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UPDATE / *MISE AU POINT*

Pharmacology and Toxicology of the Synthetic Cannabinoid Receptor Agonists

Pharmacologie et toxicologie des agonistes synthétiques des récepteurs cannabinoïdes

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Abstract The synthetic cannabinoid receptor agonists (SCRAs) are a large group of new psychoactive substances (NPS) that have emerged over the last 5–10 years. There have been 134 SCRAs reported in Europe which makes them the largest group amongst the NPS. SCRAs are active at the cannabinoid receptors and most are very potent CB1 receptor agonists. They are generally sold in smoking mixtures but are also available in incenses and in powder form. This article discusses the numerous reports of acute toxicity related to the use of SCRA products. In summary, these reports suggest that in addition to cannabis like neuropsychiatric effects the SCRAs are also associated with stimulant features (e.g., agitation, tachycardia, hypertension, seizures) and there are reports of SCRA-related ischaemic stroke, acute coronary syndrome, and acute kidney injury.

Keywords Synthetic cannabinoid receptor agonists · Spice · Acute toxicity · Psychosis

Résumé Les agonistes synthétiques des récepteurs aux cannabinoïdes (ASRC) représentent un groupe important de nouvelles substances psychoactives (NPS) qui ont émergé au cours des cinq–dix dernières années. Environ 134 ASRC ont été identifiés en Europe, ce qui en fait le plus grand groupe de NPS. La plupart des ASRC sont de très puissants agonistes des récepteurs CB-1. Ils sont généralement vendus dans des mélanges prêts à être fumer, mais sont également disponibles sous forme de poudres et d'encens. Cet article discute les différentes toxicités aiguës attribuées aux ASRC. Les études publiées suggèrent qu'en plus des effets neuropsychiques communs avec le cannabis, les ASRC sont à l'origine de propriétés psychostimulantes (agitation, tachycardie, hypertension et convulsions) et d'un risque significatif d'accident vasculaire cérébral ischémique, de syndromes coronariens aigus et d'insuffisance rénale aiguë.

Mots clés Agonistes synthétiques des récepteurs cannabinoïdes · Épice · Toxicité aiguë · Psychose

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Introduction

The synthetic cannabinoid receptor agonists (SCRAs) are a large group of legal and illegal substances that bind to one or both of the known cannabinoid receptors [1–3]. Many of the SCRAs were initially researched in the 1950s and 60s for their potential therapeutic use in a variety of disorders, but adverse effects, such as depression and increased rate of suicide stopped these substances from reaching therapeutic use [4] The SCRAS have probably been available as new psychoactive substances (NPS) in smoking mixtures in Europe since 2006 but the first SCRA to be characterised as an NPS was JWH-018 in 2008 [3]. When sold and used as NPS the SCRAs are often known as Spice (particularly in Europe), K2 (particularly in the USA), K9, black mamba, Kronic and they are mostly sold as smoking mixtures or incense [5]. There has been a rapid increase in the number of SCRAs available as NPS since 2009 — there were 9 new SCRA reported to the Early Warning System at the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2009, this increased to 29-30 per year from 2012 to 2014 [6]. There have been a total of 134 SCRA reported since December 2008 which makes them the largest group of NPS monitored by the EMCDDA [6]. SCRA have been reported not just in Europe, but throughout the world, 28% of the 348

NPS reported to the United Nations Office on Drugs and Crime from 2008 to 2013 were SCRAs [7].

Whilst these substances were originally NPS (often referred to as "legal highs"), various countries (including many European countries (e.g. the UK, Germany, France, Poland), the USA, Australia and New Zealand) have now classified many of the SCRAs [3,8–13]. This has led to manufacturers developing and producing new compounds that are yet to be scheduled [3,5,14,15] often requiring further legislative attempts to cover these new compounds. In the UK, for example, the third generation of SCRAs were captured in legislation in 2014/5 [13].

This review will discuss the pharmacological properties of the SCRAs, as well as reviewing the known data on the patterns of acute and chronic toxicity, and their potential dependence.

Chemistry

The SCRAs are substances that bind to cannabinoid receptors, broadly these substances can be classified into seven different groups. These groups are the classical cannabinoids, non-classical cannabinoids, aminoalkylindoles, aminoalkylindazoles, eicosanoids, fatty acid amide hydrolase inhibitors, and others (for example diarylpyrazoles, naphthoylpyrroles, naphthylmethylindenes). While most of the SCRAs are water insoluble and lipid soluble, water-soluble cannabinoids have been described [16–18]. The SCRA are often sold sprayed onto plant material as smoking mixtures. There is little information on the plant products that are used and whether there may be the potential for toxicity associated with these constituents. In addition to their availability in smoking mixtures, SCRAs are also sold as incense and in powder form [2]. In one study investigating the components of various substances seized by law enforcement, SCRAs were only found in powder formation [19]. A number of studies have shown that there is variation in the SCRAs found in products [1,5,20]. In a previous study from our group, we studied the SCRA components of various "spice" products that were purchased from Internet legal high websites [5]. Thirty-six products were purchased altogether (16 prior to and 20 after UK control of SCRA). Multiple different SCRA were identified from these products (9 in the pre-control group, and 16 in the post control group although 8 of these were the same as the pre-control group). No SCRA were detected in three of the post-control products.

Pharmacokinetics

Whilst the pharmacokinetics of these substances remains largely unknown, there are some data available from a combination of clinical cases, studies and self-experiments [1,16,21–23] (Gardin 2009). Because of the wide chemical diversity of the SCRAs it is not possible to extrapolate pharmacological properties between, and potentially within, different SCRA classes.

From the available data, oral bioavailability appears to be less than inhaled for some substances. Grigoryev et al investigated AB-001, an aminoalkylindole [23]. Four subjects ingested this drug, at doses of either 13 or 26 mg. Urine was tested for metabolites of AB-001 at various times up to one week after drug administration. Numerous major and minor metabolites were found in the analysis, confirming absorption. No subjects experienced physiological effects at these doses. The same authors also investigated another aminoalkylindole, AM-694 [1]. In this study, one subject initially ingested 10 mg of AM-694. Two months later, the same subject smoked 1 mg of the same substance. Again, analysis was performed on urine samples up to one week post administration. This analysis found six metabolites of AM-694. No physiological effects were noted on oral administration. The authors did not mention whether effects were noted after smoking 1 mg.

Oral absorption is affected by whether ingestion is on an empty stomach or associated with food ingestion. A randomized, two-way crossover trial compared ingestion of 40 mg CRA13 in fasting versus a high-fat, high-calorie intake states (Gardin 2009). Serum samples were taken at numerous intervals up to 96 hours after drug ingestion. The C_{max} after food was 369 ± 136.5 ng/ml versus 193.7 ± 84.7 ng/ml in fasted subjects. Adverse events were three times more common in subjects who had breakfast, compared with those that were fasted.

The same study investigated various doses of oral CRA13 (1, 2.5, 5, 10, 20, 40 or 80 mg) or placebo in 63 fasted subjects (Gardin 2009). They found that the absorption was rapid, with plasma concentrations detectable after 15 minutes of ingestion. The C_{max} ranged from 8.0 ± 2.4 ng/ml for 1 mg up to 481.5 ± 120.6 ng/ml for 80 mg CRA13. C_{max} was reached at between 1.5 to 2 hours (T_{max}).

When smoked, "spice" products appear to have similar availability to THC. Auwärter et al found that when a 0.3 g cigarette of "spice diamond" was smoked between 2 people, symptoms of intoxication occurred [1]. These included reddened conjunctivae and increased heart rate approximately 10 minutes after smoking. Serum analysis confirmed presence of SCRA although this was not quantified or identified further. A self-experimentation study also found that physiological effects were experienced when the substance was smoked [22]. This German self-experimentation study involved 2 subjects (one male, one female) smoking one cigarette each (150 mg and 100 mg respectively) of an incense product known as "smoke". "Smoke" contains the aminoalkylindole JWH-018. Immediately after smoking,

both subjects experienced sedation, and nausea. They also reported thought disruption, burning eyes, and hot flushes. Peak concentrations of JWH-018 were seen at 5 minutes post smoking (10.2 ng/mL), while at 3 hours, concentrations had fallen to 0.25–0.41 ng/mL). By 24 hours, JWH-018 was present in very small amounts.

The aforementioned study by Gardin et al reports a terminal half-life for CRA13 of between 21.3 ± 6.1 hours for 20 mg ingestion and 35.5 ± 11.1 hours for 80 mg ingestion (Gardin 2009). Kneisel et al analysed 4200 serum samples from various clinics and treatment centers across Germany [24]. They found that in some cases (number not provided) JWH-081, JHW-122, or JWH-210 were detectable up to 120 days after cases self-reported drug cessation. This led to an estimated terminal elimination half life of up to 41 days. The authors hypothesized that possible distribution of the SCRAs into fatty tissue compartments may play a role.

Users report onset of action within minutes of nasal insufflation [1,25], and around 45 minutes after oral ingestion [26]. Speed of onset was almost identical between smoking of SCRAs and cannabis with onset being reported within 5 minutes [16]. Duration of action has been reported to vary from 1 to 24 hours, depending on the type of cannabinoid [1,25,27]. An internet based survey reported an average intoxication time of 93 minutes (SD 69, range 10-360 min) [28] Data from US poisons centers reported that effects lasted less than eight hours after use in 78.4% of cases; in the remaining cases, clinical effects remained for 8-24 hours in 16.6% and more than 24 hours in 4.9% [29].

The SCRAs initially undergo oxidation by cytochrome p450 (CYP), especially the isoenxymes CYP2C9, CYP1A2 and to a lesser extent CYP2D6 [30]. CYP2C9 is expressed in the intestine, linking it to metabolism following oral administration, whereas CYP1A2 is expressed in the lung (for inhalation metabolism) [31,32]. CYP2D6 is hypothesized to play a role in brain concentration regulation, being expressed in the cerebral cortex, hippocampus and cerebellum [30]. Both JWH-018 and AM2201 are metabolized by cytochrome P450 (CYP2C9, CYP1A2), producing some common metabolites [32].

Metabolites are excreted in urine and bile [33]. Glucuronide metabolites have been found in urine, with conjugation occurring by the enzymes UDP-glucuronosyltransferases (UGTs) [30]. The major UGT isoforms involved in the metabolism of JWH-018 and JWH-073 were UGT1A1, UGT1A9 and UGT2B7 in the liver [30,34]. Other isoforms were found to contribute outside the liver included UGT1A10, UGT1A7 (in lung), UGT1A3 and UGT 2B7 (both in brain) [30,34].

A volunteer study investigating the metabolites of AB-001 found that they were detectable for up to 160 hours following oral administration [35], while metabolites of AM-694 were detected up to 117 hours post oral ingestion [23]. Analysis of thirty-four urine samples collected from patients admitted with suspected drug intoxication revealed metabolites of JWH-203 (n = 28), JWH-251 (n = 8), JWH-250 (11 of the JWH-203 samples) and JWH-018 (1 of the JWH-203 samples) [36]. Six of these samples had self-reported timing of drug ingestion. From these samples, metabolites were detected up to 7 (JWH-251) and 10 (JWH-203) days after reported drug use.

Pharmacodynamics

The endocannabinoid system has actions across a range of physiological processes, including blood pressure regulation, the sleep-wake cycle, and the reward system [37]. There are currently 2 known receptors - CB1 and CB2 receptors; these receptors are G-protein coupled [38]. CB1 receptors are situated mainly in the brain and spinal cord, while CB2 receptors are in the spleen and immune system cells [39,40]. CB1 help regulate GABA and glutamate transmission [41].

Seely et al report that the majority of SCRAs have been characterised as CB1 receptor agonists [19]. Studies investigating this have demonstrated that SCRAs have a higher biological activity and are full agonists, compared with delta-9-tetrahydrocannabinol (Δ9-THC), a partial agonist [32,42–46].

Studies on the metabolites of JWH-018 and AM2201 have shown that the metabolites are active at the CB1 receptor [32]. JWH-018 and AM2201 as well as their metabolites ω-OH and ω-1-OH were all found to have high affinity for the CB1 receptor. Both JWH-018 and AM2201 had higher affinity for CB1 receptor compared with THC, whilst their metabolites ω-OH and ω-1-OH had similar affinity [32]. This study also found that both JWH-018 and AM2201 as well as their metabolites ω-OH and ω-1-OH had statistically greater intrinsic G-protein activation compared with THC.

Prevalence of use

There is limited population level data investigating the prevalence of use of the SCRAs. There are some data from England and Wales, and from Germany. Past year use for people aged 16 to 59 years in the British Crime Survey was reported as 0.2% in 2010/11 and 0.1% in 2011/12 [47,48]; data has not been collected in subsequent years due to this low prevalence rate. Higher rates of past year use of “spice” were found in Germany in 2009, with 0.8% of 8030 respondents 18-64 years reporting use; although it is notable that this survey only had a 50.1% response rate [49]. A 2014 survey of 18-64 year olds in France reported lifetime use of spice in 1.7% of respondents; use was higher in men (2.3% men vs 1.2% women), and in those under 35 years (4.0% 18-34 years vs 0.6% 35-64 years) (Baromtre Sante in EMCDDA 2015 [3]).

There have been a number of subpopulation studies investigating the use of "Spice". Use of "spice" has been found to be higher among young people, those who frequent the night-time economy, people who continue in education, and those subject to routine drug screening (e.g. athletes) [50–54].

In a 2012 survey of 27,503 students aged 14-18 years in Spain, the reported lifetime, last year and last month prevalence of use of "spice products were 1.4%, 1.0% and 0.6% respectively [55]. A longitudinal study program in the USA, called the Monitor the Future program, surveys secondary and college students [54]. In 2011, 45000 secondary students (16000 8th graders, 14900 10th graders, 14100 12th graders) were surveyed. SCRA use was added to the survey in 2011 [56]. The highest rate of past year use was 11.4% (95% CI 10.3-12.6) amongst students in the 12th grade (aged 17-18 years on average). Comparatively, 8.5% of college students aged 19-24 years and 7.4% of subjects aged 19-28 years reported last year use. The 2012 survey asked about SCRAs in younger school aged children as well. They reported last year use of "synthetic marijuana" in 4.4% in those 13-14 years old, 8.8% in 15-16 years olds and 11.3% in 17-18 year olds [50]. The prevalence of last year use had decreased in the 2013 surveys to 4% (95% CI 3.2-4.9) among 13-14 year olds (total 14600 students); 7.4% (95% CI 6.3-8.8) among 15-16 year olds (total 12900 students), and 7.9% (95% CI 6.6-9.3) among 17-18 year olds (total 12600 students) [Monitor the Future 2014]. In a different study 8% of the 852 (36% response rate to mailed questionnaire) college students surveyed in the Florida, USA reported lifetime use of "spice" [52]. Prevalence rates are similar in studies in Germany, with 9% of 15-18 year old respondents in 2010 reporting previous use of "spice and other smokeable blends" [51]. The MixMag survey of UK clubbers reported high levels of lifetime use (10.3% respondents) and last year (2.2%) use of spice in 2010/11 [57]. A higher rate of last year use of SCRAs were reported by US respondents compared with those from the UK in the Global Drug Survey in 2011/12 (14% vs 3.3%) [58]. Overall, of the 14966 participants in the 2011/12 Global Drug Survey 16% (n = 2513) had ever used SCRAs, and 40.6% of participants (n = 980 of 2417) had used in the past 12 months [59]. These rates for UK clubbers were confirmed by an in situ nightclub questionnaire (9.0% lifetime use, 2.2% last month use) of 315 respondents in 2011 in South London, UK [60].

As part of an anti-doping testing program, urine from 5956 athletes in the USA were analysed for JWH-018 and JWH-073 and their metabolites [61]. Neither JWH-018 nor JWH-073 (parent drugs) were detected, but metabolites of these were detected in 4.5% of the samples. The US army reported a study on soldiers presenting to their medical center Emergency Department from October 2010 to September 2011 [53]. This study tested for SCRAs and "bath salts" on soldiers presenting to the Emergency Department who either admitted to use of these drugs or were suspected of use. Of the 155 soldiers tested, 7.7% (n = 12) were positive for "spice".

Seely et al reported that of the 3481 drug items submitted to a crime laboratory by law enforcement in Arkansas USA from 2010 to 2012, SCRAs were the most frequently identified drugs [18]. The most common cannabinoids were AM2201, JWH-018, JWH-122, JWH-210 and XLR11.

Kronstrand et al tested blood samples from subjects suspected of petty drug offences, or driving under the influence in Sweden. Of the 3078 subjects, 28% were positive for SCRAs [62]. The most common substance was AM-2201, with two emerging SCRAs (MAM-2201 and UR-144) also detected.

Motivation for use

Many subjects across different studies have stated that their main aim for using SCRAs was to get "high"; others report use to avoid detection from drug testing, and because of the legality of such substances [25,27,63–65]. Other reasons given from various studies include curiosity, liking the effects, availability, recreational effects, relaxation, and cost [25,27,28].

Acute toxicity

Introduction

Data on the pattern of acute toxicity associated with the SCRAs is available from a combination of sources; as with other NPS, triangulation of data from these sources can be used to more reliably determine clinical features associated with toxicity [66]. These include data from user surveys, structured interviews, data from Poisons Information Services and clinical case reports [21,25,28,58,63,67]. In addition to clinical case reports of SCRA toxicity based on self-reported SCRA use there are reports of analytically confirmed acute SCRA toxicity, which provide the most reliable data on the patterns of toxicity [21,68–71]. There is also information available from one human volunteer study of the SCRA CRA13. Unintentional overdose can occur due to the variability both in concentration of and type (and therefore potentially the potency) of SCRAs in smoking mixtures [1,72,73].

Typical effects include sedation, cognitive dysfunction, postural hypotension, dry mouth, ataxia, light headedness and psychotropic effects [22,74]. Many patients with acute SCRA often have tachycardia and/or hypertension [21,22,26,67,69–71,75,76]. There have been cases of ischaemic stroke and

myocardial ischaemia associated with SCRA use [78-82], while other reports have suggested an association with seizures [26,75,82,83]. Recently, concern has been raised regarding a potential link between SCRA use and acute kidney injury [84,85]. We will now discuss each of these data sources in more detail.

Randomised Volunteer study

A human volunteer study investigated the pharmacokinetics, safety and tolerability of the SCRA CRA13, which has effects on both the CB1 and CB2 receptor. Sixty-three males were randomized to receive a single varying dose of oral CRA13 (1, 2.5, 5, 10, 20, 40 or 80 mg) or placebo. Six other males were initially given a single 40 mg oral dose of CRA13 fasting, then after a 2-week washout period, the same amount of CRA13 after a high-fat breakfast. This study found a dose-dependent increase in reported adverse events, as well as after the high-fat breakfast. The authors report adverse events for subjects in the 10 mg, 20 mg, 40 mg (both fasting and fed-state), and 80 mg groups. Dizziness was the most common symptom among subjects ingesting CRA13 (n = 6; 1 at 10 mg, 1 at 20 mg, 1 at 40 mg fed state, and 3 at 80 mg), followed by headache (n = 5; 1 at 20 mg, 1 each at 40 mg fed/fasted state, and 2 at 40 mg), and nausea (n not reported).

Surveys/Interviews

Barrett et al. reported an online survey of 316 Australian synthetic cannabinoid users in the community [27]. Respondents were recruited via a combination of social media, online discussion forums, business cards in shops and print media. Most of the cohort (210, 70%) reported having used SCRA on ten or more occasions. The respondents were questioned on their last use of SCRA; 64% had concurrently used other drugs. These included tobacco (40%), alcohol (33%) and cannabis (13%). At least one adverse event was reported by 68% but only 2.1% felt that their symptoms were serious enough to consider seeking help. Reported adverse effects included motor incoordination (38%), fast/irregular heart beat (33%), dissociation (22%), dizziness (20%), paranoia, confusion, headache (each 18%), slurred speech, sweating (each 14%), nausea/vomiting (9%), depression and psychosis (each 4%). Respondents who reported concomitant alcohol ingestion reported significantly more adverse effects (median 2 vs 1 p = 0.02). This was not true for respondents reporting concomitant use of cannabis.

An international internet-based survey recruited 168 participants via internet postboards and email listings related to "spice" [28]. SCRA were used with other drugs by 109 (65%) participants, with alcohol (54%), cannabis (40%) and tobacco (38%) being most frequently reported. Adverse effects reported included dry mouth (34% sometimes, 30% most of the time, 14% every time), lightheadedness (43% sometimes, 18% most of the time, 13% every time), drowsiness (55% sometimes, 17% most of the time, 3% every time), memory difficulties (43% sometimes, 16% most of the time, 5% every time), heart racing (43% sometimes, 10% most of the time, 6% every time), and anxiety (41% sometimes, 11% most of the time, 2% every time). Less frequent adverse effects included feeling clumsy, paranoia, dizziness, nausea, slurred speech, hallucinations, decreased appetite, ringing in ears, and vomiting.

The 2012 Global Drug Survey incorporated questions regarding SCRA use [59]. The most commonly reported adverse features include panic and anxiety (n = 19, 83%), paranoia (13, 56.5%), breathing difficulties (13, 56.5%), feeling scared, very sweaty (12 each, 52.2%), and seeing things. (11, 47.8%).

In 2010, 15 male patients from a New Zealand low security forensic inpatient unit participated in semi-structured interviews about SCRA [86]. All had used cannabis in the past, but none tested positive for THC in their last urine screen. All of the 13 (87% of total) patients that admitted to SCRA use described psychoactive effects (no further details were given). Anxiety was noted by 2 (15%) patients, while psychotic symptoms were either witnessed or experienced in 69% of users (n = 9). Five (38% of the SCRA users) experienced features that were felt to be consistent with a psychotic relapse within 24 hours of smoking SCRAs.

Poison Centre Data with no analytical confirmation of SCRAs

The Texas poison center network reported a series of SCRA and marijuana cases that they were called about during 2010 [67]. Cases that involved other substances were excluded. A total of 418 SCRA and 99 marijuana cases were reported. Compared with the cases exposed to marijuana, SCRA cases were older (242 (57.9%) SCRA cases over 20 years vs 42 (42.4%) marijuana cases), and more had "moderate" (as scored by poison centre staff) clinical features (176 (42.1% vs 16 (16.2%) RR = 2.61 95%CI 1.56-4.66). The most frequently reported adverse event in the SCRA cases was tachycardia (153, 36.6%), followed by agitation (80, 19.1%), drowsiness (73, 17.5%), vomiting (62, 14.8%) and hallucinations/delusions (47, 11.2%).

In 2010, the Rocky Mountain Poison and Drug Centre in Denver, USA, retrospectively reviewed SCRA reports to the National Poison Data System [29]. Of the 1898 exposures to SCRA identified over a 9 month period, 1353 were single agent exposures and included in the analysis. Median age was 20 years (IQ range 17, 25 years), and 74% (n = 1005) were male. Acute exposures comprised the majority (n = 1193, 88.2%) of cases, followed by 3.25% (n = 44)

being chronic, 3% (n = 43) acute on chronic, and 5% (n = 75) unknown exposures. Tachycardia was the most common side effect (n = 541, 40%), followed by agitation (n = 317, 23.4%), vomiting (n = 207, 15.3%), drowsiness/lethargy (n = 183, 13.5%), confusion (n = 164, 12%), nausea (n = 139, 10%), hallucinations/delusions (n = 127, 9.4%), hypertension (n = 110, 8.1%), dizziness/vertigo (n = 99, 7.3%) and chest pain (n = 64, 4.7%). Other cardiac effects reported included syncope (n = 29, 2.1%), hypotension (n = 18, 1.3%), and bradycardia (n = 17, 1.3%). Seizures were noted in 52 patients (3.8%), with 2 patients reported to have status epilepticus. Patients were treated with varying medications, including intravenous fluids (n = 343, 25.3%), benzodiazepines (n = 217, 16%), oxygen supplementation (n = 79, 5.8%), and antiemetics (n = 64, 4.7%).

Case Reports/Series with no analytical confirmation of SCRA(s)

A case series of 6 patients presenting to a US Emergency Department after self-reported use of "Spice" reported clinical features seen at presentation [75]. There was no analytical confirmation of SCRAs and/or other drugs that individuals may have used. The major clinical features at the time of presentation were agitation/combativeness (n = 2), seizures (n = 2), hallucinations (n = 2), syncope (n = 1), nausea and vomiting (n = 1), and inability to move the arms (n = 1). Five of the 6 cases had tachycardia (104 to 180 beats/min) on arrival. The two cases with seizures were admitted for observation, neither had subsequent seizure activity.

Another report, described SCRA use in 11 adolescents (mean age 17.3 years) who were evaluated at a USA addiction treatment centre [63]. All of them smoked the substances and the majority (10, 91%) were male. Four (36%) reported smoking SCRAs multiple times per day; use of alcohol and marijuana was also reported by 10 (91%). All reported experiencing both euphoria and memory changes; the majority (9, 82%) reported experiencing a negative mood change, such as irritability and anxiety. The most common physical effect reported was palpitations (3, 27%), followed by appetite changes (2, 18%).

A 17 year old male became dizzy, confused and lethargic after smoking K2 [87]. He also vomited, and was found to be hyperventilating and responding inappropriately by the paramedics (GCS 9/15). He was tachycardic (HR 132 bpm), hypertensive (BP 158/86 mmHg) and tachypnoeic (RR 30 breaths per minute) on arrival, he improved during a (unstated) period of observation.

There are numerous case reports suggesting an association between SCRA use and psychiatric symptoms, including acute psychosis. A case report from Germany, published in 2010 details a potential association between SCRA use and psychotic episodes [88]. The report is of a 25-year-old male with a background history of THC induced recurrent psychotic episodes. Prior to this presentation, he had been stable on amisulpride (800 mg daily) for 2 years, and had had no drug or alcohol use until one month prior to presentation, when he began smoking "spice". He smokes 3g on three occasions. He presented with increasing anxiety over the past month. On examination, he was psychotic with a theme of feeling manipulated. He believed he was being controlled through a chip that had been implanted into his abdomen. The patient's mother stated that since smoking spice, he had experienced auditory and paranoid hallucinations, which he had never previously experienced. Management and outcome of the patient were not described.

Three cases of spice use in active US military personnel have been reported [89]. Two were male, and all were aged from 19 to 23 years. Symptoms included paranoia (2 cases), agitation (2 cases), visual hallucinations (1 case), sedation (1 case), amnesia (1 case), and delusions (1 case). All three cases were normothermic, and two were tachycardic (HR 110 and 114). One case required no medication, while the other two cases received lorazepam (1 case 2 mg intravenously, 1 case 4 mg). All were admitted to hospital for observation, with resolution of all symptoms within 3 to 6 hours of observation.

Another three cases of SCRA associated with psychiatric symptoms were published in 2012 [90]. One case was a 16 year old girl who had catatonia, tachycardia (HR 105), vertical nystagmus and slightly increased lower limb tone after smoking K2. These resolved over time, and after diphenhydramine (50 mg IV) and lorazepam (4 mg IV). The second case was an 18 year old boy who was agitated, diaphoretic, aggressive, tachycardic (HR 131), tachypnoeic (RR 24) after smoking spice. His symptoms improved over a few hours and lorazepam (2 mg IV). The final case in this series was a 16 year old boy with agitation, dysarthria, pressure of speech, dystonia, and some confusion after also smoking spice. He also had hypertonia and hyperreflexia. He received 1L intravenous fluids and lorazepam (4 mg IV), and improved over 3-4 hours.

There have been a number of reports which suggest the potential for acute kidney injury (AKI) associated with SCRA use. The first of these was a 22 year old man admitted in Florida, US [85]. He presented with three days of nausea, vomiting and flank pain and admitted to smoking "fake weed". On admission, his heart rate was 62 beats/min and BP 123/68 mmHg. He was treated with intravenous fluids. A renal biopsy revealed acute tubular necrosis (ATN). Urine drug screen was negative (although this was a limited screen that would not have picked up SCRAs). Four more cases of previously healthy males (age range 20-30 years) presenting with self-limiting AKI associated with Spice use were reported from Alabama, USA [84]. All four cases presented

with two or three days of nausea, vomiting and abdominal pain, with one case reporting diarrhoea. Synthetic cannabinoid use was elicited through history, but no specific testing for SCRA was performed on biological specimens. All cases received intravenous fluid rehydration. Three cases underwent renal biopsy, all of which revealed acute tubular necrosis. All cases improved. Urine drug screen, infective and autoimmune screens were negative. The authors suggest that pre-renal renal failure secondary to dehydration is less likely to be the cause of the AKI in three of the four cases, due to the lack of orthostatic BP changes.

There have been reports of seizures related to SCRAs, a 48 year old man, who had previous cannabis use, developed seizures after his first ever oral ingestion of two different SCRA products [26]. He initially felt "high" after ingestion of the first product ("K2 summit blend") before ingesting the second product ("JWH-018 powder"). He then became nauseated, "detached" and sedated. He was found by his wife having a tonic-clonic seizure and severe diaphoresis. In the emergency department he was tachycardic (HR 136 beats/min), GCS 6/15 (post lorazepam from the ambulance) and in respiratory distress. He was intubated. Around 14 hours post admission the patient became hyperthermic (exact temperature not stated), tachycardic (HR186-214) and hypotensive (BP 59/43). His ECG revealed bigeminy, then supraventricular tachycardia. He received 1x DC shock, which reverted him to sinus rhythm. The rest of his admission was unremarkable. His urine toxicology screen was negative, but there was no specific investigations for SCRA nor their metabolites. Two of the six cases detailed in the US series described above were reported to have had seizures [75]. The first case was a 19 year old female in whom witnesses reported jerking motions of her extremities after smoking "Bayou Blaster". In the emergency department, she was found to be somnolent, not interacting (but episodically stating "is this real?"), hypertensive (153.84 mmHg), tachycardic (116 beats/min), and hyperreflexic. She was admitted to hospital for observation with ongoing somnolence. During her admission, she expressed depressive and suicidal thoughts, and was admitted to a mental health ward. Her urine drug screen was negative. The second case from this series was a male, also 19 years old. His mother reported finding him hallucinating and frightened, before "seizure-like activity", followed by foaming at the moth, cyanosis and remaining unresponsive. He was tachycardic (initially 200bpm, then 180 bpm). His background was of heavy THC use, and more recently, SCRA use (for 2 months). He was admitted for observation. His urine drug screen was positive for THC; samples were not specifically screened for SCRA(s).

A 17 year old male presented with chest pain and palpitations after smoking K9 [91]. He was found to have a sinus tachycardia (HR 140 bpm on arrival), which changed to a sinus bradycardia and intermittent functional bradycardia. He had 4 troponin tests over 24 hours, all of which were negative. Analysis of the K9 substance revealed the presence of JWH-018 and JWH-073 (biological samples were not analysed to confirm use of this substance and/or exclude other drugs). Mir et al. [80] report 3 cases of acute myocardial infarction (AMI) after SCRA use in 16 year old males. All three had ECG's that resembled ST-elevation AMI, and two underwent both echocardiogram and coronary angiography, all of which were normal. All three cases admitted to previous use of marijuana. All had urine drug screens performed. Two were positive for THC. One case had urine screen for two synthetic cannabinoid metabolites (JWH-081 and JWH-073) that was negative, however other SCRA(s) were not screened for. There has been a second, more recent, report of myocardial ischaemia related to SCRAs [81]. A 16 year old male who was a cigarette smoker and had a history of asthma and attention deficit hyperactivity disorder presented with chest pain which started two hours after using K2. A 12-lead ECG showed infero-lateral ST segment elevation. The chest pain continued for four days and troponin I peaked at 8.29 ng/mL; coronary angiography on hospital day four showed normal coronary arteries. A sample was taken for an SCRA screen but this was lots in transit to the reference laboratory.

There is a report of two cases of ischaemic stoke temporally associated with use of SCRA [78]. The first case was a 22 year old female who had no risk factors for stroke other than being on the oral contraceptive pill and she had a patent foramen ovale. She developed palpitations and dyspnoea whilst smoking K2 and a few hours later developed left-sided weakness, dysarthria and drowsiness. Urine toxicology was positive for cannabis and benzodiazepines, no testing was undertaken for SCRA. MRI demonstrated a right middle cerebral artery acute ischaemic stroke. At follow up after hospital discharge she had continued left arm weakness and poor mobility. The second case was a 26 year old female who developed left-sided numbness the morning after smoking "Peak Extreme". She also had a right middle cerebral artery stoke on MRI. Her symptoms had settled by the time of hospital discharge. Another report from the USA describes an acute ischaemic stroke temporally related to use of an SCRA product [79]. A 33 year old man with no previous history presented to the Emergency Department with right sided weakness and aphasia ten minutes after smoking an SCRA product called "WTF". CT demonstrated a left insular infarct. The SCRA XLR-11 was found in the product smoked by the patient but not in biological samples. His neurological features settled gradually over a 3 day period.

There has recently been a report of significant SCRA toxicity related to ingestion of chocolate brownies containing the SCRA AM-2201 [92]. Eleven hospital staff each ate a

chocolate brownie during their lunch break and within an hour they developed numbness and tinnglilng (n = 11), dry mouth (n = 11), difficulty focusing (n = 11), light headedness (n = 11), memory impairment (n = 10), giggling (n = 4) and presented to the ED. These symptoms settled within 4-10 hours. The remaining chocolate brownie was analysed and found to contain the SCAR AM-2201, no biological samples were analysed for SCRAs.

Poison Information Centre Data, Case reports and Case Series with biological sample confirmation of SCRA(s)

Hermanns-Clausen et al undertook a retrospective study investigating the acute toxicity of the SCRAs [21]. Twenty-nine patients admitted to hospital in Freiburg, Germany were identified through the Poisons Information Centre Freiburg. All 29 had confirmation of SCRAs in serum samples. These were CP-47,497-C8 (1 patient), JWH-015 (one patient), JWH-081 (eight patients), PWH-073 (one patient), JWH-081 (seven patients), JWH-122 (11 patients), JWH-210 (11 patients), JWH-250 (four patients), and AM 694 (one patient). Six patients had two, and another five patients had three synthetic cannabinoids present concurrently. All patients were also tested for other substances. Four patients had analytical confirmation of co-intoxicants. These include amphetamines (n = 2), and Δ^9-THC (n = 2 reaching levels that would be associated with effects). Benzodiazepines were found in three patients, and haloperidol in two. Tachycardia (HR 90-170 beats/min, median 130 beats/min) was the most frequently reported clinical feature (n = 22, 76%), followed by restlessness/agitation (12, 41%) and changes in perception/hallucination and mydriasis (each 11, 38%). Ten (38%) patients were reported to have hypertension (150-200 mmHg systolic, median 160 mmHg; 80-100 mmHg diastolic, medial 85 mmHg). The majority of adverse effects were reported in association with JWH-122 and JWH-210, but all major SCRAs were associated with clinical features in these cases.

The Swedish Poisons information Centre analysed cases from 2007 to October 2010 and where possible material and/or biological analysis was obtained [93]. Over the time period, 214 cases were found. The majority of cases were male (n = 167, 78%) and aged under 25 years (n = 204, 96%). Where possible, cases (n = 145) were graded by the poisoning severity score. The majority (n = 107, 74%) were classified as mild, 26% (n = 38) were moderate, with no cases being classified as either severe or lethal. The common symptoms included tachycardia (51%, definition not stated), drowsiness (36%), mydriasis (28%), muscular symptoms (26%), hypertension (13%, definition not stated), and vomiting (12%). Serum samples were available for 22 cases. Of these, 14 were positive for SCRA. JWH-081 was the most common SCRA (11 cases), followed by JWH-015 (3 cases), JWH-250 (2 cases) and JWH-018 (2 cases).

There have been a number of case series of acute SCRA toxicity from the USA over the past few years with analytical confirmation of the SCRA(s) involved. Monte et al reported an increase in presentations to the emergency department over the space of 1 month in 2013 (n = 76) [70]. Clinical features included altered mental status (n = 48, 67.6%), agitation (n = 32, 42.1%), and seizures (n = 11, 14.4%). Patients were found to be initially tachycardic (median HR 100 [IOR:82,115]). The majority (n = 68, 89.5%) were managed in the emergency department only, with 7 patients admitted to the intensive care unit, and 1 directly to the ward. An SCRA ADB-PINACA was found in the various substances patients provided. Twenty cases had co-ingestents confirmed either by case admission, or positive urine drug screen. The co-ingestents included marijuana, methamphetamine, methadone, cocaine, hydrocodone/paracetamol, ecstasy, and alcohol. Another report in 2013 from Georgia, USA described 22 individuals - median age 25 years, 18 (82%) male - presenting to the emergency department over an eighteen-day period [94]. Adverse effects included hypoerglycaemia (n = 13, 59%), hypokalaemia (n = 9, 41%), acidosis (n = 7, 32%), unresponsiveness (n = 7, 32%), seizure (n = 3, 14%), rhabdomolysis (n = 1, 4%) and acute myocardial infarct (n = 1, 4%). Six of the cases were admitted to the intensive care unit, with five requiring assisted ventilation. Serum was tested on seven patients and ADP-PINACA was found in five samples. It was not stated whether the samples were tested for other substances. In another series, Scwartz et al described 9 cases who developed toxicity related to smoking a product containing ADB-PINACA [95]. Seven of the patients had been smoking the same product ("Crazy Clown") at a party and were brought to the Emergency Department with delirium and agitation, three of the patients required sedation and intubation for severe agitation. The eighth patient developed disorientation and delayed seizures several days after smoking the same product. The ninth patient was a Drug Enforcement Administration (DEA) agent who had been handling the SCRA product; he developed anxiety, insomnia, nausea and vomiting and chest discomfort which were managed with benzodiazepines. Serum/plasma samples were available from 8 of the cases and ADB-PINACA was found at concentrations ranging from 50-307 ng/mL together with the metabolite ADB-PINACA 5-pentanoic acid in concentrations ranging from 12-109 ng/mL.

Sweden has set up a nationwide project investigating novel psychoactive substances (STRIDA) [68]. The first phase of their project included 103 consecutive cases that either admitted to, or were suspected of recreational drug intoxication after presentation to the emergency department; biological samples from these cases were sent for toxicological analysis. In 44% (n = 45) of cases, more than one substances was identified. This included either more than one new psychoactive substance or conventional drug, or a

combination of both. Synthetic cannabinoids were confirmed in plasma samples of 22 (21%) cases. The types of cannabinoids found were JWH-015, JWH-018, LHW-019/-122, JWH-081, JWH-210 and JWH-250. The majority of cases were young (range 13-54 years, median 18.5 years) and were male (n = 80, 78%). All reported smoking the SCRAs. The most common clinical features for the SCRA positive cases reported were tachycardia (77%), mydriasis (73%), drowsiness (36%), tremor (27%), agitation (23%), hypertension (23%), and nausea/vomiting (23%).

Another report described three cases (males aged 19, 21 and 25 years) presenting to the same emergency department after smoking SCRAs [69]. Two of the cases presented with an altered conscious level, agitation, reports of "shaking limbs", and elevated lactate (5.7 mmol/L and 3.3mmol/L). One of the cases was tachycardic (122 beats/min), while the other case was hypertensive (BP 204/103 mmHg). The third case presented with a "small time frame of amnesia". His friends reported that he had been delusional and acting bizarrely. All three cases had their urine tested for metabolites of JWH-018 and JWH-073: all three were positive for metabolites of JWH-018 and two were also positive for metabolites of JWH-073. Other urine drug screen and blood alcohol levels were negative.

Schneir et al reported 2 cases of SCRA intoxication [71]. Both patients were women, aged 20 and 22. Together they smoked an over the counter "spice" product. Shortly after smoking, they both felt "as if they did not know who they were", and called an ambulance. The first patient's symptoms included self-limited anxiety, tremulousness, palpitations. Her examination was normal and she was discharged home asymptomatic 1 hr later. The second patient mainly experienced anxiety, and stated she felt "psychotic". She was tachycardic (HR 126 beats/min), but otherwise had a normal examination. She chose to discharge while still tachycardic (HR 110 beats/min), stating she felt better. Analysis of the product smoked revealed the presence of the naphthoylinndole SCRAs JWH-018 and JWH-073.

Freeman et al report on ischaemic stroke associated with the use of JWH-018 in two siblings [77]. The first was a 26 year old male who presented to the emergency department with dysarthria, right face and arm weakness, and expressive dysphasia. Non contrast CT brain showed a hyperdense left middle cerebral artery (MCA). He went on to have a CT angiogram, which confirmed a left MCA clot. He was treated with tissue plasminogen activator and his symptoms resolved. Urine drug screen was positive for cannabinoids, but not tested specifically for SCRA. The second sibling was a 19 year old female who presented to emergency after sudden loss of consciousness and limb shaking a few minutes after smoking Spice. In hospital she was noted to have aphasia, right hemiplegia and sensory loss. She was tachycardic (HR 120 beats/min) with a blood pressure of 143/73. CT angiogram revealed an irregular contour of the proximal M1 segment of left MCA without dissection, but with thrombus noted in the insular branches. Her MRI brain supported an embolic event as cause for her CVA, with a large left MCA territory infarction and punctate infarcts in the right cerebral hemisphere. Similar to her brother, the urine drug screen was positive for cannabinoids. In both cases, no other secondary causes for stroke were identified; a serum sample confirmed JWH-018 in the second case. The second case had ongoing right hemiparesis and expressive aphasia at follow-up. Her brother's outcome is unknown as he did not return for follow-up.

The first European case report of a seizure related to SCRAs, with analytical confirmation of AM-2201 was published in 2013 [82]. The case was of a 20 year old male with a background history of poorly controlled type 1 diabetes and G6PD deficiency. He presented after a self-limiting 2-3 minute witnessed generalised tonic-clonic seizure. This was after smoking "black mamba". He had also omitted his morning insulin dose, and then post seizure advised his friends to inject 50 units of actrapid. On presentation to the ED he had a GCS 14/15 (this improved over the first half-hour), his blood sugar was 24.3 mmol/L (improved to 9.3 mmol/L) and he a mild metabolic lactic acidosis on arterial blood gas (pH 7.341, pCO2 6.0 kPa, pO2 13.23 kPa, HCO3 23.8 mmol/L, lactate 6.3 mmol/L). Other biochemistry testing and examination were normal. The patient discharged against medical advice after 2 hours of observation. Urine analysis revealed the presence of AM-2201 metabolites. In another report, a 48 year old man presented to hospital with 2 seizures after smoking 3 g of "spice" [83]. His urine tested positive for the primary metabolite of JWH-081. A 19 year old male also experienced generalized seizures in association with use of a SCRA. He had been previously well, and proceeded to have 2 witnessed tonic clonic seizures after smoking "Happy tiger Incense". The only abnormality on examination was hypertension (BP 177/82 mmHg), which improved over time to 123/68 mmHg. He was discharged home after a period of observation. The substance was analysed, and 4 SCRAs were found (JWH-018, JWH-081, JWH-250 and AM-2201). The final report of seizures related to SCRA was a previously healthy 48 years old man who experienced a generalized tonic-clonic seizure 30 minutes after oral ingestion of a white powder with alcohol [76]. His recovery was complicated by a second seizure, then supraventricular tachycardia (SVT). Metabolites of JWH-018 were found on analysis of a urine sample. Seizures have been reported in other case series related to other SCRA including ADP-PINACA [95].

Recently, cases have emerged that suggest a potential association between the SCRAs and acute kidney injury (AKI). The first series from the USA reports AKI associated with SCRAs in 16 cases spread across six different states

[96]. The majority of cases had nausea or vomiting as their presenting complaint (n = 15, 93.8%), with 12 (75%) reporting abdominal/flank/back pain. Eight cases had a renal biopsy performed. Of these, six has acute tubular injury, and three had acute interstitial nephritis. Serum creatinine peak occurred 1-6 days (median = 3 days) after the onset of symptoms. Five patients required haemodialysis. Most patients' AKI resolved within 3 days of their serum creatinine peak. For seven of the cases, the product, and/or serum/urine samples were analysed for SCRA. Five products contained XLR-11, with one also containing UR-144. Of the biological specimens, five cases were positive for a XLR-11 metabolite. Given the majority of cases had vomiting, and six of the eight biopsies revealed acute tubular necrosis, it is highly possible that the AKI was secondary to pre-renal renal failure due to dehydration. The report states that none of the cases reported potentially toxic medication use, and that other causes of AKI were not found.

A further case report regarding a 26 year old male admitted to hospital with AKI and use of "Mr Happy" has been published [97]. He experienced abdominal pain, nausea, vomiting and low back pain. He admitted to smoking "Mr Happy" 2 to 3 times per day for the past year. Analysis of his serum and urine revealed SCRAs XLR-11 and UR-144, and their metabolites. The AKI resolved and the patient was discharged home 6 days post admission.

A more recent case series also reports an association between SCRA use and AKI [98]. This described 9 cases from Oregon and Washington from May to October 2012. The cases were all males with a median age of 18 years (range 15–27 years) with no known history of kidney disease. All of the cases had been smoking SCRA products and the median time from last SCRA use to symptom onset (typically nausea and abdominal/back pain) was 8-12 hours. The median peak creatinine concentration was 7.9 mg/dL (range 2.6 – 17.7 mg/dL). Other causes of AKI were excluded. One patient was treated with corticosteroids and one patient required haemodialysis; 5 patients had follow up at 2-9 months and creatinine was 0.8–1.8 mg/dL). SCRA products (n = 2) and biological specimens (n = 9) were available for analysis from 5 patients – XLR-11 was detected in the SCRA products and in serum, urine and renal biopsy samples.

Chronic Toxicity

There is minimal data published on chronic toxicity of SCRAs. Alhadi et al report a case of a 21 year old man with suspected hypersensitivity pneumonitis secondary to smoking SCRA products [99]. He presented to the Emergency Department after a motor vehicle accident, which occurred after a syncopal event while driving. He was found to be hypoxic (SaO_2 75% room air, 95% on 15 L/min O2 via non-rebreather face mask), tachypnoeic (RR 45 breaths/min), tachycardic (HR 118 beats/min) and hypertensive (BP 182/108). His respiratory status deteriorated in the emergency department, requiring mechanical ventilation and transfer to the intensive care unit. Chest Xray revealed diffuse hazy nodular densities bilaterally. CTPA ruled out traumatic pulmonary contusions, and demonstrated extensive, diffuse airspace nodules distributed peribronchovascularly. His admission was complicated by a left sided pneumothorax with subcutaneous emphysema and pneumomediustinum which required chest thoracostomy tube. He underwent a bronchoscopy with transbronchial biopsies taken, and a broncho-alveolar lavage. This revealed lymphocytic infiltrate, and macrophages containing a refractile brown pigment. He was treated with broad spectrum antibiotics and high dose methylprednisone. He improved, and was extubated on day 8. Screening for the cause of the lung disease was unable to find any cause other than the hypothesis of SCRA induced hypersensitivity pneumonitis. Blood, urine and saliva specimens were tested and were positive for AM-2201, JWH-122, JWH-210 and JWH-018. His urine drug screen was positive for THC only. Additional history from his wife and family revealed a 2 month history of chronic cough and occasional haemoptysis. He also smoked marijuana almost daily, and over the previous four months had been regularly smoking SCRAs. There is also another case series suggesting an association between SCRA use and pulmonary changes [100]. Berkowitz et al report four mean aged 18–24 years who presented with shortness of breath (n = 4), chest pain (n = 1), cough (n = 3) and hypoxia (n = 4, oxygen saturations 79-84% on room air). Chest Xray revealed diffuse micronodular shadowing and CT showed diffuse centrilobular necrosis and tree-in-bud pattern; biopsies from three of the patients showed organizing pneumonia. One patient died during their initial hospital admission and the other three had ongoing shortness of breath and exercise intolerance at follow up. The duration of SCRA use was not documented and no testing of either SCRA products or biological samples was undertaken.

Three published case series/reports suggest an association between SCRA use and chronic psychosis. Hurst et al report 10 usually healthy patients admitted to a psychiatric ward [64]. They were all male and aged between 21-25, and admitted to smoking SCRAs from 4 times in a 3 week period, to daily for 1.5 year. The most common features were paranoid delusions (n = 9), disorganized behavior (n = 7), flat effect (n = 6), insomnia (n = 6), psychomotor retardation (n = 6), and auditory hallucinations (n = 4). Three patients had ongoing psychosis for 5 months; the other patients had full resolution within 5-8 days of admission. Two adolescent males were admitted to an acute psychiatric unit in Philadelphia USA, after developing psychosis [101]. Both had

family histories but no personal history of psychosis related mental health. Both admitted to taking K2. Both were re-admitted with relapses of their psychosis. In New Zealand, 17 patients with self-reported SCRA ("K2") use with a total of 21 admissions to a psychiatry ward were reported [102]. Thirteen people had previous psychiatric admissions. Presentations varied from psychosis, anxiety, depression and severe suicidal ideation.

Dependence

There is a small amount of literature regarding dependence, including animal studies, human survey data and case reports [28,103-107].

Animal Data

A study trained rhesus monkeys to discriminate THC, JWH-018, JWH-073 from vehicle [103]. The duration of action was four, two and one hour respectively. All three compounds were found to attenuate the rimonabant discriminative stimulus in animals chronically treated with THC. This effect was dose dependent. The results lead to the authors concluding SCRAs JWH-018 and JWH-073 had similar effects to THC, and the shorter duration of action has the potential to increase the risk of dependence with the SCRA.

Another rhesus monkey study investigated the effects of pre-treatment with THC on SCRA tolerance [104]. The animals were pre-treated with either three or 14 days of THC before testing tolerance of CP-55,940, JWH-073, and JWH-018. The three days of pre-treatment had no effect on tolerance of any SCRA; but 14 days of pre-treatment resulted in decreased sensitivity of all four substances (THC 9.2-fold, CP-55,940 3.6-fold, JWH-018 4.3-fold, and JWH-073 5.6-fold). It was concluded that the differences in sensitivity changes may indicate a difference in the potential for dependence.

Human Data

Vandrey et al published data on abuse and dependence from their online survey across 13 different countries including the USA [28]. Thirty-seven percent of respondents (total respondents = 168) met the DSM IV criteria for abuse, with 12% fulfilling the dependence criteria. None of the respondents had ever sought help for this. There was no data reported about length of SCRA use in these specific respondents. They reported that withdrawal symptoms after stopping Spice were rare. Symptoms that were reported include headache, anxiety, coughing (all 15%), insomnia (14%), irritability (13%), and impatience (11%). Other symptoms included difficulty concentrating (9%), restlessness (9%), nausea (7%) and depression (6%).

There are case reports regarding withdrawal from "Spice" [105-107]. Nacca et al reported 2 cases of suspected SCRA withdrawal in 2013 [105]. The first case was a 22 year old female who had abruptly ceased smoking "Mr Nice Guy Original Flavour" 6 days prior to presentation. She reported smoking 3 g/day of this substance for at least 1 year. Her symptoms included sweats, chills, cravings, headache, severe anxiety, insomnia then vivid dreams, and anorexia with significant weight loss (approximately 20 pounds). She presented to hospital after developing progressive cramping to her arms and legs. She had mild tachycardia (HR 100 beats/min), tachypnoea (RR 28 breaths/min) and carpo-pedal spasm on examination, and was reported as being very anxious. She improved with 2 litres of intravenous rehydration and 2 mg intravenous lorazepam. Follow-up 1 week later revealed she was improving, with no further benzodiazepine requirement. The second case was of a 20 year old male, whom had also ceased 18 months of daily use of 3 g of "Mr Nice Guy" 6 days prior to presentation (he had decreased his use to 1 g/day the month before). His symptoms included chest pain, palpitations, shortness of breath, headache, tremor and diaphoresis. He had attempted to alleviate his symptoms with the use of marijuana, but this did not help. He was admitted to hospital for his degree of tachycardia (HR 120) and anxiety that was not relieved by low-dose benzodiazepines, hydroxyzine, nor diphenhydramine (doses not stated). He was given 50 mg of quetiapine, after the patient stated this had helped in the past. The quetiapine relieved his symptoms, and he was discharged home on quetiapine; no long-term follow up was detailed in the report.

A 20 year old male was admitted to hospital in Germany for detoxification of "Spice Gold" [106]. He had been using this daily for 8 months, with a rapid increase in daily use to 3 g daily. His past history included pituitary insufficiency, attention deficit hyperactivity disorder (ADHD), and previous drug use. At the time of his dexotification, "spice gold" was the only recreational substance he was using, but he had also been self-withdrawing use of nocturnal zopiclone. Withdrawal symptoms began on day 2. These included "internal unrest", sweating, tachycardia, (HR to 125 bmp), hypertension (180/90 mmHg), nausea, tremor, headache, and nightmares. A one-off dose of zopiclone was trialed with nil result. His hypertension had been treated with a singe oral dose of both promethazine (25 mg) and clonidine (0.175 mg). This decreased his BP, but had no effect on his symptoms. The patient felt well on day 7, but the "internal unrest" returned on day 8. This was treated from day 11 with 0.175 mg pramipexole at night. This was titrated to 0.35 mg at night by day 18, where the patient reported improvement in his symptoms. Follow-up 4 months after discharge revealed the patient had not consumed any further SCRAs.

Rominger et al also reported a case of inpatient withdrawal from "Spice Gold" [107]. This patient was a 23 year old male, who had been using cannabis since the age of 14 years. He changed to "spice gold", but had to progressively increase his dose to 10 g daily. After failed attempts to cease at home, he was admitted for supervised detoxification. Withdrawal symptoms began after day 1, lasting 3-4 days. Withdrawal symptoms included cravings, anxiety, crying fits, and mood instability, special disorientation, pain, shortness of breath, sweating and restlessness. The authors did not report whether the patient received any medical therapy for his withdrawal. During his admission, he underwent PET scanning on arrival, and 1 week later. The PET scan revealed reversible alterations in dopamine D2/3 receptor availability.

Synthetic cannabinoid related fatalities

There have been numerous reports in the popular press about deaths apparently related to the use of SCRAs, however there are only a few reports of SCRA related fatalities in the scientific literature [62,108-110].

Patton et al report a fatal case of a 23 year old man who had smoked material containing high concentration of AM2201 [108]. After reportedly being well in the day, he was found on the ground of his bedroom covered in blood, after approximately half an hour of stomping noises. Post mortem revealed many blunt and sharp force wounds, with the likely fatal injury a self-inflicted stab wound to his neck. AM2201, and metabolites, were confirmed on serum testing along with JWH-018 metabolites. The authors suggested this could either be due to previous exposure to JWH-018, or due to metabolism of AM2201 itself; no other drugs were detected.

Kronstrand et al reported a fatal intoxication associated with JHW-210 in a 17 year old male had been smoking a herbal mixture with a friend outdoors [62]. The friend reported feeling dizzy and losing touch perception and so he returned indoors, leaving his friend to continue to smoke. The 17 year old was later found dead and the cause of death was determined to be hypothermia combined with psychotropic substance intoxication - JHW-210 was confirmed on analysis of post-mortem samples.

There are two reports in the published scientific literature describing the detection of the SCRA 5F-PB22 in post-mortem samples [109,110]. The first report described three individuals [106]: i) A 17 year old male who collapsed after drinking alcohol and using drugs whilst at a friend's house. He subsequently was pronounced dead in the Emergency Department. Post-mortem toxicology was positive for ethanol (33 mg/dL) and 5F-PB22 (1.1 ng/mL). The cause of death was listed as "5F-PB22 intoxication. ii) An 18 year old who was found dead after having been two several parties on the two nights before his death. Post-mortem toxicology was positive for 5F-PB22 (1.5 ng/mL) only. The cause of death was listed as "suspected acute drug intoxication using the synthetic cannabinoid 5F-PB22". iii) A 27 year old who presented to the Emergency Department with a history of anorexia, fever, vomiting and abdominal pain. The patient had acute liver failure, acute kidney injury and a coagulopathy. He rapidly deteriorated despite aggressive treatment and dies the following day. Post-mortem toxicology was positive for carboxy-THC (246 ng/mL) and 5F-PB22 (1.3 ng/mL). The cause of death was listed as "fulminant liver failure in the setting of THC (marijuana) and 5F-PB22 (synthetic cannabinoid) exposure". The second report also described these three cases together with an additional case [110]. The additional case was a 19 year old male who had been at a party and the following day felt 'light-headed' and went to bed; he was found dead in bed the next day. Post-mortem toxicology was positive for 5F-PB22 (1.5 ng/mL). The cause of death was listed as "suspected acute drug intoxication using the synthetic cannabinoid 5F-PB22".

Shanks et al describe two cases from the USA of deaths related to the SCRA XLR-11 [111]. The first was a 29 year old female who was found dead in her bedroom, she was last seen alive the day before by her boyfriend who stated that she was "intoxicated and agitated". She was a known user of synthetic cannabinoids and empty packages of a product named ''Black Dragon'' were found at the scene. XLT-11 was found in post-mortem blood samples at a concentration of 14 ng/mL along with diphenhydramine at a concentration of 81ng/mL; the medical examiner rules the cause of death as synthetic cannabinoid toxicity. The second case was a 32 year old female with had a history of drug use including methamphetamine, heroin and synthetic cannabinoids who presented to the Emergency Department with chest pain, nausea, and agitation. She was diagnosed with anxiety and left the hospital, later in the day she was found unresponsive in a bedroom at the friend's house; she was pronounced dead on arrival in hospital. XLR-11 was found in post-mortem blood samples at a concentration of 0.6ng/mL, no other drugs were found. The medical examiner ruled the cause of death as undetermined, with significant findings of positive toxicology for XLR-11.

Conclusion

SCRAs comprise a large varied group of substances. They are sold in smoking mixtures, often sprayed onto plant products, having names such as Spice, K2, K9, "black mamba", and Kronic. They have in common their action on the CB1 and CB2 receptors. Much remains unknown regarding the pharmacology and toxicology of these substances. What is known is largely based on case reports, self-experimentation, and

user surveys. Use of these substances are more prevalent among various sub-populations, including young people still in further education, people subjected to regular drug screening (eg: athletes and soldiers), and people who frequent the night time economy. Common symptoms in those presenting with acute SCRA toxicity are palpitations, anxiety, hallucinations, nausea/vomiting, psychosis and paranoia. Tachycardia, and hypertension are often seen. In addition, there are reports of seizures, acute kidney injury, acute myocardial infarct, cerebrovascular accident, and death associated with SCRA use. It is becoming apparent that the SCRAs have dependence potential and there are reports suggesting withdrawal from SCRAs. Withdrawal symptoms include sweating, paranoia, headache, nausea and/or vomiting, difficulty concentrating, irritability and impatience.

Conflict of interest None.

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