

The adverse health effects of synthetic cannabinoids with emphasis on psychosis-like effects

Jan van Amsterdam¹, Tibor Brunt² and Wim van den Brink¹

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Abstract

Cannabis use is associated with an increased risk of psychosis in vulnerable individuals. Cannabis containing high levels of the partial cannabinoid receptor subtype 1 (CB₁) agonist tetrahydrocannabinol (THC) is associated with the induction of psychosis in susceptible subjects and with the development of schizophrenia, whereas the use of cannabis variants with relatively high levels of cannabidiol (CBD) is associated with fewer psychotic experiences. Synthetic cannabinoid receptor agonists (SCRAs) are full agonists and often more potent than THC. Moreover, in contrast to natural cannabis, SCRAs preparations contain no CBD so that these drugs may have a higher psychosis-inducing potential than cannabis. This paper reviews the general toxicity profile and the adverse effects of SCRAs with special emphasis on their psychosis-inducing risk. The review shows that, compared with the use of natural cannabis, the use of SCRAs may cause more frequent and more severe unwanted negative effects, especially in younger, inexperienced users. Psychosis and psychosis-like conditions seem to occur relatively often following the use of SCRAs, presumably due to their high potency and the absence of CBD in the preparations. Studies on the relative risk of SCRAs compared with natural cannabis to induce or evoke psychosis are urgently needed.

Keywords

Spice, cannabis, new psychoactive substances, NPS, risk analysis

Introduction

Synthetic cannabinoid receptor agonists (SCRAs) constitute a heterogeneous group of psychoactive drugs often classified as “Spice” among the New Psychoactive Substances (NPS) (Corazza et al., 2012). Similar to other NPS, data on their pharmacological profile and toxicity in animal studies and human data on the prevalence and side effects of SCRAs are still scarce. However, SCRAs attract considerable interest from users, therapists and regulators, and there is a need for an overview of what is currently known. This is especially true for the risk of psychosis.

In the last decade, the presumed association between cannabis use and the risk of psychosis in vulnerable individuals (Arendt et al., 2005; Dragt et al., 2012; Large et al., 2011; Martinotti et al., 2012; Moore et al., 2007; Van Os et al., 2002) has been a major issue in the medical literature, because of its potential negative health impact. Considering the growing interest in the use of SCRAs, it is therefore important to compare the use of traditional cannabis and SCRAs with respect to their psychosis-inducing potential. This is especially important since there is strong evidence that exposure to the cannabis compound tetrahydrocannabinol (THC) during adolescence is responsible for the increased risk of psychosis and even schizophrenia later in life, whereas the cannabis compound cannabidiol (CBD) seems to play a protective role (Bossong and Niesink, 2010; Kuepper et al., 2011). In contrast to natural cannabis, SCRAs do not contain CBD and may thus create a bigger risk for psychosis than natural cannabis (see below).

Between 1999 and 2004, the average THC content of Dutch cannabis (Nederwiet, Skunk) significantly increased to approximately 17%, whereas the CBD content went down to (almost) zero percent. Similar developments have been taking place in other countries. In three recent naturalistic studies in the United Kingdom and the Netherlands, associations between the use of variants of cannabis with different THC–CBD ratios and the occurrence of psychotic symptoms were found (Schubart et al., 2011a; Morgan et al., 2010, 2012). Cannabis variants with high levels of THC were associated with the induction of psychosis in susceptible subjects and the development of schizophrenia (D’Souza et al., 2004; Murray et al., 2007), whereas the use of cannabis variants with relatively high levels of CBD was associated with fewer psychotic experiences (Schubart et al., 2011b), probably because CBD has anxiolytic and antipsychotic properties (Leweke et al., 2005; Zuardi et al., 2006a, 2006b, 2012). Furthermore, the use of

¹Amsterdam Institute for Addiction Research, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

²Trimbos Institute (Netherlands Institute of Mental Health and Addiction), Utrecht, The Netherlands

Corresponding author:

Jan van Amsterdam, Department of Psychiatry, Academic Medical Center, University of Amsterdam, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands.

Email: jan.van.amsterdam@amc.uva.nl

“skunk”, which is virtually free of CBD, was found to lead to a higher risk of psychosis (Di Forti et al., 2009).

THC is an agonist of cannabinoid subtype 1 and 2 receptors (CB₁ and CB₂ receptors), whereas the mechanism of action of CBD remains largely unknown. In low concentrations, CBD antagonizes the action of CB₁/CB₂ receptor agonists, including THC (Pertwee et al., 2002; Thomas et al., 2007). Furthermore, CBD inhibits the degradation and reuptake of the endogenous cannabinoid anandamide, thus potentiating its CB₁ and CB₂ receptor-mediated effects, and acts as an agonist at TRPV1, adenosine and 5-HT_{1A} serotonergic receptors and modulates intracellular calcium (Izzo et al., 2009; Pertwee, 2008a, 2008b). “Spice” is a herbal preparation generally containing one or a variety of SCRA that may have a high psychosis-inducing potential, because of their often much higher affinity to CB₁ receptors compared with their parent compound THC and the lack of CBD. The availability of “Spice”/SCRAs in different countries is not very well known, but its popularity may increase for reasons indicated below. Based on evidence from human studies only, this paper reviews the general toxicity profile of SCRAs with special emphasis on their psychosis-inducing risk.

Methods

Relevant data from 250 papers about SCRAs were retrieved by PubMed using the following search string: (“Spice/poisoning”[Majr] OR “Spice /toxicity”[Majr] OR “Spice /adverse effects”[Majr] OR (“Spice “[majr] OR “Spice “[ti] OR Spice *[ti] OR “Spice “[ti] OR “SCRA”[ti] OR “JWH-*”[ti] OR “CP-*”[ti] OR “Cannabinoids”[Majr] OR “synthetic cannabinoid” OR “synthetic marihuana”) AND (dependence[ti] OR dependenc*[ti] OR addiction[ti] OR addict*[ti] OR abuse[ti] OR misuse[ti] OR adverse[ti] OR toxicology[ti] OR intoxication[ti] OR intoxicat*[ti] OR poisoned[ti] OR poisoning[ti] OR toxicity[ti] OR toxic[ti] OR toxicolog*[ti] OR fatal[ti] OR fatal*[ti]) AND (english[la] OR dutch[la] OR german[la] OR french[la])). Papers describing animal studies, analytical assays of SCRAs and their metabolism and were not included. In addition, the free text search string (“synthetic cannabinoids” AND 2013) was used. Finally, the reference lists of the retrieved papers were used to trace data not retrieved via the search string.

Synthetic cannabinoids: history and prevalence

“Spice” products are herbs combined with varying amounts of a variety of potent SCRAs, with brand names like “K2”, “Spice”, “Black Mamba”, “Aroma”, “Synthetic Marijuana”, “Mr. Nice Guy” and “Dream”. “Spice” is sold as a herbal preparation containing the synthetic cannabinoid “sprayed” over the herbs, or as a white powder in small plastic or aluminium bags. It is not known in which country the SCRAs are synthesized. According to the EMCDDA, 48% of the 115 online shops that were surveyed offered “Spice”, most of which were in the UK (53%), followed by Romania, Ireland and Latvia (EMCDDA, 2009). SCRAs are not very expensive and are easily available on the growing internet market (Barratt, 2012). The average price for a bag with 3 g of “Spice” was 20–30 Euros, with one bag being sufficient for about seven joints (EMCDDA, 2009). In 2005,

“Spice” products appeared in Europe and from 2009 on they were sold in the United States as “K2”. Presently, SCRAs are available worldwide and marketed with attractive labels that appeal to teenagers, young adults and first-time drug users. To circumvent drug laws, the products are packaged with designations such as “not for human consumption” and “odouriser” (Seely et al., 2012). According to the description on the packets, “Spice” contains 0.4–3 g of a mixture of herbs, of which some are psychoactive (EMCDDA, 2009). However, not the herbs but the SCRAs added to the herbs, usually in a dose of 1 mg or more, are responsible for the psychoactive effect of “Spice”, but this is not mentioned on the packaging. When using the bags, the powder is spread on loose tobacco (roll-your-own (RYO) tobacco), rolled in a joint and smoked.

Since 2008, at least 200 different SCRAs have been isolated from herbal mixtures and the list of SCRAs that appear on the market is still growing (EMCDDA, 2011; Hudson and Ramsey, 2011; Kikura-Hanajiri et al., 2011; Uchiyama et al., 2010). SCRAs are declared illegal in most countries with, to our knowledge, only one known exception: in The Netherlands SCRAs have not yet been classified as illegal drugs. Considering the huge variation, regulators encounter many problems in banning SCRAs from the market, which is a common problem for all NPS. With mostly generic legislation, the authorities try to reduce the use of and the trade in these products (Van Amsterdam et al., 2013), but drug users keep using these drugs despite their prohibition (of a particular synthetic cannabinoid or group of SCRAs) or seek certain SCRAs that are not yet placed under legal control, mostly because they appeared on the market very recently (Corazza et al., 2012; Vandrey et al., 2012).

Several recent reviews are available on the large variety of SCRAs that can, based on their chemical structure, grossly be classified in seven different groups (King, 2014). SCRAs bind to the CB₁ receptor (Table 1) and/or the CB₂ receptor, but show differences in their selectivity for these two receptor subtypes (up to 660-fold), their potency (K_i-value ranges from 0.06 to >10,000 nM) and their function (agonist, partial agonist or an antagonist) (Dossou et al., 2013; Lan et al., 1999; Psychoyos and Vinod, 2013; Wiley et al., 2013). As a consequence, SCRAs may have a 40–660-fold higher functional potency than THC, with HU-210 being one of the most potent SCRAs (Guhring et al., 2001). SCRAs are all quite volatile so that they can be easily smoked.

The prevalence of the use of “Spice” products is not very well known, but seems to vary largely between European countries (Van Amsterdam et al., 2013). Furthermore, between the United States and Europe notable differences in use of “Spice” were observed. For instance, in 2011 the 12 months prevalence of SCRA use among high school students in Michigan was 11.4% (Univ Michigan, 2011), whereas two household surveys held in the UK in 2011/2012 reported a lifetime prevalence for adults of only 0.1% (ONS, 2012), and the last month prevalence of SCRA use among 25,000 Spanish students (14–18 years of age) was only 0.4% (Clinical Committee, 2011). However, among particular groups (e.g. clubbers) higher prevalence rates of SCRA use were recently reported in the UK: 10.3% lifetime and 2.2% last year prevalence (Mixmag, 2012). In Germany, the lifetime prevalence of SCRA use increased between 2008 and 2010, then slightly decreased and has remained stable since, with lifetime and last month use of SCRAs products in 2012 by 15–18-year-olds being 7% and 2%, respectively. Lifetime use of SCRAs (but

Table 1. Affinity (expressed as K_i -values in nM) of THC and SCRA for CB₁ receptors (Auwarter et al., 2013; Howlett et al., 2002; UNODC, 2011).

Ligand	K_i -value	Ligand	K_i -value
THC	40.7, 67	JWH-122	0.69 ± 0.05
HU-210	0.73, 0.06	JWH-210	0.46 ± 0.03
JWH-007	9.5 ± 4.5	JWH-250	11 ± 2
JWH-015	383	UR-144	29 ± 0.9
JWH-018	9 ± 5	AM-2201	1.0
JWH-051	1.2	CP-47,497-C8	4.7
JWH-073	8.9 ± 1.8	R-(+)-WIN55212	1.89

not last month use) was higher in males than in females (11% vs. 3%) (Bernhard et al., 2013).

Variation of the product

Various reports have documented the isolation of SCRA from herbal blends (Hudson and Ramsey, 2011; Uchiyama et al., 2010; Zuba et al., 2011). JWH-018 and JWH-073 were most often found in the more than 140 herbal mixtures that were analysed (Dresen et al., 2010). Alongside SCRA, substances such as harmaline, oleamide, caffeine, O-desmethylnadol, nicotine, vitamin E and vegetal compounds were often found in the samples as well (Dresen et al., 2010). Some of these other ingredients have psychoactive properties or may have psychotropic effects via interaction (Zuba et al., 2011) with the SCRA, and are thus responsible for (at least) some of the side effects of these products (Dresen et al., 2010). Dresen et al. (2010) further showed that the composition of many products repeatedly changed over time, often as a reaction to a ban or the prosecution of retailers (Auwarter et al., 2009; Fattore and Fratta, 2011; Kikura-Hanajiri et al., 2013; Lindigkeit et al., 2009).

The combinations and concentrations of the SCRA in “Spice” products differ by brand, and even by batch of the same brand (Psychoyos and Vinod, 2013). Moreover, the active compounds are not homogeneously distributed within the product. Such variations may increase the risk of accidental overdose (Auwarter et al., 2009; Dresen et al., 2010). Because of their relative high potency as compared with THC, the usual dosage of a SCRA is less than one mg per gram of herb mix. In all the thus far analysed “Spice” products with JWH-018, the concentration of JWH-018 was 2–30 mg/g (EMCDDA, 2009; Kikura-Hanajiri et al., 2011; Uchiyama et al., 2010; Wiley et al., 2011). The concentration of (±)-CP-47-C8 0.497 and JWH-073 in 46 other “Spice” products of different brands varied between 1 and 17 mg/g and 6 and 23 mg/g, respectively (Lindigkeit et al., 2009; Uchiyama et al., 2010). Other investigations showed that JWH-018 and JWH-073 purchased from three different online suppliers had a similar purity, although the products differed from each other in colour, texture and smell (Ginsburg et al., 2012). Others (Kikura-Hanajiri et al., 2013; Lindigkeit et al., 2009; Uchiyama et al., 2010) also found a large variation in the SCRA levels of the products, with some of these products even containing as much as 80 mg per gram of herb (Uchiyama et al., 2010). It is interesting to note that 11% of the frequent users of “Spice” reported variable and unpredictable effects to occur when they used the

same brand of “Spice” on different occasions (Vandrey et al., 2012). In the experience of drug users, “Spice” effects ranged from mild to strong, and were either very similar to those of cannabis or completely different (EMCDDA, 2009).

Reasons to use SCRA

There are special reasons for using SCRA instead of cannabis (Table 2). SCRA can be used, for example, to circumvent drug use-related prosecution such as those reported by prisoners on probation in Sweden (EMCDDA, 2011), US army personnel (Bebarta et al., 2012; Hurst et al., 2011a; Johnson et al., 2011; Loeffler et al., 2012), and miners in Australia (Dillon and Copeland, 2012). Furthermore, SCRA such as JWH-018 and JWH-073 are popular in Germany, because the user cannot be penalized for driving under the influence of cannabis (Werse, 2010) due to the fact that SCRA are (or were) not detected by routine drug testing methods (Lindigkeit et al., 2009).

Users with at least some experience with both drugs generally prefer cannabis over SCRA. In a large anonymous online survey, 2513 (17%) respondents reported to have used SCRA in 2011, of which roughly 40% (980) had used SCRA in the last year. Almost all of them also had experience with natural cannabis. Cannabis was rated more positively than SCRA by 93% of users, because of the pleasant effects during the “high” ($p < 0.001$, $d = -1.22$) and better functioning after using the drug ($p < 0.001$, $d = -0.45$). SCRA use was associated with stronger negative effects, including hangover-like effects ($p < 0.001$; $d = 0.22$) and paranoia ($p < 0.001$; $d = 0.27$) (Winstock and Barratt, 2013). In an internet survey, 21% of the adults who had ever used SCRA considered SCRA their favourite drugs. The main reasons mentioned for using SCRA were curiosity (78%), positive effect of the drug (58%), relaxing effect (48%), getting “high” without the risk of being tested positive (30%) and more acute subjective effects compared with those of cannabis (85%) (Vandrey et al., 2012). Similar reasons to use SCRA have also been reported by others (Barratt et al., 2013; EMCDDA, 2009; Schifano et al., 2009).

Unwanted negative effects

The toxicity profile of SCRA is similar to that of highly dosed THC, but the use of SCRA presumably leads to more frequent and more serious side effects as compared with the use of cannabis, especially in younger and less experienced users. Users of SCRA are generally not adequately informed about the differences between natural cannabis and SCRA and how to properly use (how and how much) SCRA. Lack of experience with the use of SCRA may lead to accidental overdosing, with serious complications that may require admission to an intensive care unit. For instance, the USA Drug Abuse Warning Network (DAWN) study on drug-related emergency room (ER) admissions reported that in 2010 the consumption of SCRA led to 11,406 visits to an ER (DAWN, 2012). In addition, ER professionals who treat SCRA overdosing often do not know what specific SCRA was used by the patient or whether SCRA were used at all, and most of them are ignorant of the health risks of these agents (Lank et al., 2013; Simonato et al., 2013). Moreover, the type and amount SCRA may differ per product or

Table 2. Reasons to use SCRA.

Reason to use SCRA	Reference
To circumvent drug use-related prosecution (prisoners on probation, army personnel, miners)	(Bebarta et al., 2012; Dillon and Copeland, 2012; EMCDDA, 2011; Hurst et al., 2011a; Johnson et al., 2011; Loeffler et al., 2012; Vandrey et al., 2012)
To avoid being penalized for driving under the influence of cannabis	(Lindigkeit et al., 2009; Werse, 2010)
Pleasant effects during the “high”, better availability and better functioning after using the drug	(Barratt et al., 2013; Winstock and Barratt, 2013)
Curiosity, positive effect of the drug, relaxing effect	(Barratt et al., 2013; EMCDDA, 2009; Schifano et al., 2009; Vandrey et al., 2012)
Aid in reduction or cessation of cannabis use, legal status, therapeutic effects	(Barratt et al., 2013)

even per batch, which obviously implies an increased risk of becoming intoxicated.

Acute adverse effects

Users of SCRA (type not specified) have reported that, compared with cannabis, the effects of SCRA have a shorter duration and peak earlier (Winstock and Barratt, 2013). However, there are major differences in the pharmacokinetics across the SCRA used. For instance, the C8-homologue of CP-47-497 induces a relatively long effect (5–6 h), whereas JWH-018 has a much shorter effect (1–2 h) (Winstock and Barratt, 2013).

The use of SCRA can lead to a variety of acute adverse effects. Typical acute neurological and mental effects of SCRA include (the desired positive effect of) euphoria, followed by drowsiness, paranoia, delusions, hallucinations, anxiety, panic attacks, agitation, nausea, vomiting, seizures and dizziness, as well as short-term memory and cognitive deficits. Although not reported, it is likely that – as is the case for cannabis use (Fried et al., 2005) – the use of SCRA may lead to sustained but reversible cognitive impairments. The prolonged cognitive impairment may be due to slow elimination of (the synthetic) THC (analogues), down-regulation of cannabinoid receptors (Hirvonen et al., 2012) or a decrease in endocannabinoid activity (Morgan et al., 2013). Frequently occurring cardiovascular side effects of SCRA use include tachycardia and hypertension, and hyperglycemia and hypokalemia have also been observed. The most common symptoms of acute unwanted negative effects following SCRA use are tachycardia, extreme agitation/irritability, drowsiness/lethargy and hallucinations (Barratt et al., 2013; Brewer et al., 2014; Forrester, 2013; Hermanns-Clausen et al., 2013b; Hoyte et al., 2012; Piggee, 2009). For instance, a retrospective study in 29 ER patients (aged 14–30 years) after recreational use of an SCRA showed that – in addition to tachycardia, hallucinations, hypertension, slight increase in blood glucose and vomiting – agitation, seizures, hypertension and hypokalemia were characteristic of SCRA overdosing (Hermanns-Clausen et al., 2013b). The presence of the SCRA intoxication was confirmed by clinical chemical analyses in all 29 cases (Hermanns-Clausen et al., 2013b) and four subsequent cases (Hermanns-Clausen et al., 2013a). Clinical symptoms in ER patients with an overdose of SCRA have also been described in several case reports (Muller et al., 2010; Oluwabusi et al., 2012; Peglow et al., 2012; Schneir and Baumbacher, 2012; Vearrier and Osterhoudt, 2010; Young et al., 2012) and in a number of case series (Bebarta et al.,

2012; Mir et al., 2011; Schneir et al., 2011; Simmons et al., 2011a, 2011b). However, in these case studies the consumption of SCRA was confirmed by clinical chemical analysis in four cases (six urine samples for metabolites of JWH-018 and JWH-073 positive), and poly-drug use could not always be excluded.

Although seizures are rarely seen after cannabis use, they were recently reported following the use of SCRA (Jerry et al., 2012; Lapoint et al., 2011; Schneir and Baumbacher, 2012). Furthermore, a case of serious rhabdomyolysis associated with the use of SCRA was recently reported (Durand et al., 2013). Currently, the Centers for Disease Control and Prevention (CDC) in the USA investigate the link between SCRA use and acute kidney injury (CDC, 2013) following several cases of acute kidney injury after the use of a novel fluorinated SCRA (XLR-11) (Bhanushali et al., 2013; CDC, 2013; Thornton et al., 2013). Symptoms, such as paranoia, agitation, anxiety, and even convulsions induced by SCRA may be explained by the stronger inhibition of GABA-mediated neurotransmission by SCRA as compared with THC (Hoffman and Lupica, 2000) due to the disruption of the endogenous cannabinoid system by the SCRA that have a much higher affinity and intrinsic activity to CB₁-receptors than THC. As a result neurotransmitter release (GABA/glutamate) is disturbed, which affects projections from the prefrontal cortex, leading to over-activation of the dopaminergic system in the prefrontal cortex and striatum (psychosis); see Bossong and Niesink (2010) for further details. Moreover, compared with cannabis, SCRA preparations lack CBD which retains an anxiolytic effect (Schier et al., 2012).

No confirmed fatal cases of overdose as the result of SCRA use have been described so far. Although 12 fatal cases after SCRA use have been reported, the cause of death was not confirmed by clinical/toxicological evaluation. It is probable that toxic combination(s) of the SCRA with other drugs or SCRA-induced psychiatric complications (hallucinations, paranoia, delusions) were the primary cause of death. For instance, SCRA-induced hallucinations probably drove an 18-year-old man to commit suicide after smoking “Spice” (Reynaud and Strong, 2010). A second example concerned a 23-year-old man who had used an SCRA (AM2201; confirmed by metabolites in post-mortem blood) and was found dead with severe self-inflicted stab wounds due to psychiatric complications (Patton et al., 2013).

Long-term adverse effects

Prolonged or intensive use of cannabis can lead to cannabis dependence and tolerance (Zimmermann et al., 2009). Tolerance

for SCRA develops quickly, suggesting that SCRA may have a relatively high abuse and dependence liability (Zimmermann et al., 2009). Indeed, three experienced cannabis users, who also regularly smoked SCRA products, met criteria for cannabis dependence. An illustrative example is a 20-year-old patient who was seen with withdrawal symptoms who had smoked "Spice Gold" (containing JWH-018 and CP 47497) daily for 8 months. Due to the developing tolerance, he had increased the dose rapidly to 3 g per day (Zimmermann et al., 2009). No studies so far have described the long-term adverse effects of SCRA use.

Young people at risk

Overdosing with SCRA occurs relatively more frequent in drug-naïve users and users who have little experience with cannabis, that is, in relatively young users. For example, between September 2008 and February 2011, the Poisons Information Centre in Freiburg (Germany) was consulted by physicians regarding 29 cases of SCRA overdose, with 12 of them (41%) reporting that they had used the 'herb mixture' for the first time (Hermanns-Clausen et al., 2013b). Similarly, nearly half (43%) of the 464 synthetic cannabinoid overdoses reported to Texas poison centres in 2010 were subjects under 20 years of age (Forrester et al., 2011). Poison centres in the USA received an increasing number of telephone calls about SCRA, with 7000 calls in 2011 (AAPCC, 2012; Hu et al., 2011), including 60% with an age under 25 years. Similarly, most patients with an SCRA overdose visiting the ER in the DAWN study were relatively young (75% were aged 12–29 years; 33% were 12–17 years old) (DAWN, 2012). The average age of patients who needed ER assistance following the use of cannabis was 30 years, whereas this was 24 years in those referred for SCRA use. Furthermore, male patients required ER assistance significantly more often after "Spice" use than after cannabis use (78% and 66%, respectively), whereas for the female patients this was the reverse (22% and 34%, respectively) (DAWN, 2012). These figures suggest, but do not prove, that the use of "Spice" has a higher risk than the use of cannabis with respect to ER visits. On the other hand, based on their research, the Global Drug Survey (GDS) recently estimated that the use of SCRA is associated with a 30 times higher risk of seeking ER as compared with traditional cannabis (Winstock, 2014).

In another American study, 60% of SCRA overdoses occurred in people under 25 years of age (AAPCC, 2012; Hu et al., 2011), and 57% were younger than 20 years old (Forrester et al., 2011). The review by Papanti et al. on psychopathology after SCRA use ($n = 2207$) showed that patients were on average only 23.0 years old (Papanti et al., 2013). Apparently, new and/or young SCRA users are particularly sensitive to the toxic effects of SCRA (Hermanns-Clausen et al., 2013b). Finally, note that data based on ER admissions may be biased due to under-reporting, because not all of those who experience severe adverse reactions following SCRA use will visit the ER.

SCRA-induced acute psychosis

Unlike cannabis, "Spice" contains no CBD. Moreover, most SCRA are full agonists and have a higher affinity to the CB₁-receptor than THC (EMCDDA, 2009; Fattore and Fratta, 2011). Similar to what has been described for the use of (natural) cannabis (Koethe et al., 2006; Martinotti et al., 2011; Verdoux et al.,

2003), the use of SCRA triggers psychotic episodes in sensitive or vulnerable individuals and may lead to aggravation of prodromal psychotic symptoms. US poison centres noted psychotic episodes in 14–40% of SCRA overdoses that came to their attention (AAPCC, 2012). In 10 psychiatric patients who had never experienced psychosis before their first use of an SCRA, a "new-onset psychosis" precipitated after repeated SCRA use. All patients had smoked SCRA on more than one occasion, ranging from four occasions with SCRA use over a 3-week period to daily use of SCRA for 1.5 years. In seven of these patients, the psychotic symptoms resolved after some days (5–8 days), but in the other three patients psychotic symptoms persisted for more than 5 months after presentation. The time to onset of psychotic symptoms after SCRA use varied greatly (Hurst et al., 2011b).

Gunderson et al. (2012) conducted a systematic review of the clinical effects of SCRA and indeed reported acute anxiety and psychosis as the two most prominent side effects of SCRA use. Evidence that psychopathology, such as hallucinations and delusions, can occur during acute or chronic SCRA use was also shown in a recent systematic review of 41 papers, which included 25 case reports, 11 studies conducted in a psychiatric institution, 15 studies conducted in ERs, and nine reports from poison information centres (Papanti et al., 2013). The reviewed studies described various forms of psychosis, such as an acute transient psychosis and the relapse and worsening of a pre-existing psychosis. Possible confounding factors in the reviewed studies were attention deficit hyperactivity disorder, post-traumatic stress disorder and poly-drug use (especially alcohol and cannabis use). For instance, in one case reported by Hermanns-Clausen et al. (2013b), a young woman experienced severe psychosis after repeated use of JWH-081 for 6 days, but she had also been taking cannabis and thus the causal role of SCRA could not be established. Interestingly, the ER studies and studies in which the presence of a SCRA was confirmed by clinical chemistry mentioned a higher rate of psychotic disorders (18–41%) than the studies based on interviews only (9–11%) (Forrester et al., 2012; Hoyte et al., 2012). Forrester et al. (2012) showed that a cannabis-associated psychopathological syndrome (identified as experiencing hallucinations and delusions) was less likely in cannabis users (2%) than in SCRA users (11%). Compared with psychotic episodes in cannabis users, those related to SCRA use (associated with agitation, behavioural problems and loss of control) occur more frequently or are more severe (Brakoulias, 2012). The exact risk of psychosis after SCRA abuse, such as after using cannabis (Arseneault et al., 2002), cannot be estimated, because good prospective cohort studies in SCRA users and/or good comparative studies (cannabis vs. SCRA) are not available.

To understand or even explain these findings one has to realize that the relationship between the endocannabinoid system and psychosis is rather complex. Presynaptic CB₁ receptors are abundant in brain regions that have been implicated in the putative neural circuitry of psychosis such as the cerebral cortex, particularly frontal regions, basal ganglia, hippocampus, anterior cingulate cortex, and cerebellum (Egertova and Elphick, 2000; Elphick and Egertova, 2001; Glass et al., 1997). In rodents, activation of presynaptic CB₁ receptors by cannabinoids reduces GABA release by interneurons in the hippocampus (Foldy et al., 2006; Katona et al., 2000; Lee and Soltesz, 2011; Szabo et al., 2002) and/or inhibits post-synaptic NMDA receptor signalling (Sanchez-Blazquez et al., 2014), thereby causing dopaminergic stimulation (Javitt, 2007). As a result, pyramidal cell activity in hippocampal

neurons is desynchronized (Hoffman and Lupica, 2000; Wilson and Nicoll, 2002), eliciting psychotic symptoms (reviewed in Elphick and Egertova, 2001; Freund et al., 2003). Indeed, such disruption or inhibition of synchrony has been observed for both THC and SCRA (e.g. HU-210) (Goonawardena et al., 2011; Morrison and Stone, 2011). In psychosis-free humans, intravenously administered THC induces a range of schizophrenia-like positive and negative symptoms (D'Souza et al., 2004).

Although THC was reported not to stimulate the dopaminergic system (Barkus et al., 2011; Stokes et al., 2009) or to do so only weakly (Bossong et al., 2009), others have claimed that higher mesolimbic dopaminergic activity following CB₁ receptor activation by THC may be responsible for the positive psychotic symptoms (Chen et al., 1990; French, 1997; Pistis et al., 2001). As SCRA is in general more potent than THC, these compounds are likely to give an even stronger dopaminergic stimulation, so that more frequent and more severe psychotic-like symptoms are observed following the use of these drugs. Together, these results indicate that the complexity of the interactions of the endocannabinoid system with neurotransmitter systems including the dopamine system is responsible for the inconsistent results observed (Kuepper et al., 2010). The importance of potency or dose is further corroborated by previously published findings (Di Forti et al., 2014; Morgan and Curran, 2008; Morgan et al., 2012; Wylie et al., 1995). For example, Di Forti et al. (2014) have shown that the use of high-potency cannabis (skunk) leads to an earlier onset of psychosis (hazard ratio of 1.42). Moreover, as observed for natural cannabis (Galvez-Buccollini et al., 2012), the age at onset of SCRA use may be an important risk factor for an earlier onset of psychosis.

SCRA use as self-medication in schizophrenia

It has been claimed that early cannabis use may lead to schizophrenia (Andreasson et al., 1987; Arendt et al., 2005; Arseneault et al., 2002; Dragt et al., 2012; Large et al., 2011; Martinotti et al., 2012; Moore et al., 2007; Van Os et al., 2002), although a causal relationship was never established (Castle, 2013; Van Amsterdam et al., 2004). However, it is known that patients with schizophrenia use cannabis relatively frequently, with a lifetime prevalence 97% and last-year prevalence 49% (Moore et al., 2012). The reason for the high consumption of cannabis by this group is because they use cannabis as self-medication to alleviate negative symptoms (blunted affect, apathy), depression or negative affect (anxiety, agitation, depression) or the side effects of antipsychotic medication (apathy, depression). In the opinion of others (Kolliakou et al., 2011) there is little support for 'self-medication', and they prefer to explain the relatively high rate of cannabis consumption by its 'alleviation of dysphoria'.

It remains, however, unclear whether SCRA may ever serve as an alternative to cannabis for self-medication purposes. Indeed, on the one hand SCRA gives the desired 'high' and 'feel good factor', but on the other hand the use of SCRA may have a detrimental effect on the symptoms and course of schizophrenia because these potent compounds may cause an exacerbation of positive symptoms (e.g. hallucinations). Moreover, because SCRA preparations do not contain CBD they fail to reduce negative affect (e.g. anxiety).

Limitations of this review

In contrast to natural cannabis, SCRA has only been in use for a decade. Therefore, the number and the quality of studies on the possible harm of SCRA and comparing the frequency of adverse effects of cannabis and SCRA is limited. For instance, diagnostic details were not always properly described so that psychotic episodes could not always be discriminated from psychotic-like episodes. Similarly, medical history data were often insufficient to determine the causal relation between the use of SCRA and the occurrence of a psychotic episode, since the presence of pre-existing pathology and concomitant use of other (illicit) drugs could not always be excluded. As such, we often had to rely on case reports and collected data described in reviews. In addition, considerable differences in the prevalence rate and the patterns of use between European and American users were seen (EMCDDA, 2013). As a result of these limitations, the current review and the conclusion that follows need to be interpreted with caution.

Conclusions

The main reasons to use SCRA instead of using cannabis are the 'legal status' of at least some SCRA in some countries, easy access to them via the internet and curiosity about the drug. SCRA are THC analogues that have a very similar profile of action to that of THC. However, in general, SCRA are more potent than THC, which may result in more frequent and more severe side effects and, especially in younger users, more often in intoxications. The most common symptoms of acute unwanted side effects of SCRA are tachycardia, extreme agitation and hallucinations. Considering the dose-effect relationship, more pronounced tachycardia and seizures may be induced at higher dose or by the relatively more potent SCRA. While a number of fatal cases after using SCRA have been described, causality was never proven. Being unfamiliar with the use of the agent, and the lack of knowledge about the long-term effects and experience regarding the use and side effects of SCRA in emergency departments increases the risks of SCRA use compared with cannabis. Compared with natural cannabis, which contains CBD, the use of SCRA offers no protection against the provocation of psychosis in susceptible persons or patients with schizophrenia. Indeed, the provocation of psychosis by SCRA has been reported relatively often. As adequate studies on the relative risk of SCRA compared with natural cannabis to induce or evoke psychosis are lacking, research on this issue is urgently needed.

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