinical and pharmacology/toxicology findings relating to SC and describe how they could impact on health, with a particular focus on mental health. Hence, a systematic search and descriptive analysis of the available evidence on psychopathological issues related to SC misuse was here performed. The search was carried out on Pubmed/Medline databases with the use of a set of keywords, including "hallucination*", "psychosis", "schizophrenia", "addiction", "withdrawal"; in combination with the following: "spice", "synthetic cannabinoid", "SC", and "cannabinoid receptor (CB-rs) agonists". The search was restricted to humans. In total, 225 potentially relevant references were identified, followed by further 56 references cited in the identified papers, together with a range of conference proceedings and national/international agencies' reports. Some 120 documents were full-text articles and were assessed for eligibility, with 53 having finally been considered here as suitable and consistent with the aims of the paper.

Pharmacology

It has been suggested (Schifano, 2013) that some 220 SC compounds are available at present, but it is likely that this is an underestimate. Overall, SC contained in Spice elicit a potent agonist effect on the endocannabinoid system (Fattore and Fratta, 2011). They belong to chemically different families of compounds and have different functional dynamics, e.g. some are CB-rs agonists whilst others are enzymes involved in the metabolism and transportation of endocannabinoids (Lewin *et al.*, 2013). The endogenous cannabinoid system is widely distributed throughout the body (Lewin *et al.*, 2013). In the central nervous system (CNS), the CB-rs CB-1 are responsible for the cannabis psychoactive properties and are mainly expressed in basal ganglia, cerebellum, hippocampus, amygdala, and cortex. Conversely, CB-2 receptors are more typically expressed in the immune system whilst being identified as well in the microglia and oligodendroglia (Molina-Holgado *et al.*, 2002; Stella, 2010). CB-1 receptor agonists produce an inhibitory effect on GABAergic neurons that project to the nucleus accumbens (NAc). Hence, the NAc dopaminergic neurons are disinhibited, an effect which is being associated with an activation of the mesolimbic dopaminergic pathway (Fadda *et al.*, 2006; Szabo *et al.*, 2002). These pharmacological activities may contribute to the rewarding properties and abuse liability associated with cannabinoids' use (Fadda *et al.*, 2006). Cannabis contains more than 60 exo-phytocannabinoids, possessing different actions on the endocannabinoid system (Ashton, 2001). THC, the main psychoactive compound in cannabis/marijuana/hashish, shows a range of psychotomimetic properties (D'Souza *et al.*, 2004). Conversely, cannabidiol (CBD), the second more prevalent cannabinoid in natural-grown marijuana, seems to possess anxyolitic/antipsychotic/anticraving properties (Zuardi *et al.*, 2006; Morgan *et al.*, 2013a). CBD acts as either an inverse agonist or an antagonist, depending on its dosage, on CB-rs (Pertwee, 2004, 2008). Furthermore, CBD displays an inverse agonism activity on CB-2

receptors (Thomas *et al.*, 2007) whilst interacting with other types of non-CB receptors (Mecholaum *et al.*, 2007; Pertwee, 2004). Similarly, the presence in marijuana, but not in Spice, of both the terpenoid compounds and tetrahydrocannabivarin may soften the THC psychotomimetic effects (Russo, 2011; Pertwee, 2008).

Moreover, SC show binding affinities between five and 10,000 times higher than THC for CB-rs (Pertwee, 1999). SC compounds are full agonists on the CB-rs, whilst THC is only a partial agonist (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2009). Hence, SC are more potent and possess higher dose-response efficacy levels than THC itself (Fattore and Fratta, 2011; Brents and Prather, 2014). Furthermore, it is of interest to note that, in mice, administration of multiple SC can produce additive and/or synergistic agonistic interaction effects on the endocannabinoid system (Brents *et al.*, 2013; Brents and Prather, 2014). Several SC metabolites retain high-binding affinity and activity levels on CB-rs, whilst cannabis has just a single active THC metabolite (Brents *et al.*, 2011, 2012; Chimalakonda *et al.*, 2012). It is therefore possible that SC ingestion, especially if this occurs through the various combinations found in Spice products, may be associated with higher levels of CB-rs activation. As a consequence, this activation may be severe enough to produce significant physiological/psychological disturbances (Brents and Prather, 2014).

Interestingly, it has been suggested that the chronic activation of CB-2 receptors results in the upregulation of serotonin 5-HT2A receptors in the prefrontal cortex of mice (Franklin and Carrasco, 2013; Franklin *et al.*, 2012). Modification in 5-HT2A receptors' neurotransmission has been associated with psychosis (Morgan *et al.*, 2013b), and 5-HT2A receptors are the primary site of action for hallucinogenic drugs (Fantegrossi *et al.*, 2008). Indeed, a number of SC (e.g. JWH-018; MAM-2201; 5F-PB-22; XLR-11; UR-144; STS-135; WIN 55,212-2; and many others) contain an indole moiety, either in their basic structure or in their substituent(s) (Kavanagh *et al.*, 2013; Wiley *et al.*, 2014). Indoles are groups structurally similar to serotonin, are active on 5-HT receptors, and are typically identified in indoleamine hallucinogens such as dimethyltryptamine/DMT (Halberstadt and Geyer, 2011). From this point of view, it could be argued that ingestion of indole SC compounds may be associated with both particularly high levels of serotonin receptors' activation and hallucinatory experiences (Wells and Ott, 2011; Yip and Dart, 2014).

Finally, it has been suggested that, at high dosages, SC compounds may possess as well some levels of monoamine oxidase inhibitory properties (Fisar, 2010). This element may further increase the risk of occurrence of the serotonin syndrome in SC misusers.

Toxicology

Due to the relatively recent occurrence of the "Spice phenomenon", the long-term health risks related to Spice products' ingestion cannot be properly assessed. The acute SC intoxication is usually characterized by elevated heart rate/blood pressure levels; visual/auditory hallucinations; mydriasis; agitation/anxiety; hyperglycaemia; hypokalaemia; dyspnoea/tachypnoea; nausea/vomiting; and seizures (Hermanns-Clausen *et al.*, 2013; Spaderna *et al.*, 2013; Papanti *et al.*, 2013; Winstock and Barratt, 2013b). Interestingly, nausea and seizures are very uncommon in marijuana use, due to the suggested anticonvulsivant/antiemetic properties of cannabis (Russo, 2011; Grotenhermen, 2003). Other medical issues related to the acute intake of SC may include stroke; encephalopathy; myocardial infarction; acute kidneys injuries; and features of a serotonin-like syndrome (Freeman *et al.*, 2013, 2014; Mir *et al.*, 2011; Centers for Disease Control and Prevention, 2012). Indeed, tachycardia, hypertension, mydriasis, agitation, nausea, vomiting, seizures, and rarely stroke are issues characteristic of both an SC intoxication and the serotonin syndrome (Boyer and Shannon, 2005; Singhal *et al.*, 2002).

A chronic cough in habitual SC users has been described (Gunderson *et al.*, 2012; Alhadi *et al.*, 2013), with pneumotorax, pneumomediastinum, and diffuse pulmonary infiltrates having been reported as well (Alhadi *et al.*, 2013; Froberg and Bauer, 2012).

Super-concentrations of SC (e.g. "hot-spots") in herbal blends, originating from a non-optimal homogenization between SC and the vegetal substrate, can result in overdoses/intoxications

and "bad trips" in users (Drugs-Forum, 2013). Finally, a number of deaths have been related to SC ingestion, either on their own or in combination, in analytically confirmed reports (Wikstrom *et al.*, 2013; Shanks *et al.*, 2012; Saito *et al.*, 2013; Kronstrand *et al.*, 2013; Schaefer *et al.*, 2013; Drug Enforcement Administration, 2014; Savasman *et al.*, 2014; Corkery *et al.*, 2014).

Trends in SC misuse

Over the last few years, Spice has gained popularity and especially so in adolescents and young adults. These increasing levels of popularity are possibly associated with a number of factors, including its quasi-legal market; large availability; and acceptable affordability levels (e.g. about £10/€12 per gram of product; Psychonaut Web Mapping Research Group, 2010). Many users do not seem to be aware of the serious adverse effects related to SC misuse, since these compounds may be perceived to be somehow equivalent to marijuana and hence "safe" and "natural" (Schifano *et al.*, 2009). Most clinicians, on the other hand, do not appear to be well trained on treatment/management issues relating to novel psychoactive substances (NPS), including SC, misuse, and intoxication (Simonato *et al.*, 2013; Lank *et al.*, 2013).

While marijuana use can be detected with a simple screening test, this proves to be far more difficult with SC. Indeed, due to the lack of appropriate reference samples, SC compounds are difficult to be identified even with adequate chromatography detection tests (Assi *et al.*, 2011). Hence, similarly to what happens with ingestion of a range of remaining NPS, on site/immediate results' tests are almost invariably not available to the emergency settings (Assi *et al.*, 2011).

Characteristics of SC misusers

Spice may be used in an attempt to avoid detection in environments where routine THC screening is undertaken. This issue has been particularly highlighted for some subgroups of populations, including mining workers (Dillon and Copeland, 2012); military forces (Walker *et al.*, 2014); prisoners/clients on probation (EMCDDA, 2009); and athletes (Heltsley *et al.*, 2012). A few surveys have described the prevalence of SC misuse but their generalizability remains limited (European Monitoring Centre for Drugs and Drug Addiction, 2013). The most robust prevalence data comes from the 2013 US "Monitoring the Future" survey of students, which identified last year prevalence for SC use at 7.4 and 7.9 per cent of those aged 15/16 years and 17/18 years, respectively, with Spice products being the second used drugs after marijuana and the most popular designer drugs for 12th graders (Johnston *et al.*, 2013). Overall, SC intake seems to be more represented in adolescents and youths, with male users accounting for 70-88 per cent of the samples from a range of settings, including: accidents and emergency departments; poison centres; psychiatric wards; forensic testing centres; and online surveys (Substance Abuse and Mental Health Services Administration, 2012; Papanti *et al.*, 2013; Winstock and Barratt, 2013a; Kronstrand *et al.*, 2013). No studies so far have however estimated the prevalence of SC intake in populations in treatment for substance misuse.

Psychotropic effects, psychiatric sequelae, pharmacological management

Case-reports/series and toxicology retrospective cohort studies have represented the only sources of knowledge about the clinical consequences associated with SC ingestion (Papanti *et al.*, 2013). So far, no clinical trials or longitudinal studies to evaluate the impact of acute/long-term effects of Spice products' ingestion have been carried out in humans.

Conversely, a relevant corpus of epidemiological evidence on the relationship between cannabis use and the occurrence of schizophrenia already exists. Cannabis use may increase the risk for psychosis in both psychosis-free people and vulnerable subjects (Van Os *et al.*, 2002), whilst leading to an earlier onset of psychosis (Large *et al.*, 2011). From this point of view, high potency marijuana/"Skunk" misuse (e.g. characterized by both 12-18 per cent of THC, and no CBD being identified) is associated with a significant risk of psychosis (Di Forti *et al.*, 2009). Similarly, the use of high-CBD cannabis strains is associated with fewer psychotic experiences (Schubart *et al.*, 2011).

Spice products' effects have been anecdotally described by users as intense and "trippy" marijuana-like, with hallucinatory experiences being associated with higher levels of intake (Shroomery, 2010; Erowid, 2012; Drugs-Forum, 2012). In comparison with cannabis, SC compounds may be associated with quicker "kick off" effects; significantly shorter duration of action; larger levels of hangover effects; and more frequent/intense paranoid feelings (Winstock and Barratt, 2013a).

A full range of symptoms belonging to the schizophrenia-like spectrum disorder have been described in relation to SC use. This includes hallucinations, which in SC misusers are frequently visual as opposed to mainly auditory in cannabis misusers (Murray, 2013). Both the occurrence of "*ex novo*" psychosis in previous psychosis-free subjects and the exacerbation/relapse of a primary psychosis have been described in association with SC misuse (Papanti *et al.*, 2013). A transient psychotic episode is most typically identified in SC misusers, although several cases of long-standing/persistent schizophrenia-like disorders/"Spiceophrenia" have been described (Papanti *et al.*, 2013). A number of further psychopathological disturbances have been identified in SC/polydrug (Chan *et al.*, 2013; Thornton *et al.*, 2012) misusers, including: paranoid thoughts/combativeness/irritability; confusion; agitation/anxiety/panic attacks/restlessness (Papanti *et al.*, 2013); depression/suicidal ideation (Hurst *et al.*, 2010; Hermanns-Clausen *et al.*, 2013; Glue *et al.*, 2013); and post-traumatic stress disorder (Van der Veer and Friday, 2011; Peglow *et al.*, 2012). Three complete suicides following a SC intake have been described as well (Rosenbaum *et al.*, 2011; Shanks *et al.*, 2012; Patton *et al.*, 2013).

Tolerance, dependence, and withdrawal related to SC misuse have all been described (Gunderson *et al.*, 2012; Spaderna *et al.*, 2013). According to a recent survey (Vandrey *et al.*, 2012), 36 per cent of SC users may have experienced levels of tolerance and 12 per cent dependence. Long-term SC misuse may be associated with a severe withdrawal syndrome, characterized by drug craving, tachycardia, tremor, profuse sweating, nightmares/insomnia, headache, anxiety/irritability, feelings of emptiness/depressive symptoms, and somatic complaints (Zimmermann *et al.*, 2009; Nacca *et al.*, 2013; Rominger *et al.*, 2013; Vandrey *et al.*, 2012). Psychopathological disturbances related to SC misuse may be managed with benzodiazepines and antipsychotics, with antidepressants being administered in case of concurrent depression (Spaderna *et al.*, 2013). If facing with a psychotic disorder associated with chronic SC misuse, one could argue that the use of second-generation antipsychotics (SGAs) may be considered a rational approach. Indeed, with respect to first-generation molecules, SGAs present with lower risk of increase in drug cravings (Álvarez *et al.*, 2013), and a more significant antagonism on 5-HT2A receptors (Seeman, 2002). In case of an acute SC intoxication it is advised to perform an electrocardiogram, because misusers may present with vomiting and associated hypokalaemia (Monte *et al.*, 2014).

Discussion

SC represent a large class of NPS mainly used by young adults; intake of these molecules has been increasingly associated with morbidity and mortality levels (Fantegrossi *et al.*, 2013). Hence, SC may represent a serious problem of public health, with the related long-term effects of misuse not yet fully known.

It has been reported that SC can trigger/fasten the occurrence of psychotic episodes/disorders (Papanti *et al.*, 2013). Children/adolescents may be particularly vulnerable to drugs that interact with CB-rs, because this process could impact on the CNS neurodevelopment (Sundram, 2006; Malone *et al.*, 2010). More in particular, CB-ergic drug misuse may be associated with levels of "neuro-re-development" (Hutchins, 2013; Bossong and Niesink, 2010), which may make young misusers more vulnerable to psychosis and addiction (Rubino *et al.*, 2012; Chambers *et al.*, 2003).

Because of the levels of similarities in the psychoactive effects perceived, a proportion of SC misusers may use these compounds as cannabis alternatives. However, it appears from here that SC are different from phytocannabinoids in terms of both their pharmacological activity and toxicity profile (Auwärter *et al.*, 2013; Gurney *et al.*, 2014). More in particular: first, in any given batch of Spice, a range of different/multiple SC are being identified, and some/all of these

molecules will be transformed into active metabolites when ingested; second, levels of synergistic interaction between the different SC molecules have been reported; third, in a range of SC compounds, specific moieties acting on non-cannabinoid/5-HT neurotransmitters' systems have been identified, which may add to the SC toxicity profile uncertainties; fourth, a number of other psychoactive substances/plants in SC herbal blends have been identified; fifth, the typical pattern of ingestion of SC, together with a range of remaining drugs of misuse is a reason of concern; sixth, there are individual variability levels of SC drug metabolism and excretion; and finally, there is the risk of ingesting "hot spotted"/high-dosage compounds when self-administering with Spice drugs. Due to the above reasons, drafting of a treatment/management clinical approach to cope with medical/psychiatric consequences of acute/subacute SC intake episodes may prove particularly challenging.

It is therefore of upmost importance to clarify the effects related to SC exposure to humans, in order to design appropriate clinical guidelines for treatment and management. However, for both ethical and methodological (e.g. hundreds of SC molecules are being made available; Schifano, 2013) reasons, a proper study design may prove very difficult to be implemented. From this point of view, to obtain a more comprehensive scenario it may be useful to triangulate data made available from a range of sources (Wood and Dargan, 2012), including: case reports/series; cross-sectional studies; enforcement agencies, analysing both street and web-based Spice products; and online posts commenting on self-reported adverse effects after SC ingestion.

In facing the emergence of novel compounds, the creation of an international agency of toxicovigilance would facilitate the implementation of a non-biased/"real-time" database with relevant information immediately available to be disseminated. The regular update of reports could avoid the protracted timescales of academic publishing, whilst at the same time boosting and continuously updating the research agenda. A spontaneous reporting system for adverse drug effects open to users and clinicians could promote the exchange of knowledge about existing NPS in a relative short period of time (Sumnall *et al.*, 2011).

Conclusions

SC compounds represent a large and diverse class of NPS showing a toxicity profile that may be a reason of concern. Further investigations need to be performed to better assess the pharmacological activity of the different SC compounds; their prevalence of use; and acute/long-term effects associated with their ingestion. Appropriate, non-judgemental, prevention campaigns with a special focus on the differences between SC and cannabis may need to be organized on a large scale. At the same time, clinicians need to be regularly updated about NPS, including SC, to promptly recognize signs/symptoms of intoxication.

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