Novel Psychoactive Treatment UK Network

NEPTUNE

Harms of Synthetic Cannabinoid Receptor Agonists (SCRAs) and Their Management

Dr Dima Abdulrahim and Dr Owen Bowden-Jones on behalf of the NEPTUNE group

This document is a summary of the chapter on synthetic cannabinoid receptor agonists (SCRAs) published in a systematic review of the literature, *Guidance on the Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances*. Novel Psychoactive Treatment UK Network (NEPTUNE). London, 2015 (www.neptune-clinical-guidance.co.uk)

The Health Foundation
Inspiring Improvement

NEPTUNE (Novel Psychoactive Treatment UK Network)
Club Drug Clinic
Central and North West London NHS Foundation Trust (CNWL)
69 Warwick Road
Earls Court
SW5 9HB
www.neptune-clinical-guidance.co.uk

The guidance is based on a combination of literature review and expert clinical consensus. We accept no responsibility or liability for any consequences arising from the use of the information contained in this document.

The recommended citation of this document is:

Abdulrahim D, Bowden-Jones O, on behalf of NEPTUNE group. *Harms of Synthetic Cannabinoid Receptor Agonists (SCRAs) and Their Management*. London: Novel Psychoactive Treatment UK Network (NEPTUNE), 2016.

NEPTUNE is funded by the Health Foundation, an independent charity working to improve the quality of health care in the UK.
www.health.org.uk

This document has been written as part of the wider suite of clinical guidance and tools that aim to provide evidence-based knowledge to inform the management in clinical practice of harms related to the use of 'club drugs'. It is a supplement to, and should be read in conjunction with, *Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances* (www.neptune-clinical-guidance.co.uk).

Quality of the research evidence
The international evidence on the management of the acute and chronic harms related to the use of SCRAs is limited and still emerging; randomised control trials in particular are not available. Evidence mainly consists of case reports and series and a small number of prospective observational studies, retrospective cohort studies and analysis of patient records. Despite these limitations, data/evidence from these sources is relatively consistent.

Editorial production and page design by Ralph Footring Ltd, www.footring.co.uk

NEPTUNE

Contents

1. Introduction

Synthetic cannabinoid receptor agonists (SCRAs) are a large group of drugs, which have a strong effect on the endocannabinoid system. Approximately 200 different SCRA compounds are now available. In 2015, they represented the largest group of novel psychoactive substances (NPS) reported globally and in Europe.

Products used for recreational purposes are typically an inert herbal product that has been sprayed with one or more SCRAs (Figure 1) and that is smoked. Oral, powder and injectable SCRA preparations have also been reported to be available; in addition they are sold as an e-liquid (the liquid used in electronic cigarettes).

There are a large number of brands sold on the UK market (Figure 2), containing different SCRAs, with different levels of potency. Herbal products are marked 'not for human consumption' but are presented in attractive and colourful packaging.

Figure 1. SCRA products such as Spice are typically sold as an inert herbal product that has been sprayed

Figure 2. The packaging of a selection of products and brands

What particular brands contain is likely to vary, and certainly brand names are not reliable indicators of what is consumed. Analytical tests have shown that the cannabinoid constituents and dosage can vary greatly both between products and between batches of the same brand. There may even be differences within the same package, if for example the SCRA has been sprayed unevenly on the herbal product. There is also evidence that some products contain a combination of different SCRA compounds.

SCRA products in the UK are sometimes known generically as 'Spice', the name of a popular brand. However, not all products labelled 'Spice' are SCRAs. Stimulant drugs also branded 'Spice' have been sold (Figure 3), suggesting once again the hazards associated with relying on brand names.

At the time of writing of the report, the Psychoactive Substance Act 2016 had just come into force. The trade in 'legal highs' became illegal and the police were given the power to shut down 'headshops' and UK-based on-line sellers. It is too early to identify its impact on patterns of substance use, including 'distribution' and the packaging of what were previously 'legal highs', although there is some anecdotal evidence that SCRAs are increasingly being sold in plain plastic packets by street dealers. It is not yet clear whether this represents a more lasting trend and whether SCRAs will be sold on the illicit market (and if so how). More research is needed.

In the UK, information on the prevalence of use of SCRAs remains limited. The use of SCRAs appears to be more prevalent among prisoners and homeless populations, and concerns have been voiced about its impact on these groups.

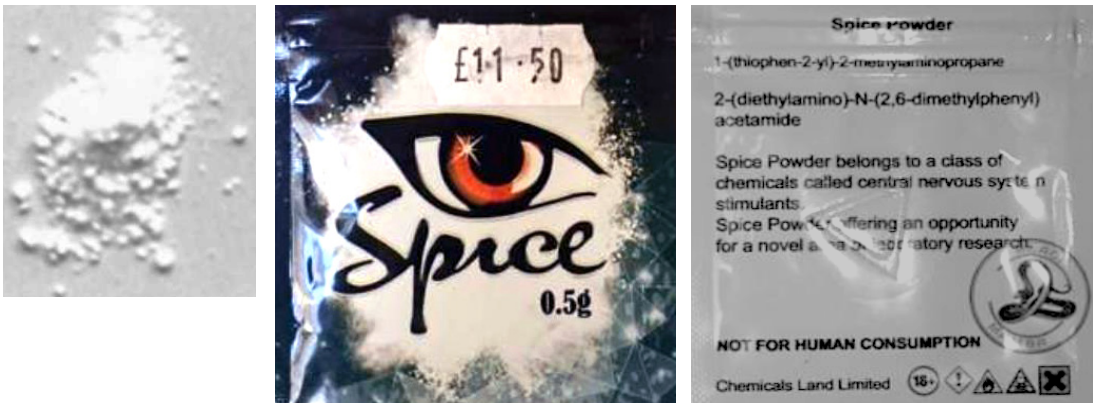

Figure 3. Stimulant drug (left) branded as 'Spice' (front and back of package shown right)

2. Pharmacology and effects of SCRAs

SCRAs are a large and chemically diverse group of molecules with some functional similarity to natural cannabis, the chief psychoactive constituent of which is delta-9-tetrahydrocannabinol (THC), as well as to other phytocannabinoids. However, many of the SCRAs are not structurally related to natural cannabinoids or THC. Table 1 compares SCRAs with natural cannabis.

Table 1. Comparison of SCRAs and natural cannabis

	Natural cannabis	SCRAs
Primary psychoactive substance	THC (delta-9-tetrahydro-cannabinol)	One or more of a wide array of molecules that stimulate the brain's cannibanoid receptors
Presence of cannabidiol (CBD)	Contains CBD	Do not contain CBD

Over 200 SCRAs have been detected on the global drug market, with an estimated 150–160 available to UK consumers. There are wide differences between the various SCRAs, including in metabolism, potency, toxicity and duration of effects.

- Both SCRAs and natural cannabis (THC) bind to the CB1 and CB2 receptors. Generally speaking, the greater the affinity to the CB1 receptor, the higher is the psycho-pharmacological activity of the agonist compound.
- SCRAs usually have a much higher affinity for those receptors than natural cannabis. As a result, SCRAs can produce stronger effects, especially those that act as full agonists on the CB1 receptor.
- Although SCRAs produce effects that have similarities to those produced by THC, they are not the same. SCRAs may have other biological actions, which may explain some of the differences in severity and features of toxicity between SCRAs and natural cannabis.
- Some SCRA compounds incorporate indole-derived moieties, which are structurally similar to serotonin and may be associated with particularly high levels of activation of serotonin receptors.
- It has been suggested that at high doses some SCRA compounds may also possess monoamine oxidase and 5-HT reuptake inhibitory properties, which may increase the risk of serotonin syndrome. (For more information on the serotonin syndrome see NEPTUNE, *Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances*, p. 147.)

- In contrast to natural cannabis, SCRAs do not contain cannabidiol (CBD), a chemical which moderates the effects of THC and may possess anxiolytic, antipsychotic and anti-craving properties.
- It has been reported that, in comparison with natural cannabis, SCRAs are characterised by quicker onset of effects, significantly shorter duration of action, worse hangover effects and more intense visual hallucinations, paranoid feelings and behavioural disturbances.

Onset and duration of action

The onset of the action of SCRAs is usually within minutes of smoking, but longer following oral consumption. The length of the effect of SCRAs varies. Although there are no controlled studies in humans, there are reports that the duration of action of SCRAs can range from 1–2 hours for some compounds to up to 6–8 hours for others.

Potency

Most SCRAs are more potent than natural cannabis, and some have long half-lives. There are differences between the various SCRAs, with some having significantly greater potency than others. Products containing SCRAs can range from those with potency similar to natural cannabis to those that are up to 100–800 times more potent than natural cannabis typically is.

Effects

The desired effects of SCRAs include relaxation, altered consciousness, disinhibition and euphoria, and a state of 'being energised'. Reports describe sedative-like effects, and hallucinogenic effects have also been reported. People who use SCRAs have indicated that they can produce unique subjective effects, discernible from the effects of natural cannabis, and there are suggestions that when products are smoked people are able to differentiate between the effects of natural cannabis and those of SCRAs.

3. Harms of acute toxicity

Acute toxicity

The evidence base on the harms associated with the use of SCRAs and their management is still emerging and remains limited. Little is known about the metabolism and toxicology of SCRAs in humans. It cannot be assumed that the risks associated with their use will be comparable with those of cannabis and there are concerns that they may have a greater potential to cause harm. SCRA products can also have unpredictable effects. There is emerging evidence that the risks of requiring emergency medical treatment as consequence of using SCRAs are much greater than for natural cannabis. There is also evidence that some more recent formulations may be more potent than earlier ones and be associated with greater harms.

Box 1. Symptoms of acute toxicity

The literature on the adverse effects of SCRAs remains limited, but the following adverse effects linked to the use of the drugs have been reported.

Neurological, cognitive and psychiatric effects

- Anxiety, irritability and psychosis-like effects
- Inappropriate or uncontrolled laughter, anger, sadness, flat affect, depression and suicidal thoughts, excitability, agitation, combativeness, aggressiveness, thought disorganisation, panic attacks, paranoid thinking, delusions and auditory and visual hallucinations, changes in perception, acute psychosis
- Reduced levels of consciousness; coma
- Numbness, tingling, light-headedness, dizziness, pallor, tinnitus, diaphoresis, tremor, somnolence, syncope, unresponsiveness, nystagmus and convulsions
- Short-term memory and cognitive deficits, confusion, sedation and somnolence, thought blocking, nonsensical speech, amnesia, increased focus on internal unrest

Cardiovascular effects

- Tachycardia, hypertension, hypotension, hypokalaemia, chest pain and palpitations, myocardial ischaemia, myocardial infarction, ischaemic strokes
- Neuromuscular and musculoskeletal effects
- Hypertonia, myoclonus, myalgia, rhabdomyolysis

Renal effects

- Acute kidney injury

Other effects

- Hyperglycaemia, hypoglycaemia, acidosis, respiratory acidosis, cold extremities, dry mouth, dyspnoea, mydriasis, vomiting, loss of sight and speech

Serotonin syndrome

In addition, SCRAs have been linked to the serotonin syndrome. For more information on serotonin syndrome see NEPTUNE, *Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances*, p. 147.

The symptoms of acute toxicity are listed in Box 1. Acute SCRA toxicity appears to have a similar clinical presentation to the toxicity of natural cannabis and THC, although differences have been reported, with convulsions and hypokalaemia particularly noted. At least some SCRAs have led to severe and even life-threatening intoxication when taken in sufficiently large doses, particularly in the case of compounds that act as a full agonist at the CB1 receptor.

Individual susceptibility to SCRA-related harm remains unclear. The harmful effects of SCRA may be greater in SCRA users who are drug naive or those with only limited previous exposure to cannabis.

Reported harms associated with SCRAs include a range of psychiatric problems, the most prominent of which are anxiety (which can be severe), irritability, agitation and psychosis-like effects. Other adverse effects include negative mood changes, hallucinosis and 'hangover' effects.

Common physical effects of SCRAs include tachycardia and nausea. SCRAs are also reported to be cardiotoxic. Widely reported sympathomimetic effects include seizures, hypertension, diaphoresis, hyperthermia, agitation and aggression. SCRAs have also been associated with hypotension and linked to severe kidney injury and rhabdomyolysis (muscle damage).

There has been particular concern over a number of SCRAs, including MDMB-CHMICA, which have been associated with severe adverse effects across Europe.

SCRA-induced psychosis

Psychotic symptoms appear to occur relatively frequently following SCRA consumption. More research is needed, but this may be linked to the high potency of the drugs and the fact that, unlike natural cannabis, SCRAs do not contain cannabidiol (CBD), a chemical which appears to possess antipsychotic properties.

It has been suggested that SCRA users are more likely than people who use natural cannabis to experience hallucinations and delusions.

In comparison with psychotic episodes associated with the use of natural cannabis, psychotic episodes associated with SCRAs occur more frequently, are more severe and are linked to greater agitation.

- There are reports of SCRA-associated acute transient psychosis, as well as reports that some individuals may experience psychosis that persists for weeks after the acute intoxication, or even longer.
- Psychosis has been reported in otherwise healthy people; however, there is particular concern about the risk of SCRAs precipitating psychosis in vulnerable individuals, including those with a current or previous history of psychosis.

4. Management of acute harms

SCRA intoxication

The ingestion of SCRA will not necessarily have adverse effects that require an intervention.

- Adults who have used SCRAs and who do not present with symptoms of acute intoxication are unlikely to require any monitoring, investigation or treatment.
- Even when the person presents with symptoms of SCRA intoxication, these will usually be self-limiting and resolve spontaneously.

Some people will, however, suffer SCRA-related adverse effects and these could be severe. Acute SCRA intoxication has been characterised as generally short-lived, with reported symptoms including elevated heart rate and blood pressure, visual and/or auditory hallucinations, mydriasis, agitation, anxiety, hyperglycaemia, dyspnoea, tachypnoea, nausea and vomiting.

Box 2. Guidance on when to call the emergency services for unwell recreational drug users

Call 999 or 112 if any one of the following is present:

- **Unconsciousness** – if the patient does not respond to vocal commands, requires painful stimulus (e.g. pressure across the fingernails) to respond, or does not respond at all
- **Significant agitation** (e.g. pacing around the room) or aggression, not settling within 15 minutes
- **Seizures** (e.g. a convulsion similar to an epileptic fit)
- **Breathing difficulties**, such as fast breathing rate, not settling within 5 minutes
- **Heart rate** over 140 beats per minute, not settling within 5 minutes
- **Temperature** over 38.5°C, not settling after about 5 minutes of rest or, if no thermometer is available, if very flushed and feels very hot
- **Blood pressure**: Systolic ('upper pressure') over 180 mmHg, or diastolic ('lower pressure') over 110 mmHg on two repeated measurements
- If there are **any other concerns** (e.g. severe headache, chest pain)

If in doubt call 999 or 112

Source: The Euro-DEN Project. See David M. Wood, Alison M. Dines, Fridtjof Heyerdahl, Christopher Yates, Isabelle Giraudon, Raido Paasma, Knut Erik Hovda, Paul I. Dargan (2016) Review of European-Drug Emergencies Network (Euro-DEN) training package for non-specialist workers to assess acute recreational drug and new psychoactive substance toxicity in nighttime economy environments. *Drugs: Education, Prevention and Policy*, 23:1, 73–7. doi: 10.3109/09687637.2015.1081379. See also http://www.emcdda.europa.eu/system/files/attachments/1947/INT19_Euro-DEN%20 2015-final.pdf

When to call an ambulance

As part of its aims to improve the recognition and assessment of acute drug toxicity by training staff working in recreational settings, the Euro-Den project has developed guidance on when to call the emergency services (by telephoning 112 or 999 in the UK) for unwell recreational drug users. See Box 2 for information on when to call emergency services.

Identification and assessment of acute harms in acute care settings

SCRAs cannot be detected by the screening tests for THC, the active ingredient in natural cannabis. Clinicians working in emergency care should be vigilant for SCRA-induced toxicity despite negative drug-screening results. Laboratory techniques have been developed to detect some SCRAs, but these are currently not widely available and do not detect all SCRAs; the regular appearance of new compounds is challenging because of the lack of reference samples in laboratories to identify them. In addition, more than one SCRA can be found within the same mixture or product.

The identification of acute SCRA toxicity is also complicated by the unpredictable effects of the drug and the lack of a clear toxidrome to distinguish SCRAs from other recreational substances. There are no pathognomonic features of SCRA toxicity.

SCRA intoxication should be included in the differential diagnosis of adolescents or young adults presenting with an acute and otherwise unexplained alteration of mental state associated with autonomic disturbances. The use of SCRAs should also be considered in atypical presentations, such as acute unexplained kidney injury or myocardial infarction in an otherwise healthy young person.

Managing acute intoxication and toxicity

For up-to-date information on the management of the harms of SCRAs consult TOXBASE® (www.toxbase.org). Non-UK readers should consult their local or national guidelines.

The management of SCRA toxicity is symptomatic and supportive, as no antidotes exist.

- Hydration and monitoring may be enough for patients with mild to moderate intoxication.
- Supportive treatment is dependent on a patient's specific presentation (e.g. agitation, delirium, hypertension, convulsions).

In a minority of cases, SCRA consumption can be associated with severe cardio-vascular, cerebrovascular, neurological, psychiatric and renal effects. Interventions will focus on the prevention of rhabdomyolysis and the monitoring of cardiac or cerebral ischaemia.

There is some evidence that benzodiazepines are of benefit to patients with symptoms of anxiety, panic and agitation. The use of intravenous benzodiazepines has been reported for the management of seizures and in some cases of SCRA-related psychosis.

There are a small number of reports describing antipsychotic medication being indicated for some patients, especially those who present with agitation or aggression, when the patient has a history of psychotic disorders, and when the psychotic symptoms do not remit with supportive care. There are also a small number of reports that describe antidepressants being administered in cases where there is concurrent depression.

Drug interactions are discussed in section 7 of this document.

Care bundle

A number of steps must be carried out to support the effective management of the adverse effects of SCRAs at the time of presentation to hospital and beyond. This can be enhanced through, for example, a care bundle, which is a quality improvement tool that supports reliable and effective care (see www.ihi.org/Topics/Bundles). It provides a small, straightforward set of evidence-based practices that, when performed collectively and reliably, improve outcomes. Compliance with components of the care

Box 3. A care bundle for people experiencing acute harm from SCRA use: assessment and management

Tick when action completed

- ☐ Base your diagnosis of acute SCRA intoxication on clinical assessment and recognition of symptoms of toxicity. Do not depend on urinalysis. SCRAS cannot be detected by screening tests for THC. Many new SCRA compounds will not appear in existing tests for SCRAs. Also, brand names can be misleading. Do not depend on the name to determine the type of compound, its potency, duration of action or specific harms
- ☐ Consider the use of more than one substance, including alcohol (polydrug use)
- ☐ Determine ingestion mode of SCRAs
  SCRAs are typically smoked. The onset of effects is much longer in cases of oral ingestion of SCRAs
- ☐ Provide supportive and symptomatic care
  Refer to TOXBASE® for up-to-date information on the management of acute SCRA harms (www.toxbase.org)
- ☐ Complete the Illicit Drug Reactions Reporting and Intelligence System (IDRRIS) form of Public Health England (PHE) and the Medicines and Healthcare Products Regulatory Agency (MHRA) (to be launched in autumn 2016)

At discharge

- ☐ Brief advice and information on behaviour change and harm reduction. Where harmful or dependent use has been identified, signpost or refer to specialist drug treatment and recovery services
- ☐ Give patient information and harm-reduction leaflet (see Box 4)

bundle can easily be recorded by a 'Yes' or 'No' (or tick or cross). Care bundles do not replace clinical judgement, nor diminish responsibilities of clinicians. A care bundle for the management of acute SCRA intoxication is outlined in Box 3.

Discharging patients: brief advice and information

Most patients will benefit from information, brief advice and signposting. This may take no longer than a few minutes, and could form part of a wider conversation about a health problem. The aim is to address SCRA-related harms and their reduction. The focus should also be on making changes to substance use in order to improve both health and social outcomes (for more information see www.neptune-clinical-guidance.co.uk).

Patients may also benefit from printed information on the reduction of SCRA-related harms which they can take with them. An example of what to include in a patient information sheet is given in Box 4.

A number of organisations also offer harm-reduction advice to people who use drugs, such as Crew (www.crew2000.org.uk) and Frank (www.talktofrank.com).

Box 4. Harm reduction advice for SCRA users

- There is no safe way to use synthetic cannabinoid receptor agonists (e.g. 'Spice').
- SCRAs are not the same thing as natural cannabis.
- SCRAs appear to be stronger than natural cannabis and more unpredictable.
- SCRAs usually vary from batch to batch, so different packets can produce different effects, even if the packaging looks the same.
- Different SCRA compounds have different strengths and potency, with some significantly stronger than others.
- If you are going to use an SCRA, start with small doses. Consider a quantity no larger than a match head.
- Wait before the effects have gone before smoking some more.
- Synthetic cannabinoids should not be taken on their own, but always with a 'mixer' (e.g. tobacco or dried herbs).
- SCRAs should not be used together with natural cannabis.
- You should avoid smoking synthetic cannabinoid products through pipes or 'bongs', as it can increase the risk of an overdose or bad reaction.
- Regular use of SCRAs can lead to dependence (addiction) and withdrawal.
- SCRAs can cause severe harms. If you experience a sustained period of fast heart rate or chest pains, call an ambulance.
- SCRAs can increase anxiety or paranoia. Only use them in an environment where you feel safe and with people you trust. If you suffer from anxiety or mental health problems, avoid using them.
- Avoid mixing SCRAs with other drugs, medicines and alcohol.
- Do not drive or operate machinery under the influence of SCRAs.

5. Harms associated with frequent and long-term (chronic) use

Harmful and dependent use

The evidence remains limited, but research has shown that SCRAs have a potential for misuse and dependence.

- There is increasing evidence that the chronic use of SCRAs may be associated with tolerance. Tolerance may develop more quickly for SCRAs than for natural cannabis.
- There are some reports of withdrawal symptoms following prolonged and frequent use (see Box 5).

Box 5. Reported features of SCRA withdrawal

- Headaches
- Anxiety
- Coughing
- Insomnia/sleep disturbance
- Impatience, difficulty concentrating
- Anger/irritability
- Restlessness
- Nausea
- Depression
- Craving
- Diaphoresis
- Tremor
- Hypertension
- Tachycardia

Physiological, psychological and psychiatric long-term effects

We know little about the long-term effects and harms of SCRA use.

- Although no experimental data are available, because SCRAs are lipophilic compounds, it would be expected that they would have a high volume of distribution. It is therefore likely that chronic use will lead to accumulation of SCRAs and their metabolites in fat-containing compartments in the body. The clinical implications of this are as yet unclear.
- Psychosis has been reported among people who use SCRAs frequently (see section 3, p. 6, for more information on SCRA-induced psychosis). Some studies suggest that new-onset psychosis may be precipitated by repeated use or even single use of SCRAs.
- Cognitive impairment has been described with chronic daily use.

- There is speculation that some SCRAs, particularly the aminoalkylindoles, may have carcinogenic potential.
- There are reports that SCRAs can cause cannabinoid hyperemesis syndrome (persistent vomiting).
- SCRAs would be expected to be associated with lung disease, as they are mainly smoked. There is no evidence to draw upon as yet.
- Catatonic states induced by chronic persistent high-dose SCRA use have been reported.

6. Management of the harms associated with long-term and frequent use

Very little evidence is available on the management of the harmful or dependent use of SCRAs; it is suggested that clinicians adopt the evidence-based approaches used for other drugs – particularly natural cannabis.

There is no evidence to suggest that a particular approach is linked to successful outcomes for SCRA users.

Suggested psychological and social interventions include motivational approaches, relapse prevention and reintegration with non-using social networks.

No specific medications are indicated for SCRA harmful use or dependence and no substitute prescribing is currently available.

Symptomatic management of withdrawal symptoms may be indicated in some cases.

Whatever approaches are used, interventions should also address issues specific to SCRAs and to particular populations who appear to be using them. Underlying drivers of use can include misuse of other substances, mental health and physical health co-morbidity, issues associated with homelessness and deprivation, and involvement in the criminal justice system and incarceration.

There is no risk-free way to use SCRAs, so it is important that people who continue using them have information to help them reduce adverse effects and harms.

7. Drug interactions

Information on the interactions of SCRAs with other drugs, including prescribed medication, is currently very limited. No guidance is available and decisions on prescribing medication should be made on a case-by-case basis.

Some of the interactions of SCRAs with other drugs may be similar to those of natural cannabis. It is possible that sedative medication may have stronger sedative effects when used with SCRAs. SCRAs may also increase the adverse effects of drugs with a similar side-effect profile.

Some SCRA compounds may be associated with activation of serotonin receptors. This implies that serotonergic therapeutic agents should be prescribed with care to minimise the risk of serotonin syndrome or poisoning (including SSRIs, MAOIs, St John's wort etc.).

Drug interactions concerning (natural) cannabis may be applicable to SCRAs. Case reports suggest that the concurrent use of cannabis with tricyclic antidepressants (TCAs) or anticholinergic drugs can produce significant tachycardia, resulting from the beta-adrenergic effects of cannabis added to the anticholinergic effect of tricyclic antidepressants. It has been suggested that clinicians monitor the heart rate of patients receiving treatment with anticholinergic medication and who use cannabis.

As with patients who use natural cannabis, patients receiving treatment with protease inhibitors who also use SCRAs should receive regular monitoring of viral indicators to confirm the effectiveness of the antiviral treatment.

References

The full chapter on synthetic cannabinoid receptor agonists (SCRAs) published in *Guidance on the Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances* drew on the following references:

Advisory Council on the Misuse of Drugs (ACMD). *Benzofurans: A Review of the Evidence of Use and Harm*. ACMD, November 2013.

Advisory Council on the Misuse of Drugs (ACMD). *Further Consideration of the Synthetic Cannabinoids*. ACMD, October 2012. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119042/synthetic-cannabinoids-2012.pdf.

Alhadi S, Tiwari A, Vohra R, Gerona R, Acharya J, Bilello K. High times, low sats: diffuse pulmonary infiltrates associated with chronic synthetic cannabinoid use. *J Med Toxicol.* 2013;9(2):199–206.

Alvarez Y, Pérez-Mañá C, Torrens M, Farré M. Antipsychotic drugs in cocaine dependence: a systematic review and meta-analysis. *J Subst Abuse Treat.* 2013 Jul;45(1):1–10. doi: 10.1016/j.jsat.2012.12.013.

American Association of Poison Control Centers (AAPCC). *Fake Marijuana Spurs More Than 2,500 Calls to U.S. Poison Centers This Year Alone*. AAPCC, 2010.

Ashton JC. Synthetic cannabinoids as drugs of abuse. *Curr Drug Abuse Rev.* 2012;5(2):158–68.

Atwood BK, Huffman J, Straiker A, Mackie K. JWH018, a common constituent of 'Spice' herbal blends, is a potent and efficacious cannabinoid CB receptor agonist. *Br J Pharmacol.* 2010;160(3):585–93.

Auwärter V, Dresen S, Weinmann W, Müller M, Pütz M, Ferreirós N. 'Spice' and other herbal blends: harmless incense or cannabinoid designer drugs? *J Mass Spectrom.* 2009 May;44(5):832–7. doi: 10.1002/jms.1558.

Banerji S, Deutsch CM, Bronstein AC. Spice ain't so nice. *Clin Toxicol.* 2010;48:632 (abstract 137). http://informahealthcare.com/doi/pdf/10.3109/15563650.2010.493290 (accessed 15 November 2013).

Barratt MJ, Cakic V, Lenton S. Patterns of synthetic cannabinoid use in Australia. *Drug Alcohol Rev.* 2013 Mar;32(2):141–6. doi: 10.1111/j.1465-3362.2012.00519.x.

Bebarta VS, Ramirez S, Varney SM. Spice: a new 'legal' herbal mixture abused by young active duty military personnel. *Subst Abuse.* 2012;33:191–4.

Behonick G, Shanks KG, Firchau DJ, Mathur G, Lynch CF, Nashelsky M, Jaskierny DJ, Meroueh C. Four postmortem case reports with quantitative detection of the synthetic cannabinoid, 5F-PB-22. *J Anal Toxicol.* 2014 Oct;38(8):559–62. doi: 10.1093/jat/bku048.

Benford DM, Caplan JP. Psychiatric sequelae of spice, K2, and synthetic cannabinoid receptor agonists. *Psychosomatics.* 2011;52:295.

Bhanushali GK, Jain G, Fatima H, Leisch LJ, Thornley-Brown D. AKI associated with synthetic cannabinoids: a case series. *Clin J Am Soc Nephrol.* 2013 Apr;8(4):523–6. doi: 10.2215/CJN.05690612.

Brakoulias V. Products containing synthetic cannabinoids and psychosis. *Aust NZ J Psychiatry.* 2012 Mar;46(3):281–2. doi: 10.1177/0004867411433974.

Brandt SD, Sumnall HR, Measham F, Cole J. Analyses of second-generation 'legal highs' in the UK: initial findings. *Drug Testing Analysis.* 2010;2:377–82.

Brandt SD, Sumnall HR, Measham, F, Cole J. Second generation mephedrone: the confusing case of NRG-1. *BMJ* 2010;341:c3564.

Brents LK, Prather PL. The K2/Spice phenomenon: emergence, identification, legislation and metabolic characterization of synthetic cannabinoids in herbal incense products. *Drug Metab Rev.* 2014 Feb;46(1):72–85. doi: 10.3109/03602532.2013.839700.

Canning J, Ruha A, Pierce R, Torrey M, Reinhart S. Severe GI distress after smoking JWH-018. *Clin Toxicol (Phila).* 2010;48:618.

Carroll FI, Lewin AH, Mascarella SW, Seltzman HH, Reddy PA. Designer drugs: a medicinal chemistry perspective. *Ann NY Acad Sci.* 2012;1248:18–38.

Castellanos D, Singh S, Thornton G, Avila M, Moreno A. Synthetic cannabinoid use: a case series of adolescents. *J Adolesc Health.* 2011;49(4):347–9.

Castellanos D, Thornton G. Synthetic cannabinoid use: recognition and management. *J Psychiatr Pract.* 2012 Mar;18(2):86–93. doi: 10.1097/01.pra.0000413274.09305.9c.

Centers for Disease Control and Prevention (CDC). Acute kidney injury associated with synthetic cannabinoid use - multiple states, 2012. *MMWR Morb Mortal Wkly Rep.* 2013 Feb 15;62(6):93-8.

Chan WL, Wood DM, Hudson S, Dargan PI. Acute psychosis associated with recreational use of benzofuran 6-(2 aminopropyl)benzofuran (6-APB) and cannabis. *J Med Toxicol.* 2013 Sep;9(3):278–81. doi: 10.1007/s13181-013-0306-y.

Chase PB. Signs of synthetic cannabinoid vs. marijuana intoxication as determined by police drug recognition experts. *Clin Toxicol.* 2013;51(7):667.

Choi H, Heo S, Choe S, Yang W, Park Y, Kim E, Chung H, Lee J. Simultaneous analysis of synthetic cannabinoids in the materials seized during drug trafficking using GC-MS. *Anal Bioanal Chem.* 2013 May;405(12):3937-44. doi: 10.1007/s00216-012-6560-z.

Clinical Committee of the Government Delegation for the National Plan on Drugs. *Emerging Drugs* (Report 6 of the Clinical Committee). Ministry of Health, Madrid, 2011.

Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after kidney injury: a systemic review and meta-analysis. *Kid Int.* 2012;81:442–8.

Compton DR, Johnson MR, Melvin LS, Martin BR. Pharmacological profile of a series of bicyclic cannabinoid analogs: classification as cannabimimetic agents. *J Pharmacol Exp Ther.* 1992 Jan;260(1):201–9.

Corkery J, Claridge H, Loi B, Goodair C, Schifano F. *NPSAD Annual Report 2013 – Drug-Related Deaths in the UK: January–December 2012*. National Programme on Substance Abuse Deaths (NPSAD), 2014.

D'Ambra TE, Estep KG, Bell MR, Eissenstat MA, Josef KA, Ward SJ, Haycock DA, Baizman ER, Casiano FM, Beglin NC, *et al*. Conformationally restrained analogues of pravadoline: nanomolar potent, enantioselective, (aminoalkyl)indole agonists of the cannabinoid receptor. *J Med Chem.* 1992;35(1):124–35.

Dargan PI, Hudson S, Ramsey J, Wood DM. The impact of changes in UK classification of the synthetic cannabinoid receptor agonists in 'Spice'. *Int J Drug Policy.* 2011 Jul;22(4):274–7. doi: 10.1016/j.drugpo.2011.02.006.

Davies S, Wood DM, Smith G, Button J, Ramsey J, Archer R, *et al*. Purchasing 'legal highs' on the Internet – is there consistency in what you get? *QJM.* 2010;103:489–93.

Dean A. Illicit drugs and drug interactions Illicit drugs and drug interactions. *Australian Pharmacist.* 2006;25(9).

De Brabanter N, Deventer K, Stove V, Van Eenoo P. Synthetic cannabinoids: general considerations. *P Belg Roy Acad Med.* 2013;2:209–25.

Degenhardt L, Topp L. Crystal meth use among polydrug users in Sydney's dance party subculture: characteristics, use patterns and associated harms. *Int J Drug Policy.* 2003;14(1):17–24.

Devane WA, Breuer A, Sheskin T, Järbe TU, Eisen MS, Mechoulam R. A novel probe for the cannabinoid receptor. *J Med Chem.* 1992 May 29;35(11):2065–9.

Donnelly MT. Health Advisory: K2 Synthetic Marijuana Use Among Teenagers and Young Adults in Missouri. Missouri Department of Health and Senior Services, 5 March 2010. http://health.mo.gov/emergencies/ert/alertsadvisories/pdf/HAd3-5-2010.pdf (accessed 15 November 2013).

Dresen S, Ferreirós N, Pütz M, Westphal F, Zimmermann R, Auwärter V. Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. *J Mass Spectrom.* 2010 Oct;45(10):1186–94. doi: 10.1002/jms.1811.

DrugScope. DrugScope latest street drug survey highlights risks of new designer drugs for young people, 25 November 2013. http://www.drugscope.org.uk/Media/Press+office/pressreleases/DrugScope+latest+street+drug+survey+highlights+risks+of+new+designer+drugs+for+young+people.htm (accessed 6 December 2013).

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology.* 2004 Aug;29(8):1558–72.

Elliott S, Evans J. A 3-year review of new psychoactive substances in casework. *Forensic Sci Int.* 2014;243:55–60.

Emerson B, Durham B, Gidden J, Lay JO Jr. Gas chromatography–mass spectrometry of JWH-018 metabolites in urine samples with direct comparison to analytical standards. *Forensic Sci Int*. 2013 Jun 10;229(1–3):1–6. doi: 10.1016/j.forsciint.2013.03.006. Epub 2013 Apr 9.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *EMCDDA–Europol 2012 Annual Report on the Implementation of Council Decision 2005/387/JHA*. Publications Office of the European Union, 2013.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Synthetic cannabinoids and 'Spice' drug profile. http://www.emcdda.europa.eu/publications/drug-profiles/synthetic-cannabinoids (accessed 11 December 2013).

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Synthetic Cannabinoids in Europe* (updated 28 May 2013) (Perspectives on Drugs series). EMCDDA, 2013. http://www.emcdda.europa.eu/topics/pods/synthetic-cannabinoids.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Understanding the Spice Phenomenon*. EMCDDA, 2009.

Every-Palmer S. Synthetic cannabinoid JWH-018 and psychosis: an explorative study. *Drug Alcohol Depend*. 2011;117:152–7.

Every-Palmer S. Warning: legal synthetic cannabinoid receptor agonists such as JWH-018 may precipitate psychosis in vulnerable individuals. *Addiction*. 2010;105:1959–60.

Fattore L, Fratta W. Beyond THC: the new generation of cannabinoid designer drugs. *Front Behav Neurosci*. 2011 Sep 21;5:60. doi: 10.3389/fnbeh.2011.00060.

Fisar Z. Inhibition of monoamine oxidase activity by cannabinoids. *Naunyn Schmiedebergs Arch Pharmacol*. 2010 Jun;381(6):563–72. doi: 10.1007/s00210-010-0517-6.

Forrester MB, Kleinschmidt K, Schwarz E, Young A. Synthetic cannabinoid exposures reported to Texas poison centers. *J Addict Dis*. 2011;30:351–8.

Forrester MB, Kleinschmidt K, Schwarz E, *et al*. Synthetic cannabinoid and marijuana exposures reported to poison centres. *Human Exp Toxicol*. 2012 Oct;31(10):1006–11. doi: 10.1177/0960327111421945.

Freeman MJ, Rose DZ, Myers MA, Gooch CL, Bozeman AC, Burgin WS. Ischemic stroke after use of the synthetic marijuana 'spice'. *Neurology*. 2013;81(24):2090–3.

Freeman WD, Jacksonville FL, Louh IK. Spice encephalopathy, 2014. Neurology website, http://www.neurology.org/content/81/24/2090/reply/ (accessed 5 February 2014).

Ginsburg BC, McMahon LR, Sanchez JJ, Javors MA. Purity of synthetic cannabinoids sold online for recreational use. *J Anal Toxicol*. 2012 Jan–Feb;36(1):66–8. doi: 10.1093/jat/bkr018.

Glue P, Al-Shaqsi S, Hancock D, Gale C, Strong B, Schep L. Hospitalisation associated with use of the synthetic cannabinoid K2. *NZ Med J*. 2013;126(1377):18–22.

Gordon E, Devinsky O. Alcohol and marijuana: effects on epilepsy and use by patients with epilepsy. *Epilepsia*. 2001;42:1266–72.

Gottardo R, Chiarini A, Dal Prà I, Seri C, Rimondo C, Serpelloni G, Armato U, Tagliaro F. Direct screening of herbal blends for new synthetic cannabinoids by MALDI-TOF MS. *J Mass Spectrom*. 2012 Jan;47(1):141-6. doi: 10.1002/jms.2036.

Griffiths P, Sedefov R, Gallegos A, Lopez D. How globalization and market innovation challenge how we think about and respond to drug use: 'Spice', a case study. *Addiction*. 2010;105:951–3.

Halberstadt AL, Geyer MA. Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens. *Neuropharmacology*. 2011;61(3):364–81.

Harris CR, Brown A. Synthetic cannabinoid intoxication: a case series and review. *J Emerg Med*. 2013 Feb;44(2):360–6. doi: 10.1016/j.jemermed.2012.07.061.

Hermanns-Clausen M, Kneisel S, Auwarter V. New drugs of abuse: acute intoxication by smoking herbal products containing synthetic cannabinoids. Abstracts of the 2011 International Congress of the European Association of Poisons Centres and Clinical Toxicologists, 24–27 May 2011, Dubrovnik, Croatia. *Clin Toxicol*. 2011;49(3):199.

Hermanns-Clausen M, Kneisel S, Szabo B, Auwärter V. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. *Addiction*. 2013 Mar;108(3):534–44. doi: 10.1111/j.1360-0443.2012.04078.x.

Hermanns-Clausen M, Kneisel S, Szabo B, Auwärter V. Intoxications by synthetic cannabinoids – current trends. Abstracts of the 2011 International Congress of the European Association of Poisons Centres and Clinical Toxicologists, 24–27 May 2011, Dubrovnik, Croatia. *Clin Toxicol*. 2011;49(3).

Hill SL, Najafi J, Dunn M, Acheampong P, Kamour A, Grundlingh J, Blain PG, Thomas SHL. Clinical toxicity following analytically confirmed use of the synthetic cannabinoid receptor agonist MDMBCHMICA.A report from the Identification Of Novel psychoActive substances (IONA) study. *Clin Toxicol.* 2016. http://dx.doi.org/10.1080/15563650.2016.1190980.

Hillebrand J, Olszewski D, Sedefov R. Legal highs on the Internet. *Subst Use Misuse*. 2010;45:330–40.

HM Chief Inspector of Prisons for England and Wales. *Annual Report 2013–14*. HM Inspectorate of Prisons, 2014.

Hopkins CY,Gilchrist BL. A case of cannabinoid hyperemesis syndrome caused by synthetic cannabinoids. *J Emerg Med.* 2013;45(4):544–6.

Hoyte CO, Jacob J, Monte AA, Al-Jumaan M, Bronstein AC, Heard KJ. A characterization of synthetic cannabinoid exposures reported to the National Poison Data System in 2010. *Ann Emerg Med.* 2012;60:435–8.

Hu X, Primack BA, Barnett TE, Cook RL. College students and use of K2: an emerging drug of abuse in young persons. *Subst Abuse Treat Prev Policy.* 2011;6:16–19.

Hudson S, Ramsey J. The emergence and analysis of synthetic cannabinoids. *Drug Test Anal.* 2011;3:466–78.

Hudson S, Ramsey J, King L, Timbers S, Maynard S, Dargan PI, Wood DM. Use of high resolution accurate mass spectrometry to detect reported and previously unreported cannabinomimetics in 'herbal high' products. *J Anal Toxicol.* 2010 Jun;34(5):252–60.

Huffman JW. Cannabimimetic indoles, pyrroles, and indenes: structure–activity relationships and receptor interactions. In: Reggio PH, ed. *The Cannabinoid Receptors*, pp. 49–94. Humana Press, 2009.

Huffman JW, Dai D, Martin BR, Compton DR. Design, synthesis and pharmacology of cannabimimetic indoles. *Bioorg Med Chem Lett.* 1994;4:563–6.

Huffman JW, Mabon R, Wu MJ, Lu J, Hart R, Hurst DP, Reggio PH, Wiley JL, Martin BR. 3-indolyl-1-naphthylmethanes: new cannabimimetic indoles provide evidence for aromatic stacking interactions with the CB(1) cannabinoid receptor. *Bioorg Med Chem.* 2003;11:539–49.

Huffman JW, Padgett LW. Recent developments in the medicinal chemistry of cannabinomimetic indoles, pyrroles and indenes. *Curr Med Chem.* 2005;12:1395–411.

Hurst D, Loeffler G, McLay R. Psychosis associated with synthetic cannabinoid agonists: a case series. *Am J Psychiatry* 2011;168:1119.

Hurst D, Loeffler G, McLay R. Synthetic cannabinoid agonist induced psychosis a case series. APA poster. Naval Medical Centre, San Diego, 2011. http://www.ncis.navy.mil/PI/CRP/Documents/Spice%20APA%20poster.pdf. (Abstract in *Am J Psychiatry.* 2011 Oct;168(10):1119. doi: 10.1176/appi.ajp.2011.11010176.)

Hutter M, Broecker S, Kneisel S, Auwärter V. Identification of the major urinary metabolites in man of seven synthetic cannabinoids of the aminoalkylindole type present as adulterants in 'herbal mixtures' using LC-MS/MS techniques. *J Mass Spectrom.* 2012 Jan;47(1):54–65. doi: 10.1002/jms.2026.

Kikura-Hanajiri R, Uchiyama N, Kawamura M, *et al.* Changes in the prevalence of synthetic cannabinoids and cathinone derivatives in Japan until early 2012. *Forensic Toxicol.* 2013; 31:44–53.

Kleinschmidt K, Forrester MB. A comparison of ingested versus inhaled synthetic cannabinoids. *Clin Toxicol.* 2011;49(6):530–1.

Johnson LA, Johnson RL, Alfonzo C. Spice: a legal marijuana equivalent. *Mil Med.* 2011;176:718–20.

Johnson LA, Johnson RL, Portier RB. Current 'legal highs'. *J Emerg Med.* 2013 Jun;44(6):1108–15. doi: 10.1016/j.jemermed.2012.09.147.

Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. *Monitoring the Future: National Results on Adolescent Drug Use: Overview of Key Findings, 2012*. Institute for Social Research, University of Michigan, 2013. http://www.monitoringthefuture.org//pressreleases/13drugpr_complete.pdf (accessed 19 December 2013).

Kazory A, Aiyer R. Synthetic marijuana and acute kidney injury: an unforeseen association. *Clin Kidney J.* 2013;6(3):330–3.

Keeler MH, Reifler CB. Grand mal convulsions subsequent to marijuana use. Case report. *Dis Nerv Syst.* 1967;28:474–5.

Khan M, Pace L, Truong A, Gordon M, Moukaddam N. Catatonia secondary to synthetic cannabinoid use in two patients with no previous psychosis. *Am J Addictions.* 2016;25:25–7.

Kleinschmidt K, Forrester MB. A comparison of ingested versus inhaled synthetic cannabinoids. *Clin Toxicol.* 2011;49(6):530–1.

Kronstrand R, Roman M, Andersson M, Eklund A. Toxicological findings of synthetic cannabinoids in recreational users. *J Analytical Toxicol.* 2013;37(8):534–41.

Lapoint J, Nelson LS. Synthetic cannabinoids: the newest, almost illicit drug of abuse. *Emerg Med.* 2011;43(2):26–8.

Lewin AH, Seltzman HH, Carroll FI, Mascarella SW, Reddy PA. Emergence and properties of spice and bath salts: a medicinal chemistry perspective. *Life Sci.* 2014 Feb 27;97(1):9–19. doi: 10.1016/j.lfs.2013.09.026.

Lin CY, Wheelock AM, Morin D, Baldwin RM, Lee MG, Taff A, Plopper C, Buckpitt A, Rohde A. Toxicity and metabolism of methylnaphthalenes: comparison with naphthalene and 1-nitronaphthalene. *Toxicology.* 2009 Jun 16;260(1–3):16–27. doi: 10.1016/j.tox.2009.03.002.

Lindigkeit R, Boehme A, Eiserloh I, Luebbecke M, Wiggermann M, Ernst L, Beuerle T. Spice: a never ending story? *Forensic Sci Int.* 2009;191:58–63.

Loeffler G, Hurst D, Penn A, Yung K. Spice, bath salts, and the U.S. military: the emergence of synthetic cannabinoid receptor agonists and cathinones in the U.S. armed forces. *Mil Med.* 2012 Sep;177(9):1041–8.

Lonati D, Buscaglia E, Papa P, Valli A, Coccini T, Giampreti A, Petrolini VM, Vecchio S, Serpelloni G, Locatelli CA. MAM-2201 (analytically confirmed) intoxication after 'Synthacaine' consumption. *Ann Emerg Med.* 2014 Dec;64(6):629–32. doi: 10.1016/j.annemergmed.2014.01.007.

Lovett DP, Yanes EG, Herbelin TW, Knoerzer TA, Levisky JA. Structure elucidation and identification of a common metabolite for naphthoylindole-based synthetic cannabinoids using LC-TOF and comparison to a synthetic reference standard. *Forensic Sci Int.* 2013 Mar 10;226(1–3):81–7. doi: 10.1016/j.forsciint.2012.12.012.

Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. *Pediatrics.* 2011;128(6):e1622–7.

Monte AA, Bronstein AC, Dahze JC, Heard KJ, Hoppe JA, Hoyte CO, Iwanicki JL, Lavonas EJ. Supplementary appendix to an outbreak of exposure to a novel synthetic cannabinoid. *New Engl J Medicine.* 2014;370(4):389–90. http://www.nejm.org.

Morgan CJ, Das RK, Joye A, Curran HV, Kamboj SK. Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. *Addict Behav.* 2013 Sep;38(9):2433–6. doi: 10.1016/j.addbeh.2013.03.011.

Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study. *Br J Psychiatry.* 2010 Oct;197(4):285–90. doi: 10.1192/bjp.bp.110.077503.

Müller H, Sperling W, Köhrmann M, *et al.* The synthetic cannabinoid Spice as a trigger for an acute exacerbation of cannabis induced recurrent psychotic episodes. *Schizophr Res.* 2010;118:309–10.

Musshoff F, Madea B, Kernbach-Wighton G, Bicker W, Kneisel S, Hutter M, Auwärter V. Driving under the influence of synthetic cannabinoids ('Spice'): a case series. *Int J Legal Med.* 2014 Jan;128(1):59–64. doi: 10.1007/s00414-013-0864-1.

National Poisons Information Service (NPIS). *Annual Report 2012/13*. NPIS, 2013.

Naviglio S, Papanti D, Moressa V, Ventura A. An adolescent with an altered state of mind. *BMJ.* 2015;350:h299. doi: 10.1136/bmj.h299.

Ng SK, Brust JC, Hauser WA, Susser M. Illicit drug use and the risk of new-onset seizures. *Am J Epidemiol.* 1990;132:47–57.

Ogata J, Uchiyama N, Kikura-Hanajiri R, Goda Y. DNA sequence analyses of blended herbal products including synthetic cannabinoids as designer drugs. *Forensic Sci Int.* 2013;227(1–3):33–41.

Papanti D, Orsolini L, Francesconi SF. 'Noids' in a nutshell: everything you (don't) want to know about synthetic cannabimimetics. *Adv Dual Diagn.* 2014;7:137–48.

Papanti D, Schifano F, Botteon G, Bertossi F, Mannix J, Vidoni D, Impagnatiello M, Pascolo-Fabrici E, Bonavigo T. 'Spiceophrenia': a systematic overview of 'spice'-related psychopathological issues and a case report. *Hum Psychopharmacol.* 2013 Jul;28(4):379–89. doi: 10.1002/hup.2312.

Park Y, Lee C, Lee H, Pyo J, Jo J, Lee J, Choi H, Kim S, Hong RS, Park Y, Hwang BY, Choe S, Jung JH. Identification of a new synthetic cannabinoid in a herbal mixture: 1-butyl-3-(2-ethoxybenzoyl) indole. *Forensic Toxicol.* 2013;31:187–96.

Patton AL, Chimalakonda KC, Moran CL, McCain KR, Radominska-Pandya A, James LP, Kokes C, Moran JH. K2 toxicity: fatal case of psychiatric complications following AM2201 exposure. *J Forensic Sci.* 2013 Nov;58(6):1676–80. doi: 10.1111/1556-4029.12216.

Peglow S, Buchner J, Briscoe G. Synthetic cannabinoid induced psychosis in a previously nonpsychotic patient. *Am J Addict*. 2012;21:287–8.

Pierre JM. Cannabis, synthetic cannabinoids, and psychosis risk: what the evidence says. *Curr Psychiatr.* 2011;10:49–58.

Psychonaut Web Mapping Research Group. *Psychonaut Web Mapping Project: Final Report*. Institute of Psychiatry, King's College London, 2010.

Ramsey J, Dargan PI, Smyllie M, Davies S, Button J, Holt DW, *et al*. Buying 'legal' recreational drugs does not mean that you are not breaking the law. *QJM*. 2010;103:777–83.

Rodgman C, Kinzie E, Leimbach E. Bad mojo: use of the new marijuana substitute leads to more and more ED visits for acute psychosis. *Am J Emerg Med*. 2011;29:232.

Rosenbaum CD, Scalzo AJ, Long C, Weber J, Jenkins A, Lopez G, Ragone S. K2 and spice abusers: a case series of clinical and laboratory findings. Paper presented at the North American Congress of Clinical Toxicology (NACCT), Washington, DC, 21–26 September 2011.

Saito T, Namera A, Miura N, Ohta S, Shota Miyazaki S, Osawa M, Inokuchi S. A fatal case of MAM-2201 poisoning. *Forensic Toxicol.* 2013;31:333–7.

Savasman CM, Peterson DC, Pietak BR, Dudley MH, Clinton Frazee III C, Garg U. Two fatalities due to the use of synthetic cannabinoids alone. In: *Proceedings of the 66th Annual Scientific Meeting of the American Academy of Forensic Sciences, Seattle, WA February 17–22, 2014*, p. 316. Publication Printers, 2014.

Schaefer N, Peters B, Bregel D, Kneisel S, Auwärter V, Schmidt PH, Ewald AH. A fatal case involving several synthetic cannabinoids. *Toxichem Krimtech.* 2013;80 (special issue):248.

Schifano F, Corazza O, Deluca P, et al: Psychoactive drug or mystical incense? Overview of the online available information on spice products. *Int J Cult Ment Health.* 2009;2:137–44.

Schifano F, Deluca P, Baldacchino A, Peltoniemi T, Scherbaum N, Torrens M, *et al*. Drugs on the web; the Psychonaut 2002 EU project. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006;30:640–6.

Schifano F, Papanti D, Orsolini L, Corkery JM. Novel psychoactive substances: the pharmacology of stimulants and hallucinogens. *Expert Review of Clinical Pharmacology*. 2016. http://dx.doi.org/10.1586/17512433.2016.1167597.

Schneir A, Baumbacher T. Convulsions as a complication of synthetic cannabinoid use. *Clin Toxicol.* 2011;49(6):526.

Schneir A, Cullen J, Ly BT. 'Spice' girls: synthetic cannabinoid intoxication. *J Emerg Med.* 2011 Mar;40(3):296–9. doi: 10.1016/j.jemermed.2010.10.014.

Seely KA, Lapoint J, Moran JH, Fattore L. Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012 Dec 3;39(2):234–43. doi: 10.1016/j.pnpbp.2012.04.017.

Seely KA, Prather PL, James LP, Moran JH. Marijuana-based drugs: innovative therapeutics or designer drugs of abuse? *Mol Interv.* 2011;11:36–51.

Seeman P. Atypical antipsychotics: mechanism of action. *Can J Psychiatry*. 2002 Feb;47(1):27–38.

Seifert SA, Brazwell EM, Smeltzer C, Gibb J, Logan BK. Seizure and acute kidney injury associated with synthetic cannabinoid use. *Clin Toxicol.* 2013;51(7):667.

Shanks KG, Dahn T, Terrell AR. Detection of JWH-018 and JWH-073 by UPLC–MS-MS in postmortem whole blood casework. *J Analytical Toxicol.* 2012;36:145–52.

Simmons J, Cookman L, Kang C, Skinner C. Three cases of 'spice' exposure. *Clin Toxicol.* 2011;49:431–3.

Simmons J, Skinner CG, Williams J, Kang CS, Schwartz MD, Wills BK. Intoxication from smoking 'Spice'. *Ann Emerg Med.* 2011;57:187–8.

Smith K, Flatley J, eds. *Drug Misuse Declared: Findings from the 2010/11 British Crime Survey. England and Wales* (Home Office Statistical Bulletin). Home Office, 2011.

Sobolevsky T, Prasolov I, Rodchenkov G. Detection of JWH-018 metabolites in smoking mixture post-administration urine. *Forensic Sci Int*. 2010;200:141–7.

Spaderna M, Addy P, D'Souza DC. Spicing things up: synthetic cannabinoids. *Psychopharmacology*. 2013;228(4):525–40.

Teske J, Weller JP, Fieguth A, Rothämel T, Schulz Y, Tröger HD. Sensitive and rapid quantification of the cannabinoid receptor agonist naphthalen-1-yl-(1-pentylindol-3-yl) methanone (JWH-018) in human serum by liquid chromatography–tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2010;878:2659–63.

Thomas S, Bliss S, Malik M. Suicidal ideation and self-harm following K2 use. *J Okla State Med Assoc*. 2012 Nov;105(11):430–3.

Thornton SL, Lo J, Clark RF, Wu AH, Gerona RR. Simultaneous detection of multiple designer drugs in serum, urine, and CSF in a patient with prolonged psychosis. *Clin Toxicol (Phila)*. 2012 Dec;50(10):1165–8. doi: 10.3109/15563650.2012.744996.

Tung CK, Chiang TP, Lam M. Acute mental disturbance caused by synthetic cannabinoid: a potential emerging substance of abuse in Hong Kong. *East Asian Arch Psychiatry*. 2012;22(1):31–3.

Uchiyama N, Kawamura M, Kikura-Hanajiri R, Goda Y. Identification and quantitative analyses of two cannabimimetic phenylacetylindoles, JWH-251 and JWH-250, and four cannabimimetic naphthoylindoles, JWH-081, JWH-015, JWH-200 and JWH-073, as designer drugs in illegal products. *Forensic Toxicol.* 2011;29:25–37.

Uchiyama N, Kawamura M, Kikura-Hanajiri R, Goda Y. URB-754: a new class of designer drug and 12 synthetic cannabinoids detected in illegal products. *Forensic Sci Int.* 2013;227(1–3):21–32.

Uchiyama N, Kikura-Hanajiri R, Ogata J, Goda Y. Chemical analysis of synthetic cannabinoids as designer drugs in herbal products. *Forensic Sci Int.* 2010;198:31–8.

Uchiyama N, Matsuda S, Kawamura M, Kikura-Hanajiri R, Goda Y. Two new-type cannabimimetic quinolinyl carboxylates, QUPIC and QUCHIC, two new cannabimimetic carboxamide derivatives, ADB-FUBINACA and ADBICA, and five synthetic cannabinoids detected with a thiophene derivative a-PVT and an opioid receptor agonist AH-7921 identified in illegal products. *Forensic Toxicol.* 2013;31:223–40.

Uchiyama N, Shimokawa Y, Matsuda S, Kawamura M, Kikura-Hanajiri R, Goda Y. Two new synthetic cannabinoids, AM-2201 benzimidazole analog (FUBIMINA) and (4-methylpiperazin-1-yl)(1-pentyl-1H-indol-3-yl)methanone (MEPIRAPIM), and three phenethylamine derivatives, 25H-NBOMe 3,4,5-trimethoxybenzyl analog, 25B-NBOMe, and 2C-N-NBOMe, identified in illegal products. *Forensic Toxicol.* 2014;32(1):105–15.

United Nations Office on Drugs and Crime (UNODC). *Synthetic Cannabinoids in Herbal Products*. UNODC, 2011. http://www.unodc.org/documents/scientific/Synthetic_Cannabinoids.pdf (accessed 10 December 2013).

Van Der Veer N, Friday J. Persistent psychosis following the use of Spice. *Schizophrenia Res*. 2011;130:285–6.

Vandrey R, Dunn KE, Fry JA, Girling ER. A survey study to characterize use of Spice products (synthetic cannabinoids). *Drug Alcohol Depend*. 2012 Jan 1;120(1–3):238–41. doi: 10.1016/j.drugalcdep.2011.07.011.

Vardakou I, Pistos C, Spiliopoulou C. Spice drugs as a new trend: mode of action, identification and legislation. *Toxicol Lett*. 2010;197:157–62.

Vearrier D, Osterhoudt KC. A teenager with agitation: higher than she should have climbed. *Pediatr Emerg Care*. 2010;26:462–5.

Weissman A, Milne GM, Melvin LS Jr. Cannabimimetic activity from CP-47,497, a derivative of 3-phenylcyclohexanol. *J Pharmacol Exp Ther.* 1982;223:516–23.

Wells DL, Ott CA. The new marijuana. Ann Pharmacotherapy. 2011;45(3):414–17.

Westerbergh J, Hulten P. Novel synthetic cannabinoids, CRA13, JWH-015, JWH-081 and JWH-210 – detected in a case series. (Abstracts of the 2011 International Congress of the European Association of Poisons Centres and Clinical Toxicologists, 24–27 May 2011, Dubrovnik, Croatia.) *Clin Toxicol*. 2011;49(3):199.

Wikstrom M, Thelander G, Dahlgren M, Kronstrand R. An accidental fatal intoxication with methoxetamine. *J Analytic Toxicol.* 2013;37(1):43–6.

Wiley JL, Marusich JA, Huffman JW. Moving around the molecule: relationship between chemical structure and in vivo activity of synthetic cannabinoids. *Life Sci.* 2014 Feb 27;97(1):55–63. doi: 10.1016/j.lfs.2013.09.011.

Winstock AR, Barratt MJ. Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample. *Drug Alcohol Depend.* 2013;131(1–3):106–11. doi: 10.1016/j.drugalcdep.2012.12.011.

Winstock AR, Barratt MJ. The 12-month prevalence and nature of adverse experiences resulting in emergency medical presentations associated with the use of synthetic cannabinoid products. *Hum Psychopharmacol.* 2013 Jul;28(4):390–3. doi: 10.1002/hup.2292.

World Health Organization (WHO). JWH-018. Critical Review Report Agenda Item 4.5. Expert Committee on Drug Dependence Thirty-Sixth Meeting, Geneva, 16–20 June 2014.

Wurita A, Hasegawa K, Minakata K, Watanabe K, Suzuki O. A large amount of new designer drug diphenidine coexisting with a synthetic cannabinoid 5-fluoro-AB-PINACA found in a dubious herbal product. *Forensic Toxicol.* 2014;32(2):331–7.

Yen M, Berger RE, Roberts J, Ganetsky M. Middle cerebral artery stroke associated with use of synthetic cannabinoid K2. Clin Toxicol. 2012;50(7):673–4.

Yip L, Dart RC. Is there something more about synthetic cannabinoids? *Forensic Toxicol.* 2014;32(2):340–1.

Young AC, Schwarz E, Medina G, Obafemi A, Feng SY, Kane C, Kleinschmidt K. Cardiotoxicity associated with the synthetic cannabinoid, K9, with laboratory confirmation. *Am J Emerg Med.* 2012 Sep;30(7):1320.e5–7. doi: 10.1016/j.ajem.2011.05.013.

Zimmermann US, Winkelmann PR, Pilhatsch M, Nees JA, Spanagel R, Schulz K. Withdrawal phenomena and dependence syndrome after the consumption of 'Spice Gold'. *Dtsch Arztebl Int.* 2009 Jul;106(27):464–7. doi: 10.3238/arztebl.2009.0464.

Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimarães FS. Cannabidiol, a cannabis sativa constituent, as an antipsychotic drug. *Braz J Med Biol Res.* 2006 Apr;39(4):421–9. Epub 2006 Apr 3.

Zuba D, Byrska B, Maciow M. Comparison of 'herbal highs' composition. *Anal Bioanal Chem.* 2011;400:119–26.