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A Systematic Review of Adverse Events Arising from the Use of Synthetic Cannabinoids and Their Associated Treatment

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Abstract (max 600 words)

Context: Synthetic cannabinoids (SCs) such as "Spice", "K2" etc. are widely available via the internet despite increasing legal restrictions. Currently, the prevalence of use is typically low in the general community (<1%) although it is higher among students and some niche groups subject to drug testing. Early evidence suggests that adverse outcomes associated with the use of SCs may be more prevalent and severe than those arising from cannabis consumption.

Objectives: To identify systematically the scientific reports of adverse events associated with the consumption of SCs in the medical literature and poison center data.

Method: We searched online databases (Medline, PsycInfo, Embase, Google Scholar and Pubmed) and manually searched reference lists up to December 2014. To be eligible for inclusion, data had to be from hospital, emergency department, drug rehabilitation services or poison centre records of adverse events involving SCs and included both self-reported and / or analytically confirmed consumption.

Results: From 256 reports, we identified 106 eligible studies including 37 conference abstracts on about 4000 cases involving at least 26 deaths. Major complications include cardiovascular events (myocardial infarction, ischemic stroke, and emboli), acute kidney injury, generalized tonic-clonic seizures, psychiatric presentations (including first episode psychosis, paranoia, self-harm / suicide ideation) and hyperemesis. However, most presentations were not serious, typically involved young males with tachycardia (≈ 37-77%), agitation (≈ 16-41%) and nausea (≈ 13-94%) requiring only symptomatic care with a length of stay of less than 8 hours.

Conclusions: SCs most frequently result in tachycardia, agitation, and nausea. These symptoms typically resolve with symptomatic care, including intravenous fluids, benzodiazepines, and anti-emetics, and may not require inpatient care. Severe adverse events, (stroke, seizure, myocardial infarction, rhabdomyolysis, acute kidney injury, psychosis, and hyperemesis) and associated deaths manifest less commonly. Precise estimates of their incidence are difficult to calculate due to the lack of widely available, rapid laboratory confirmation, the variety of SC compounds, and the

unknown number of exposed individuals. Long-term consequences of SCs use are currently unknown.

Introduction

Synthetic cannabinoids (SCs) first appeared in the 1960s in research laboratories exploring potential medical uses targeting cannabinoid receptors. [1] At the end of the first decade of this century, SCs reappeared through internet marketing of so-called "legal highs". The best-known common names are "Spice" and "K2". [1, 2] Although these products typically contain a variety of plant materials, most of the species reported are not believed to have psychoactive properties, with the primary active ingredients being synthetic cannabinoid (SC) receptor agonists sprayed onto the base material. [1]

The HU series (developed at the Hebrew University) the CP series (from Pfizer Inc.) and the JWH series (developed by JW Huffman) are the major groups of SCs. [3] These drugs can have a greater potency and binding affinity than Δ^9-tetrahydrocannabinol (Δ^9THC) the main intoxicant in traditional cannabis products that they mimic. [2, 3] Further, as potentially full agonists at the cannabinoid receptor (CB_1), compared with the partial agonist properties of Δ^9THC, there is likely to be an increased risk of major psychiatric complications and other adverse effects. [1, 2] Other serious side effects, particularly sympathomimetic and hallucinogenic effects related to new compounds may be due to indirect activation of other receptors via excess activation of cannabinoids receptors, direct receptor activations due to mixed receptor effects of new cannabinoids, or possibly adulterants including plant material effects. [2] Winstock and colleagues estimated that the risk of requiring emergency medical treatment is between 14 and 30 times greater following the use of synthetic compared with traditional cannabis [4], with an online survey of SC users reporting that 2.5% had sought emergency treatment in the past 12 months. [5]

Data from population surveys suggest that recent use (i.e. last year) of 'Spice' like products is low, for example 0.2% in England and Wales [6] and 0.4% in Germany. [7] However, 2013 survey data from Australia suggests increasing rates of use with 1.2% of the population reporting use within one year

and 2.5% in those under 25 years. [8] However, prevalence may be markedly higher in some sub-populations. Heltsley et al, analysed urine samples from athletes who were subject to routine screening for performance enhancing and illicit drugs and found 4.5% were using synthetic cannabis, presumably assuming that, at the time, there was a low probability of detection. [9] A survey of 852 college students in Florida reported that 8% had ever used SC [10] and the American Monitoring the Future study reported an annual prevalence of 11.4% in 12th grade students (age 17-18 years), second only to cannabis use. [11] Vandrey et al found that about 30% of SC users include the avoidance of drug testing among their reasons for using SCs, although though this figure may be higher in the United States due to the widespread testing of employees in some sectors (e.g. transportation, Federal agencies). [12, 13]

Data collection specific to emergency department (ED) presentations involving SCs began with the US National Forensic Laboratory Information System detecting 23 SC cases in 2009. By 2012, this number had grown to over 41,000 cases. [14] Similarly, the US Drug Abuse Warning Network (DAWN) recorded over 11,000 cases in 2010 and over 28,000 in 2011. [15] Similar dramatic increases have also occurred in Europe. In the UK, there was a seven fold increase in enquires to TOXBASE between 2011/12 and 2012/13 by healthcare workers in relation to poisoning presentations involving SC. [16] Nevertheless, many emergency physicians are unfamiliar with SCs and feel unprepared to care for intoxicated users. [17]

The analysis of the chemical constituents of 'Spice' shows that the quantity and type of SCs varies widely, with some products containing no active compounds or other active non-cannabinoid substances such as the synthetic opioid *O*-desmethyltramadol. [18] Chronological analysis suggests that the SCs in commercial products may have changed in response to legislative restrictions: for example, JWH-073 appeared in Germany only after JWH-018 was controlled. [18] Thus, consumers are unlikely to be able to gauge the potential effects or risks of particular products as the

constituents change over time. The method of preparation of these products further adds to the potential hazards associated with them. Production typically involves spraying chemical compounds dissolved in acetone onto a plant base. The resulting products may vary in the composition, concentration, and distribution of SCs within a batch and among batches of similar products. A further complication for medical staff assessing presentations thought to involve SCs is the lack of a simple urine or blood-screening test to confirm its presence. [19]

A recent paper on SCs adopted a comprehensive approach to examining the clinical implications arising from research into SCs, their epidemiology, receptor interactions, and human and animal pharmacodynamics. [20] The objective of this review is a more focused approach to identify the typical signs and symptoms of exposure to SCs and particular idiosyncratic presentations involving SCs from hospital presentations and poison centre data. We also aimed to summarize interventions or treatment provided in the hospital management of these cases when these data were available.

Method

In December 2014, we systematically searched Medline, PsycInfo, Embase, Google Scholar and Pubmed for reports. In brief the strategy was (emergency department OR hospital OR Poison Control Centers OR substance related disorders OR Drug Overdose) AND (Synthetic cannabis OR synthetic cannabinoid). Online data supplement 1 contains an example of the syntax (for the Ovid Medline search). Given the nascent state of the literature, we also backward searched the references of retrieved papers to identify early material such as conference presentations.

Inclusion criteria

The target substance was any SC (e.g. “Spice”, “K2” etc.). Adverse events had to be recorded by medical staff e.g. at hospitals, drug rehabilitation services, or emergency facilities as opposed to self-reporting via surveys. The exception to this were Poison Centre reports that collect data from a variety of sources, including the public, but are coded by specialists in poisons information,

including nurses, pharmacists, or scientists. [21] Both self-reported and analytically confirmed use of SCs were eligible for inclusion, as were presentations involving SCs plus other drugs.

Results

We identified 323 records from the database search. We supplemented these with 41 from hand searching references (see Figure 1, PRISMA diagram). After we had excluded duplicates and had screened titles, we reviewed 136 full texts: we subsequently excluded 30 (Online data 2). Overall, 106 papers, letters and conference abstracts were eligible for inclusion in the study, representing over 4000 cases. The tables have been arbitrarily sub-divided into case series (defined as $\geq$ 10 cases) and case studies (<10 cases) on the expectation that the former will provide the more reliable evidence on the typical symptoms while the latter will have more detail on interventions and highlight the most unusual presentations. We identified 14 case series and 55 case reports from journals (Tables 1 and 2) plus a further 15 case series and 22 case reports from conference abstracts (online data 3).

Poison Centre data, including nearly 1900 cases from the USA National Poison Data System for nine months in 2010, represented the largest samples. [22] The prototypical presentation is a young male (59-100%) with tachycardia (37-77%), agitation (16-41%) and nausea (13-94%) (see Table 1). Most cases received observation and supportive care (intravenous fluids, benzodiazepines, oxygen) and left emergency within eight hours. Nevertheless, some cases and series presented with more severe conditions. These cases typically do not include analytically confirmed exposure to SC.

Mortality

There have been both case series and case reports of deaths associated with the use of SC. Shanks and colleagues report on SC concentrations from samples collected during 18 autopsies, although the focus of the paper was primarily a methodological description of the analysis of JWH-018 and -073 from post-mortem whole blood. [23] The same team reported on a further four deaths involving 5F-PB-22, with sudden cardiac dysrhythmias or seizures suggested as a potential mechanism in

three of the cases, whilst, in the fourth, liver and kidney failure was noted. [24] Deaths have been both attributed directly to synthetic cannabinoid use [22, 25-27] (JWH-018, -081, -122, -210, -250: MAM2201: JWH-018 UR-144 N- (5-hydroxypentyl), UR-144 N-pentanoic acid) and in other instances the use appears to have indirectly caused fatalities with deaths attributed to hypothermia (unconscious outdoors in winter) [28] (JWH-210), jumping from a building [29] (SC type unknown) or suicide / self-injury [23, 30] (JWH-018 83.3 ng/ml: AM2201). The two studies by Shanks et al [23, 24] may include deaths reported in other USA case studies. Thus, a conservative estimate of the number of reported SC deaths is 22 (maximum 27) in the USA, three from Europe and one in Japan.

Cardiovascular

Tachycardia is the most prevalent clinical effect reported in the literature. Poison Centres frequently record this effect in association with hypertension as symptoms of SC presentations, with tachycardia occurring in 1/3 to 3/4 of presentations. [31-33] In some cases, there are also reports of chest pain. [34-36] In addition, there are case reports of more severe outcomes including peri-mesencephalic subarachnoid haemorrhage [37], middle cerebral artery occlusion [38-41] and three cases of myocardial infarction in adolescent males. [42] Ibrahim and colleagues also report a cardiac arrest in a 56 year-old man with an earlier four-vessel bypass graft. [43]

Acute kidney injury (AKI)

Poison Centre data show that queries on renal problems account for less than 1% of SC calls [44] but various reports describe acute kidney injury (AKI) in the setting of acute SC toxicity. The Centers for Disease Control (CDC) identified 16 AKI cases over nine months, typically presenting as nausea, vomiting and flank pain with associated elevated peak serum creatinine (range 3.3-21.0 mg/dl). SCs exposure was analytically confirmed in six of seven cases tested (XLR-11, UR-144, indole precursor). There was also evidence of elevated white blood cell count, proteinuria and haematuria. Renal biopsies in a series of eight patients found acute tubular injury (five patients), acute interstitial nephritis (two patients) or both (one person). [45] An additional four AKI cases were

reported from Alabama in otherwise healthy young men [46] and nine in Oregon (including five previously recorded by the CDC). [45] All required hospitalization for up to eight days. [47]

Generalized tonic-clonic seizure (GTC)

The Hoyte review found 52 (3.8%) poison centre reports on SCs included GTC seizures with two cases of status epilepticus (SC unknown). [22] However, in a CDC case series of emergency department SC presentations, 14% involved GTC seizures [48] and a review of paediatric (0-19 years) poison centre reports found that 15% involved seizures. [49] Seizures are also prominent in the case report literature, including those with analytically confirmed SC exposure (e.g. JWH-122, -210, -018: PB-22: BB-22, AM-2233, PB-22, 5F-PB-22, JWH-122). [50-55]

Gastrointestinal

Nausea and vomiting are often conspicuous features of SC presentations (e.g. Table 1 nausea or vomiting reported in 13-94% of presentations). Two papers report on cannabinoid hyperemesis subsequent to the use of SC.[56, 57] Both case reports outline a characteristic cycle of nausea, vomiting and abdominal pain relieved by hot showers similar to the hyperemesis syndromes seen with cannabis abuse. Hopkins and colleagues analytically confirmed SC use, with no cannabis detected in a urine screen. [56]

Psychiatric presentations

As noted in the Tables 1 and 2, many presentations include behavioural features such as agitation. However, more severe psychiatric presentations are also prevalent. Hurst et al reported on 10 cases of new onset psychosis associated with SC use from San Diego, although only two involved just the use of SCs, with the remainder consuming cannabis or alcohol either concurrently or in the recent past. [58] Hospitalization lasted between 6-10 days and in one case, symptoms persisted for more than five months. An audit of an open adult ward in New Zealand found 13% (n=17) of psychiatric admissions were probably related to SC consumption, including four first time admissions (affective, suicidal or psychotic symptoms) plus four first admissions with psychosis. [59] New onset psychosis has also been reported by others [60-64] including with significant self-injury [65], catatonic

features [66] and Capgras delusion. [67] SC use has also been described as exacerbating symptoms in those receiving psychiatric treatment [68], initiating drug induced psychosis (with no known history of drug-induced psychosis), [69] and precipitating a recurrence of cannabis induced psychosis. [70]

SC presentations also include symptoms of panic attack [51, 71], anxiety, paranoia and hallucinations. [72, 73] Two case reports have described withdrawal symptoms following the cessation of SCs [74, 75] similar to those associated with cannabis withdrawal. [76]

Discussion

The prevalence of synthetic cannabinoid (SC) consumption is low in the general population. [6-8] However, the risk of requiring medical attention following use of SC seems to be greater than that for cannabis consumption. [4] Our systematic review of adverse events found that typically events were not severe, only required symptomatic or supportive care and were of short duration. Nevertheless, a number of deaths have been attributed either directly or indirectly to SC consumption, together with other major adverse sequelae, including a significant number with persistent effects including new on-set psychosis with no family history of psychosis. [58]

We did not include popular media reports or the grey literature in the search, which would probably reveal further cases but would be less likely to contain reliable medical information. We were unable to determine the exact number of cases in the scientific literature due to the potential overlap between poison centre data and hospital reports. We could not even definitively established the number of deaths attributed to SC consumption. Of the 28,531 ED visits in 2011 recorded in the DAWN database, 119 (0.4%) led to death potentially related to SC use. [77] Our review of published cases identified only 22 fatal cases in the US through the end of 2014. As not all presentations especially for psychiatric problems or palpitations will include assessment of SC use, SC presentations may currently be seriously underreported. This suggests that the magnitude of the

health burden due to SC use is considerably greater than that currently documented. Most of the data were based on self-reported consumption of SC, with no simple screening test available yet for clinicians.

Some of the information on adverse effects of SCs arises from poison center data. Wood et al outlined the strengths and weakness of poison center data for novel psychoactive substances. [21] In brief, poison centers may detect new and unfamiliar exposures, but the rates of detection may decline with familiarity with the substances involved. In addition, the data depend upon voluntary reporting, often lack analytical confirmation, and may not discern which symptoms to attribute to a given substance, in cases of poly-drug exposure. Similarly, novel adverse events and events involving new SCs are more likely to be reported or published in the medical literature.

The consumption of cannabis affects the cardiovascular system and increases the risk of myocardial infarction. [78, 79] Similarly, cannabis has been implicated in ischemic stroke, especially multifocal intracranial stenosis among young adults. [80] The potential mechanisms include cardiac ischemia due to increased heart rate, postural hypotension, impaired oxygen supply arising from raised carboxyhemoglobin levels, especially in conjunction with tobacco smoking, and catecholamine-mediated pro-arrhythmic effects. [81] It is thus perhaps unsurprising that similar adverse outcomes have occurred following the use of SCs given their increased potency at CB_1 receptors. Whether these compounds have significant direct effects on other receptors is still unknown.

The comparatively short period for which SC have been available and used in the general community means that long-term outcomes are currently unknown. However, the occurrence of acute kidney injury has implications for future health with a meta-analysis estimating a nearly nine-fold increase in the risk of developing chronic kidney disease, and a three-fold increase in the risk for end stage renal disease, compared to those who have not had AKI. [82] Thus, even low prevalence

events with apparently limited duration, like AKI, have the potential to result in significant health costs following the resolution of acute symptoms. The other effects with long-term potential health consequences are initiation or exacerbation of psychiatric disorders, particularly psychosis. These are extremely debilitating and disabling conditions with large societal and health impacts for patients, families and the health system.

Clinical Implications

Synthetic cannabinoid intoxication appears to be a distinct and novel clinical entity. Use of SCs can cause more significant clinical effects than marijuana. There also appear to be qualitative differences in the nature of the symptoms with which patients present. The sheer number of SCs available and the rate at which they continue to change confound examinations of the scale and extent of the problem. [83] More recent formulations (in the UK termed 'Third Generation') are typically more potent that earlier SCs and seem to be associated with greater harms. [84] Trecki and colleagues report that the incidence of clusters and severity of adverse events involving SCs appears to be increasing. [85] This increase could be due to greater familiarity with presentations, better coordination between public health authorities and laboratories or the characteristics of newer SCs. [85]

The overall effects of SC can resemble those of cannabis, but other than anxiety and paranoia these are not usually the symptoms associated with acute hospital presentation. Instead, patients seem to present in EDs because of behavioural abnormalities (agitated behaviour, psychosis, anxiety) or symptoms associated with acute critical illness. The latter includes seizures (which if prolonged can lead to rhabdomyolysis and hyperthermia), AKI, myocardial ischaemia and infarction in demographic groups where this would be most unusual. The majority of mild intoxications only require symptomatic treatment and generally do not require hospital admission. Severe intoxications, involving seizures, severe agitation or mental health disturbances, arrhythmias and significant chest pain, should be admitted to hospital for further investigation.

The lack of an antidote to SCs, analogous to that for opioid overdose, complicates management, as does the unpredictable effects and lack of a clear toxidrome to distinguish SCs from other recreational drugs. [85] The differential diagnosis requires the elimination of diverse conditions including hypoglycemia, CNS infection, thyroid hyperactivity, head trauma and mental illness. [86] Benzodiazepines are usually sufficient to control agitation: while the use of haloperidol has also been described, [86] caution is advised in undifferentiated agitation. Benzodiazepine failure should prompt consideration of definitive airway control. In addition to intravenous fluids for dehydration, the primary goals are protecting the airway, preventing rhabdomyolysis and to monitor for either cardiac or cerebral ischemia. [86]

Traditionally, most recreational drug overdoses have been easily explicable based on clinical presentation alone. From an epidemiological perspective, this position should be revisited. Both the Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS) and the Australian Capital Territory Novel Substances (ACTINOS) projects, routinely analyse raw product samples in the possession of patients, associated with severe or unusual presentations. This protocol has been able to characterize novel products well before their identification by law enforcement, arguably generating important information, not just for the patient concerned but also for population health services.

Conclusions

Data from poison centers and drug monitoring systems in Europe, the UK, the US, and Australia illustrate trends of increased use of SCs. The number of unique SCs appears to continue growing, but the SCs seem to share common characteristics within the class. The most common effects include tachycardia, agitation, and nausea; these generally respond to supportive care. However,

physicians should be aware of the severe cardiovascular, cerebrovascular, neurological, psychiatric, and renal effects, which occur in a minority of cases.

Differences among compounds in the class are difficult to assess. Methods to detect, identify, and confirm new SCs lag behind the appearance of these drugs. Further, many of the cases depend upon self-report of the patients, whose information may be unreliable or inaccurate. Improving the availability of advanced laboratory resources will improve our ability to recognize SCs with higher risk of severe toxicity.

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References

1. European Monitoring Centre for Drugs and Drug Addiction. Understanding the 'Spice' Phenomenon. Luxembourg: Office for Official Publications of the European Communities: EMCDDA; 2009.
2. 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;39:234-43.
3. Vardakou I, Pistos C, Spiliopoulou C. Spice drugs as a new trend: Mode of action, identification and legislation. Toxicol Lett 2010;197:157-62.
4. Winstock AR, Lynskey M, Borschmann R, Waldron J. Risk of emergency medical treatment following consumption of cannabis or synthetic cannabinoids in a large global sample. J Psychopharmacol 2015.
5. 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;28:390-93.
6. Smith K, Flatley J. Drug misuse declared: Findings from the 2010/11 British Crime Survey England and Wales. London: Home Office Statistics; 2011. Report No.: 17597005.
7. Pabst A, Daniela P, Ludwig K, Stefanie M. Substance Use and Substance Use Disorders. Results of the 2009 Epidemiological Survey of Substance Abuse (German). Sucht 2010;56:327-36.
8. Australian Institute of Health and Welfare. 2013 National Drug Strategy Household Survey: Detailed Report. Canberra: AIHW; 2014.
9. Heltsley R, Shelby MK, Crouch DJ, Black DL, Robert TA, Marshall L, et al. Prevalence of synthetic cannabinoids in U.S. athletes: Initial findings. J Anal Toxicol 2012;36:588-93.
10. 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.
11. Johnston LD, O'Malley PM, Miech RA, Bachman JG, Schulenberg JE. Monitoring the Future National Survey Results on Drug Use: 1975-2014: Overview, Key Findings on Adolescent Drug Use. Ann Arbor: Institute for Social Research, The University of Michigan; 2015.
12. Perronea D, Helgesena RD, Fischera RG. United States drug prohibition and legal highs: How drug testing may lead cannabis users to Spice. Drugs Educ Prevent Polcy 2013;20:216-24.
13. Vandrey R, Dunn KE, Fry JA, Girling ER. A survey study to characterize use of Spice products (synthetic cannabinoids). Drug Alcohol Depend 2012;120:238-41.

14. Maxwell JC. Psychoactive substances--some new, some old: a scan of the situation in the U.S. Drug Alcohol Depend 2014;134:71-7.
15. Drug Abuse Warning Network. DAWN 2011 Emergency Department Excel Files - National Tables. Substance Abuse and Mental Health Services; 2011 [updated 2011; cited 3 Oct 2014]; Available from: http://www.samhsa.gov/data/DAWN.aspx#DAWN 2011 ED Excel Files - National Tables.
16. National Poisons Information Service. Report 2012/13. Didcot, Oxfordshire: Public Health England; 2013.
17. Lank PM, Pines E, Mycyk MB. Emergency physicians' knowledge of cannabinoid designer drugs. West J Emerg Med 2013;14:467-70.
18. 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;45:1186-94.
19. 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;44:832-37.
20. Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA. Synthetic cannabinoids: Epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend 2014;144:12-41.
21. Wood DM, Hill SL, Thomas SHL, Dargan PI. Using poisons information service data to assess the acute harms associated with novel psychoactive substances. Drug Test Anal 2014;6:850-60.
22. 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.
23. Shanks KG, Dahn T, Terrell AR. Detection of JWH-018 and JWH-073 by UPLC–MS-MS in postmortem whole blood casework. J Anal Toxicol 2012;36:145-52.
24. Behonick G, Shanks KG, Firchau DJ, Mathur G, Lynch CF, Nashelsky M, et al. Four postmortem case reports with quantitative detection of the synthetic cannabinoid, 5F-PB-22. J Anal Toxicol 2014;38:559-62.
25. Saito T, Namera A, Miura N, Ohta S, Miyazaki S, Osawa M, et al. A fatal case of MAM-2201 poisoning. Forensic Toxicol 2013;31:333-37.
26. Remane D, Auwarter V, Werner R, Schermer J, Drobnik S, Mall G, et al. Fatal poisoning involving the synthetic cannabinoids JWH-122 and JWH-210. Rechtsmedizin 2012;22 (4):286.

27. Streich HT, Rushton WF, Charlton NP. Death by spice: A case report of mortality following synthetic cannabinoid use. Clin Toxicol 2014;52:365.
28. Kronstrand R, Roman M, Andersson M, Eklund A. Toxicological findings of synthetic cannabinoids in recreational users. J Anal Toxicol 2013;37:534-41.
29. Hill SL, Cooper GA, Jackson G, Lupton DJ, Bradberry S, Thomas SHL. What's on the 'Spice' rack? Synthetic cannabinoid receptor agonist toxicity reported to the UK National Poisons Information Service. Clin Toxicol 2013;51:345.
30. Patton AL, Chimalakonda KC, Moran CL, McCain KR, Radominska-Pandya A, James LP, et al. K2 toxicity: Fatal case of psychiatric complications following AM2201 exposure. J Forensic Sci 2013;58:1676-80.
31. Forrester MB, Kleinschmidt K, Schwarz E, Young A. Synthetic cannabinoid exposures reported to Texas poison centers. J Addict Dis 2011;30:351-58.
32. Helander A, Beck O, Hagerkvist R, Hulten P. Identification of novel psychoactive drug use in Sweden based on laboratory analysis--initial experiences from the STRIDA project. Scand J Clin Lab Invest 2013;73:400-6.
33. Hermanns-Clausen M, Kneisel S, Szabo B, Auwarter V. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: Clinical and laboratory findings. Addiction 2013;108:534-44.
34. Harris CR, Brown A. Synthetic cannabinoid intoxication: A case series and review. J Emerg Med 2013;44:360-66.
35. Heath TS, Burroughs Z, Thompson AJ, Tecklenburg FW. Acute intoxication caused by a synthetic cannabinoid in two adolescents. J Pediatr Pharmacol Ther 2012;17:177-81.
36. Nacca N, Vatti D, Sullivan R, Sud P, Su M, Marraffa J. The synthetic cannabinoid withdrawal syndrome. J Addict Med 2013;7:296-8.
37. Kamat AS, Aliashkevich AF, Denton JR, Fitzjohn TP. Headache after substance abuse: a diagnostic dilemma. J Clin Neurosci 2012;19:464-6.
38. Bernson-Leung ME, Leung LY, Kumar S. Synthetic cannabis and acute ischemic stroke. J Stroke Cerebrovasc Dis 2014;23:1239-41.
39. Korya D, Kapoor A, Labiner D. Ischemic stroke in a 28-year-old woman after smoking synthetic THC Neurology 2013;80:P06.250.
40. Takematsu M, Hoffman RS, Nelson LS, Schechter JM, Moran JH, Wiener SW. A case of acute cerebral ischemia following inhalation of a synthetic cannabinoid. Clin Toxicol 2014;52:1-3.
41. Yen M, Berger RE, Roberts J, Ganetsky M. Middle cerebral artery stroke associated with use of synthetic cannabinoid K2. Clin Toxicol 2012;50:673-4.

42. Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. Pediatrics 2011;128:e1622-e27.
43. Ibrahim S, Al-Saffar F, Wannenburg T. A unique case of cardiac arrest following k2 abuse. Case Rep Cardiology 2014;2014.
44. Forrester MB, Kleinschmidt K, Schwarz E, Young A. Synthetic cannabinoid and marijuana exposures reported to poison centers. Hum Exp Toxicol 2012;31:1006-11.
45. Centers for Disease Control. Acute kidney injury associated with synthetic cannabinoid use--multiple states, 2012. Morb Mortal Wkly Rep 2013;62:93-8.
46. 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;8:523-26.
47. Buser GL, Gerona RR, Horowitz BZ, Vian KP, Troxell ML, Hendrickson RG, et al. Acute kidney injury associated with smoking synthetic cannabinoid. Clin Toxicol 2014;52:664-73.
48. Centers for Disease Control. Notes from the field: Severe illness associated with synthetic cannabinoid use - Brunswick, Georgia, 2013. Morb Mortal Wkly Rep 2013;62:939.
49. Plumb J, McDonnell W, M., Anderson KT, Crouch BJ, Caravati EM. Adverse effects from pediatric exposures to spice (cannabinoid agonists). Clin Toxicol 2012;50:708.
50. Gugelmann H, Gerona R, Li C, Tsutaoka B, Olson KR, Lung D. 'Crazy Monkey' poisons man and dog: Human and canine seizures due to PB-22, a novel synthetic cannabinoid. Clin Toxicol 2014;52:635-38.
51. Hermanns-Clausen M, Kneisel S, Hutter M, Szabo B, Auwarter V. Acute intoxication by synthetic cannabinoids - Four case reports. Drug Test Anal 2013;5:790-94.
52. Lapoint J, James LP, Moran CL, Nelson LS, Hoffman RS, Moran JH. Severe toxicity following synthetic cannabinoid ingestion. Clin Toxicol 2011;49:760-4.
53. McQuade D, Hudson S, Dargan PI, Wood DM. First European case of convulsions related to analytically confirmed use of the synthetic cannabinoid receptor agonist AM-2201. Eur J Clin Pharmacol 2013;69:373-6.
54. Schep L, Slaughter R, Hudson S, Place R, Watts M. Delayed seizure-like activity following analytically confirmed use of previously unreported synthetic cannabinoid analogues. Hum Exp Toxicol 2014.
55. Schneir AB, Baumbacher T. Convulsions associated with the use of a synthetic cannabinoid product. J Med Toxicol 2012;8:62-4.
56. Hopkins CY, Gilchrist BL. A case of cannabinoid hyperemesis syndrome caused by synthetic cannabinoids. J Emerg Med 2013;45:544-6.
57. Ukaigwe A, Karmacharya P, Donato A. A gut gone to pot: A case of cannabinoid hyperemesis syndrome due to K2, a synthetic cannabinoid. Case Rep Emerg Med 2014.

58. Hurst D, Loeffler G, McLay R. Psychosis associated with synthetic cannabinoid agonists: a case series. Am J Psychiatry 2011;168:1119.
59. Glue P, Al-Shaqsi S, Hancock D, Gale C, Strong B, Schep L. Hospitalisation associated with use of the synthetic cannabinoid K2. N Z J Med 2013;126:18-23.
60. Benford DM, Caplan JP. Psychiatric sequelae of spice, K2, and synthetic cannabinoid receptor agonists. Psychosomatics 2011;52:295.
61. Johnson LA, Johnson RL, Alfonzo C. Spice: a legal marijuana equivalent. Mil Med 2011;176:718-20.
62. Oluwabusi OO, Lobach L, Akhtar U, Youngman B, Ambrosini PJ. Synthetic cannabinoid-induced psychosis: two adolescent cases. J Child Adolesc Psychopharmacol 2012;22:393-5.
63. Peglow S, Buchner J, III, Briscoe G. Synthetic cannabinoid induced psychosis in a previously nonpsychotic patient. Am J Addict 2012;21:287-88.
64. Rahmani M, Paul S, Nguyen ML. Treatment of refractory substance-induced psychosis in adolescent males with a genetic predisposition to mental illness. Int J Adolesc Med Health 2014;26:297-301.
65. Meijer KA, Russo RR, Adhvaryu DV. Smoking synthetic marijuana leads to self-mutilation requiring bilateral amputations. Orthopedics 2014;37:e391-94.
66. Smith DL, Roberts C. Synthetic marijuana use and development of catatonia in a 17-year-old male. Minn Med 2014;97:38.
67. Van Der Veer N, Friday J. Persistent psychosis following the use of Spice. Schizophr Res 2011;130:285-86.
68. Every-Palmer S. Warning: legal synthetic cannabinoid-receptor agonists such as JWH-018 may precipitate psychosis in vulnerable individuals. Addiction 2010;105:1859-60.
69. Berry-Caban CS, Ee J, Ingram V, Berry CE, Kim EH. Synthetic cannabinoid overdose in a 20-year-old male US soldier. Subst Abus 2013;34:70-2.
70. Muller H, Sperling W, Kohrmann M, Huttner HB, Kornhuber J, Maler JM. The synthetic cannabinoid Spice as a trigger for an acute exacerbation of cannabis induced recurrent psychotic episodes. Schizophr Res 2010;118:309-10.
71. Müller H, Huttner H, Köhrmann M, Wielopolski J, Kornhuber J, Sperling W. Panic attack after spice abuse in a patient with ADHD. Pharmacopsychiatry 2010;43:152-3.
72. Bebarta VS, Ramirez S, Varney SM. Spice: A new "legal" herbal mixture abused by young active duty military personnel. Subst Abus 2012;33:191-94.
73. Schneir AB, Cullen J, Ly BT. "Spice" girls: Synthetic cannabinoid intoxication. J Emerg Med 2011;40:296-99.
74. Morris SR, Sattari R, Dorian R. Terror in the PACU. J Pain 2012;1:S47.

75. Zimmermann US, Winkelmann PR, Pilhatsch M, Nees JA, Spanagel R, Schulz K. Withdrawal phenomena and dependence syndrome after the consumption of "spice gold". Deutsches Arzteblatt 2009;106:464-67.
76. World Health Organisation. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research*. Geneva: WHO; 1993.
77. Drug Abuse Warning Network. *DAWN 2011 (SPSS dataset)*.2015 Substance Abuse and Mental Health Data Archive, Rockville, MD.
78. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. The Lancet 2009;374:1383-91.
79. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation 2001;103:2805-09.
80. Wolff V, Lauer V, Rouyer O, Sellal F, Meyer N, Raul JS, et al. Cannabis use, ischemic stroke, and multifocal intracranial vasoconstriction a prospective study in 48 consecutive young patients. Stroke 2011;42:1778-80.
81. Aryana A, Williams MA. Marijuana as a trigger of cardiovascular events: Speculation or scientific certainty? Int J Cardiol 2007;118:141-44.
82. Coca SG, Singanamala SS, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012;81:442-48.
83. European Monitoring Centre for Drugs and Drug Addiction. New psychoactive substances in Europe. An update from the EU Early Warning System (March 2015). Luxembourg: Office for Official Publications of the European Communities: EMCDDA; 2015.
84. Advisory Council on the Misuse of Drugs. 'Third Generation' Synthetic Cannabinioids: ACMD; 2014.
85. Trecki J, Gerona RR, Schwartz MD. Synthetic cannabinoid-related illness and deaths. N Engl J Med 2015;373:103-7.
86. Roberts JR. Synthetic cannabinoids: Treating toxicity. Emergency Medicine News 2015;37:12-14.
87. Castellanos D, Singh S, Thornton G, Avila M, Moreno A. Synthetic cannabinoid use: A case series of adolescents. J Adolesc Health 2011;49:347-49.
88. Centers for Disease Control. Notes from the field: severe illness associated with reported use of synthetic marijuana - Colorado, August-September 2013. Morb Mortal Wkly Rep 2013;62:1016-7.
89. Forrester MB. Adolescent synthetic cannabinoid exposures reported to Texas poison centers. Pediatr Emerg Care 2012;28:985-9.

90. Monte AA, Bronstein AC, Cao DJ, Heard KJ, Hoppe JA, Hoyte CO, et al. An outbreak of exposure to a novel synthetic cannabinoid. N Engl J Med 2014;370:389-90.
91. 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;9:199-206.
92. Bebarta VS, Ramirez S, Varney SM. Complication of spice use in a deployed combat setting—Seizure while on duty. Am J Addict 2012;21:496-97.
93. Cohen J, Morrison S, Greenberg J, Saidinejad M. Clinical presentation of intoxication due to synthetic cannabinoids. Pediatrics 2012;129:e1064-e67.
94. de Havenon A, Chin B, Thomas KC, Afra P. The secret "spice": An undetectable toxic cause of seizure. The Neurohospitalist 2011;1:182-6.
95. Derungs A, Schwaninger AE, Mansella G, Bingisser R, Kraemer T, Liechti ME. Symptoms, toxicities, and analytical results for a patient after smoking herbs containing the novel synthetic cannabinoid MAM-2201. Forensic Toxicol 2013;31:164-71.
96. Faircloth J, Khandheria B, Shum S. Case report: Adverse reaction to synthetic marijuana. Am J Addict 2012;21:289-90.
97. Jinwala FN, Gupta M. Synthetic cannabis and respiratory depression. J Child Adolesc Psychopharmacol 2012;22:459-62.
98. Pant S, Deshmukh A, Dholaria B, Kaur V, Ramavaram S, Ukor M, et al. Spicy seizure. Am J Med Sci 2012;344:67-8.
99. Papanti D, Schifano F, Botteon G, Bertossi F, Mannix J, Vidoni D, et al. “Spiceophrenia”: a systematic overview of “Spice”-related psychopathological issues and a case report. Hum Psychopharmacol 2013;28:379-89.
100. Quan D, Haase D, Levitan R. Legal drugs of abuse. Emerg Med Rep 2011;32:237-47.
101. Simmons JR, Skinner CG, Williams J, Kang CS, Schwartz MD, Wills BK. Intoxication from smoking “Spice”. Ann Emerg Med 2011;57:187-88.
102. Simmons J, Cookman L, Kang C, Skinner C. Three cases of spice exposure. Clin Toxicol 2011;49:431-33.
103. Thomas S, Bliss S, Malik M. Suicidal ideation and self-harm following K2 use. J Okla State Med Assoc 2012;105:430-33.
104. Thornton SL, Wood C, Friesen MW, Gerona RR. Synthetic cannabinoid use associated with acute kidney injury. Clin Toxicol 2013;51:189-90.
105. Tofighi B, Lee JD. Internet highs—Seizures after consumption of synthetic cannabinoids purchased online J Addict Med 2012;6:240-1.

106. Tung C, Chiang T, Lam M. Acute mental disturbance caused by synthetic cannabinoid: A potential emerging substance of abuse in Hong Kong East Asian Arch Psychiatry 2012;22:31-33.
107. Vearrier D, Osterhoudt KC. A teenager with agitation: Higher than she should have climbed. Pediatr Emerg Care 2010;26:462-65 10.1097/PEC.0b013e3181e4f416.
108. Young AC, Schwarz E, Medina G, Obafemi A, Feng SY, Kane C, et al. Cardiotoxicity associated with the synthetic cannabinoid, K9, with laboratory confirmation. Am J Emerg Med 2012;30:1320.e5-7.

Table 1 Synthetic Cannabinoids – Case series (containing reports of 10 or more cases) of adverse event

Reference / Country	Series n: sex, age	Effects	Signs & symptoms	Analysis / compounds	Treatment / length of stay
Castellanos [87] / USA	11: 91% ♂, mean 17 years	Euphoria, memory changes, auditory / visual changes (Adolescent Addiction Centre)	Paranoid thoughts 35%, palpitations 27%,	Self-report / SC (plus alcohol and cannabis)	NR / NR
CDC [88] / USA	127: 80% ♂, median age 26	Lethargy 35%; aggression 32%, agitation 32%	Systolic BP >120 64%, HR >100 57%	Self-report / various brands of SC	NR / NR (87% discharged from ED: 13% admitted, 8% to ICU)
CDC [48] / USA	22: 82% ♂, median age 25	Nausea/vomiting 36%, aggression 32%, confusion 32%, lethargy 32%: seizures 14%,	Hyperglycaemia 59%, tachycardia 59%, hypokalaemia 41%, acidosis 32%, pneumonia n=2, MI n=1, rhabdomyolysis n=1	Lab tested / (N-(1-amino-3,3-dimethy-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide)	NR / NR (27% to ICU)
CDC [45] / USA	16: 94% ♂, median age 18.5	Nausea & vomiting 94%, abdominal, flank ± back pain 75%	Creatinine peak 3.3 – 21.0 mg/dL	Self-report + 7 lab report / XLR-11, UR-144, indole precursor	Haemodialysis 31%, corticosteroids 26% / NR all admitted to hospital.
Forrester [a] [31, 44] / USA	464: 74% ♂, mean age 23	Agitation 19%, lethargy 19%, vomiting 16%, hallucinations 11%	Tachycardia 37%,	Self-report including any SC	IV fluids 39%, BZD 19%, oxygen 8% / NR
Forrester [a b] [89] / USA	305: 72% ♂, mean age 16.7	Lethargy 24%, agitation 16%, vomiting 13%, hallucinations 12%: death n=1	Tachycardia 42%, hypertension 8%,	Self-report including any SC	NR / NR
Glue [59] / New Zealand	17: 59% ♂, mean age 26	Psychiatric admissions	Psychoses 59%, affective 82%, suicidal ideation 82%, homicidal 6%	Self-report / "K2"	Antidepressants, anti-psychotics / Mean 8.5 days
Helander [32] / Sweden	22: 78% ♂, mean age 20	Emergency department admissions	Tachycardia 77%, mydriasis 73%, somnolence 36%, tremor 27%, agitation 23%, hypotension 23% emesis 23%	LC-T-MS / JWH-015, -018, -019, -021, -081, -210, -250	NR / NR
Hermanns-Clausen [a] [33]	29: 86% ♂, median age 19	Agitation 41%, hallucinations 38%, nausea / vomiting 28%, vertigo 24%, panic 21%,	Tachycardia 76%, hypertension 34%, mydriasis 38%, hypokalaemia (< 3.1 mmol/L) 28%, BGC (<200	LC-ESI-T-MS & GC-MS / JWH -015, -018, -073, -081, -122, -210, -250, AM-694, CP-47, 497-C8, Δ^9-	BZD 31%, potassium 17%, IV fluids 17%, anti-emetic 7%, Intubation n=1, haloperidol n=1,

/ Germany		dyspnoea 21%, lethargy 17%	mg/dL) 31%	THC	neuroleptic n=1 / NR median symptom duration 7.5 hours)
Hoyte [a 22] / USA	1898: 73% ♂, mean age 22.5	Agitation 23%, vomiting 15%, lethargy 14%, confusion 12%, seizure <4%, status epilepticus n=2, death n=1	Tachycardia 40%, hypertension 8%,	Self-report of single agent exposure / (various brands of SC)	IV fluid 25%, BZD 16%, oxygen 6%, anti-emetics 5% / NR (Clinical effects: < 8 hours 75%, 8-24 hours 17%, >24 hours 5%
Hurst [58] / USA	10: 100% ♂, age range 21-25	New onset psychosis	Paranoid delusions 90%, odd/flat affect 60%, hallucinations 60%	Self-report / various brands of SC	70% anti-psychotic medications / inpatients 6-10 days (symptoms 70% < 8 days, 30% > 5 months)
Monte [a 90] / USA	76:72% ♂, median age 28	Altered mental state 68%, agitation 42%, seizures 14%	HR median 100, bradycardia developed (median HR 63, time 179 minutes)	MS / ADB-PINACA (N-[1-amino-3,3-dimethy-1-oxobutan-2-yl]-1-pentyl-1Hindazole-3-carboxamide)	BZD 42%, antipsychotics 14%, ketamine 3% intubation 13% / NR
Shanks [23] / USA	18: sex & age not reported	Autopsies (blood analysis)		LC- ESI-T-MS / JWH-018, -073 Concentration JWH-0180.5 ng/ml – 199 ng/ml	NA / NA

BGC = blood glucose concentration: BP = blood pressure: BZD = benzodiazepines: GC-MS Gas chromatography mass spectrometry: IV intravenous: K = Potassium: LC-ESI-T-MS = Liquid chromatography-electrospray ionization-tandem mass spectrometry: LC-T-MS = liquid chromatography-tandem mass spectrometry: MS = mass spectrometry: NA = Not applicable: NR = not reported: RR = respiration rate: SC = synthetic cannabinoids:

[a] Poison Centre data are received from various sources but are evaluated by the poison centre staff who are trained nurses, pharmacists, or physicians.

[b] Note: analysis of events in those aged <20 (305 cases, 74% ♂ mean age 16.7) 180 in earlier paper [31] with adult cases

[c] Also reports on police samples from suspects - not eligible for review – no ED data

Table 2 Synthetic Cannabinoids – Case studies (containing reports of nine or fewer cases) of adverse events

Reference / Country	Case(s) n: sex, age	Effects	Signs & symptoms	Analysis / compounds	Treatment / length of stay
Alhadi [91] / USA	1: ♂, age 21	Chronic cough, diverse pulmonary infiltrates, severely hypoxemic	HR 118, BP 182/108, RR 42	LC-T-MS/ AM-2201, JWH-122, -210, -018	Mechanical ventilation, antibiotics, steroids / > 8 days
Bebarta [92] / USA	1: ♂, age 25	GTC seizure, vomiting	HR 107, BP 114/69, RR 14, WBC 16 k/µL	Self-report "Spice"	Diazepam 10mg IM / > 1day
Bebarta [72] / USA	a) 1: ♀, age 19 b) 1: ♂, age 19 c) 1: ♂, age 23	a) lethargy, amnestic, agitated b) paranoia, aggression, hallucinations c) panic, agitation difficulty breathing	a) BP 138/70, WBC 17 k/µL, BGC 220 mg/dL b) HR 114, BP 146/78, BGC 197 mg/dL c) HR 110, RR 28, WBC 13 k/µL	Urine TLC + GC-MS – no illicit drugs detected. Self-reported / a) "Space" b) "Space" c) "Spice'	a) lorazepam 2mg IV / 1 day b) naloxone, observation / 1 day c) lorazepam, IV fluids, antiemetic / 1 day
Behonick [24] / USA	a) 1: ♂, age 17 b) 1: ♂, age 27 c) 1: ♂, age 18 d) 1: ♂, age 19	a) dead on arrival b) died post admission c) dead on arrival d) dead on arrival	b) severe liver & kidney injury, respiratory failure c) bilateral pulmonary vaso-congestion d) bilateral pulmonary oedema	All LC-ESI-T-MS a) / 5F-BP-22 1.1 ng / ml b) / 5F-BP-22 1.3 ng/ml c) / 5F-BP-22 1.5 ng/ml d) / 5F-BP-22 1.5 ng/ml	a) intoxication: accidental b) fulminant liver failure: undetermined c) acute intoxication accidental d) acute intoxication: accidental
Benford [60] / USA	1: ♂, age 20	Anxiety & paranoia (new onset psychosis?), hallucinations, diaphoretic	Tachycardia	Self-report "Spice"	NR / NR
Bernson-Leung [38] / USA	a) 1: ♀, age 22 b) 1: ♀, age 19	a) drowsiness, inattention, dysarthria, hemibody weakness, b) left facial weakness, left-sided numbness, and dysfluency	a) dysarthria, left hemiplegia, left hemi-anesthesia: MRI cerebral artery acute ischemic stroke b) aphasia left facial droop, left hemi-anesthesia: MRI cerebral artery infarction	a) Self-report / "K2" b) Self-report "Peak extreme"	a) aspirin / NR b) warfarin / NR
Berry-Caban [69] / USA	1: ♂, age 20	Uncommunicative, agitated – drug induced psychosis	Tachycardia 160	Self-report SC	Lorazepam 2mg, 25 mg diphenhydramine, 1mg risperidone / 9 days
Bhanushali [46] /USA	4: ♂, age 20-30 years	Emesis, abdominal pain	Peak creatine 3.2 - 15.2 mg/dL, haemoglobin 12.0- 16.8 g/dL, WBC 8.1- 12.4 k/µL: 3 kidney biopsies –	Self-report "Spice"	No renal replacement therapy required / NR

			acute tubular necrosis		
Buser [47] / USA	9: ♂, median age 18	Intense nausea, flank pain (acute kidney injury)	Systolic BP 138-172, Peak creatinine median 6.6 ng/mL	Self-report SC + LC-TOFMS / XLR-11	Anti-hypertensives, steroids, dialysis (n=1) / 2-8 days
Cohen [93] / USA	3: 2 ♂, mean age 16.6	a) Catatonic, b) agitated & aggressive, c)'frozen' face, agitated	a) HR 105, BP 118/73, RR 18: b) HR 131, BP 131/89, RR 24: c) HR 62, BP 110/52, RR 12	Self-report / a) "K2", b) "Spice" c) "Spice"	a) Diphenhydramine 50mg IV, lorazepam 2mg IV x2 / 1 day b) Diphenhydramine 50mg IV, lorazepam 2mg IV / <1 day c) Normal saline 1000mL, lorazepam 4mg IV / <1 day
de Havenon [94] / USA	a) 1: ♂, age 24 b) 1: ♀, age 36	a) GTC seizure b) GTC seizure: status epilepticus	a) supratentorial sulcal CSF: EEG mildly encephalopathic b) EEG mildly encephalopathic WBC 12.4 k/µL.	Self-report / "Spice"	a) NR/ NR b) intubated, lorazepam, etomidate, vecuronium, propofol, evetiracetam, phenytoin / NR
Derungs [95] /	1: ♂, age 31	Agitation, anxiety, aggression, vomiting, transient psychotic state	HR 144, BP 160/100 GCS 13 hypokalaemia 3.2 mmol/L	GC-MS / MAM-2201	Observation / 3 hours
Every-Palmer [68] / New Zealand	5: (age / sex not reported)	Florid psychosis	Existing forensic inpatients	NR / CP47, 497, JWH-018	NR / NR
Faircloth [96] / USA	1: ♂, age 17	Emesis, confusion, lethargy	HR 132, BP 158/86, RR 30, GCS 9, BGC 121 mg/dL, hypokalaemia (3.2 mmol/L)	Self-report / SC "K2"	Normal saline, oxygen / NR
Gugelmann [50] / USA	1: ♂, age 22	GTC seizure	HR 106, BP 167/102, RR 24, GCS 3	LC-QTOFMS / synthetic cannabinoid PB-22	Ondansetron 4mg IM, midazolam 5mg IM, intubation, midazolam 4mg, etomidate, rocuronium. propofol IV / NR
Harris [34] / USA	6: 83% ♂, age 17-24	Agitation, seizures, high risk behaviours, hallucinations, inability to move limbs, emesis, syncope, chest pain	Tachycardia (83%) hyperreflexia (50%)	Self-report / SC	Observation / 1-4 days
Health [35]/ USA	a) 1: ♂, age 17 b) 1: ♂, age 15	a) stuporous & confused b) unconscious	HR 180, chest and back pain, other tests normal ranges b) HR 172, BP 162/57, RR 16	Both self-report / SC	a) adenosine 6 mg IV / 1 day b) IV fluids / 1 day
Hermanns-Clausen [51] /	4: ♂, mean age 18.25	a) GTC Seizure, emesis b) lethargy	a) (HR & BP 'normal'), BGC 128 mg/dL, WBC 14.2 k/µL	LC-ESI-T-MS / a) JWH-122, -210, -018 BZD, cannabinoids	a) intubated, midazolam IV, bronchoscopy for aspiration / 3

Germany		c) agitation, trembling, panic, emesis d) emesis, unable to communicate	b) HR 160, WBC 11.3 k/μL, c) HR 112, hypokalaemia (2.9mmol/L) BGC 161 mg/dL, d) HR 100, WBC 15.4 k/μL, hypokalaemia (3.0 U/L)	b) MAM-2201, UR-144, JWH-122, metabolite JWH-018 c) JWH-081, metabolite JWH-073 d) JWH-122 metabolite JWH-018 BZD	days b) NR / <1 day c) IV fluids, potassium / < 1day d) IV fluids, potassium, BZD / 1day
Hopkins [56] / USA	1: ♂, age 30	Intractable abdominal pain, nausea & emesis (relieved by hot showers)	Diagnosis: cannabinoid hyperemesis	GC-LC -MS / JWH-018, -073, -122, AM-2201, -694	IV fluids, Ondansetron IV, promethazine suppositories / NR
Ibrahim [43] / USA	1: ♂, age 56	Cardiac arrest, ventricular fibrillation, comatose	Sinus tachycardia, GCS 3, troponin T 0.632, CKMB 70.2 index 8.6%	Self-report "K2"	Defibrillated x2 (epinephrine, atropine, lidocaine IV), induced hypothermia / NR
Jinwala [97] / USA	a) 1: ♂, age 19 b) 1: ♂, age 15	a) seizure, altered mental state b) difficulty breathing	a) HR 68, BP 110/65, RR 7 b) RR 8	Self-report "K2" Self-report "Silver K2"	a) intubated / NR b) endotracheal intubation 2 days / 4 days
Johnson [61] / USA	1: ♂, age 23	Paranoid delusions (no history mental illness)	No abnormal readings (e.g. blood, metabolic, thyroid screens)	Self-report "Spice"	NR / NR (symptoms resolved in 24 hours).
Kamat [37]/ New Zealand	1: ♂, age 17	Severe global headache, emesis, visual disturbance	CT scan perimesencephalic subarachnoid haemorrhage & aneurysm	Self-report "Kronic Purple Haze"	MicroPlex 10 coil inserted / 22 days
Krostrand [28] / Sweden [c]	1: ♂, age 17	Dead on arrival: hypothermia + intoxication	(Intoxicated outdoors at night)	LC-T-MS / JWH-210	NA / NA
Lapoint [52] / USA	1: ♂, age 48	Generalized seizure	Sinus tachycardia HR 106: BP 140/88 RR 22	GC-MS & LC-T-MS / JHW-018	lorazepam IV, intubated, electric cardioversion / >3 days
McQuade [53] / UK	1: ♂, age 20	GTC seizure (history of poor diabetes management)	GCS 14, HR 93, BP 152/63	LC-MS / AM-2201 / self-report "Black mamba"	Normal saline / 2 hours DAMA
Meijer [65] / USA	1: ♂, age 26	(Paranoia) self-inflicted 4th degree burns hands & arms: overall 14.5% body area	(Bilateral amputation)	Self-report / SC "Black Diamond"	Extensive surgery including amputations of fingers on both hands, multiple skin grafts / NR
Mir [42] / USA	3: ♂, mean age 16	a) 3 days chest pain, b) 1 week chest pain c) 3 day chest pain	a) troponin 3 ng/mL ↑25 ng/mL: b) troponin 11.6 ng/mL c) troponin 7 ng/mL ↑12 ng/mL	Self-report / "K2"	a) NR / > 2 days b) NR / NR c) NR / NR
Müller [70] / Germany	1: ♂, age 25	(Recurrent) psychotic episode, paranoid hallucination, imperative voices	-	Self-report / "Spice"	NR / NR

Müller [71] / Germany	1: ♂, age 21	Panic attack, blurred vision, unsteady gait, palpitations, sweating (History of ADHD)	Tachycardia	Self-report / "Spice"	IV fluids, lorazepam 2mg IV / > 1 day
Nacca [36] / USA	1: ♀, age 22 1: ♂, age 20	a) Cramp, pain, chills, cravings, anxiety (withdrawal) b) Chest pain, palpitations, dyspnoea, headache (withdrawal)	a) HR 100, BP 110/78, RR 28, mild leucocytosis & acidosis b) HR 120, BP 106/58, RR 18, CPK 753 IU/L	a) Self-report / SC b) Self-report / SC	a) 2 L IV fluid, 2 mg IV lorazepam / 3 hours b) BZD, hydroxyzine, diphenhydramine, quetiapine 50 mg
Oluwabusi [62] / USA	a) 1: ♂, age 19 b) 1: ♂, age 17	a) new onset psychosis b) new onset psychosis	(both cases had subsequent re-admissions following SC use)	a) self-report / SC b) self-report / SC	a) quetiapine, aripiprazole b) olanzapine
Pant [98] / USA	1: ♂, age 48	GTC seizures	HR 106, BP 140/88, RR 22, GCS 10, creatine phosphokinase 1200 U/L	LC-T-MS / JWH-018 no other illicit drugs, alcohol 140 mg/dL	4mg lorazepam / NR
Papanti [99] / Italy	1: ♂, age 18	Confused and agitated	Tachycardia, HR 180, BP 137/90, RR 18	Self-report / "Bonzi"	Olanzapine 5 mg, bromazepine 3mg / NR (symptoms 4 weeks)
Patton [30] / USA	1: ♂, age 23	Dead on arrival – (self-inflicted) stab wound	Blunt trauma to hands, sharp force wounds head & upper extremities	LC-MS-MS / AM2201	NA / NA
Peglow [63] / USA	1: ♂, age 59	Psychotic symptoms (history of poly substance abuse 3 years prior)	-	Self-report / "Spice"	NR (return to outpatient medications) / 1 day
Quan [100] / USA	1: ♂, age 20	Anxiety & confusion	Sinus tachycardia, HR 114, BP 148/89, mild leukocytosis & elevated blood urea nitrogen /creatinine ratio	Self-report / "Spice"	IV fluids, Ondansetron 4 mg IV/ 2 hours
Rahmani [64]	a) 1: ♂, age 17 a) 1: ♂, age 17	a) Psychotic symptoms, agitation, b) Psychotic symptoms	a) Delusions, hallucinations b) Agitated (required 4 point restraint). Hallucinations, disordered thoughts	a) Self-report / "Spice" (LSD, psilocybin, mushrooms, 'bath salts', oxycodone) b) self-report / "Spice" (cannabis, LSD, ecstasy, BZD)	a) Risperidone, clozapine, lorazepam, haloperidol, valproic acid, chlorpromazine, metoprolol / 120 days b) Risperidone, clozapine, Haldol, lorazepam, valproic acid / 25 days
Saito [25] / Japan	1: ♂, age 59	Dead on arrival	Autopsy – no evidence violence / disease	LC-ESI-T-MS / MAM2201	NA / NA
Schep [54] / New Zealand	1: ♂, age 23	Seizure, emesis, discharged, seizure, CT brain scan normal	K 3.3 mmol/L, lactate 5.2 mmol/L, creatinine kinase 338 U/L, WBC 18.9k/ µL	LC-MS / BB-22, AM-2233, PB-22, 5F-PB-22, JWH-122	IV fluids, oral diazepam / <1day

Schneir [55] / USA	1: ♂, age 19	Generalized seizure, vomiting	HR 84, BP 177/83, RR 18	Lab test / JWH-018, -081, -250, AM-2201 (Urine screen BZD)	Midazolam 5mg intranasal/ NR
Schneir [73] / USA	a) 1: ♀, age 22 b) 1: ♀, age 20	Anxiety, palpitations Anxiety, "feeling psychotic"	a) Chemistry & bloods normal b) HR 126 (refused further tests)	a) GC-MS / JWH-018, -073	a) Observation / 1 hour b) Refused observation / NR
Simmons [101] / USA	a) 1: ♂, age 21 b) 1: ♂, age 27 c) 1: ♂, age 21	a) emesis & seizure b) emesis, confusion, agitation c) emesis & agitation	a) sinus tachycardia & tachypneic, WBC 14 k/µL b) WBC 14 k/µL, BGC 186 mg/dL c) Mild tachycardia, WBC 19 k/µL hypokalaemia (3.3 mmol/L)	All self-report / "Spice"	a) 2 L saline, diphenhydramine 25mg IV / 1day b) 2 L saline / 1day c) 2 L saline, lorazepam 2 mg / 1 day
Simmons [102] / USA	a) 1: ♂, age 25 b) 1: ♂, age 21 c) 1: ♂, age 19	a) possible seizure, non-verbal / non-responsive, b) unresponsive, possible seizure, agitated, c) paranoia & delusions	a) HR 122, BP 109/47, lactate 5.7 mmol/L, pH 7.24, PCO2 63 mmHg b) GCS 7, HR 48, BP 204/103, RR 8, WBC 16k/µL, BGC 198 mg/dL, lactate 3.3 mmol/L, creatinine kinase 867 U/L c) HR 85, BP 149/67, RR 16	LC-T-MS / a) JWH-018, b) metabolites of JWH-018, -073, c) metabolites of JWH-018, -073	a) IV fluids, lorazepam 4mg IV / 3 hours b) bag valve mask / NR c) NR / several hours
Smith [66] / USA	1 ♂, age 17	New Psychiatric admission, confusion, bizarre behaviour	Psychosis with catatonic features , mild hypotension	Self-report / SC (plus screened positive cannabis)	Oral lorazepam, electro convulsive therapy / NR
Takematsu [40] / USA	1: ♂, age 33	minor right hemiparesis, dysarthria, aphasia	HR 100, BP 163/63, RR 16, Head CT scan: acute infarction left insular cortex	GC-MS / XLR-11	NR / 3 days
Thomas [103] / USA	1: ♂, age 20	Agitation, confusion, suicidal ideation, self-inflicted trauma	HR 108, RR 30,WBC 18.7k, BGC 232, creatinine kinase 313	Self-report "K2" Negative urine drug screen, alcohol zero	Lorazepam, morphine / <2 days
Thornton [104] / USA	1: ♂, age 26	Abdominal & back pain, emesis,	HR 54, BP 151/40, RR 16, WBC 14 k/µL creatinine 30 mg/dL	LC-TOFMS / SC (XLR-11, UR-144)	NR / 6 days
Tofighi [105] /	1: ♂, age 48	GTC seizures	HR 136, BP 161/92, RR 20, GCS 6, creatinine kinase 2649 U/L. Became hyperthermic HR 186-214, BP 59/43, required 100 Joule shock	Self-report K2 / Negative urine drug screen, alcohol zero	BZD, IV fluids, respiratory support/ 5 days
Tung [106] / China	1: ♂, age 36	(History of psychotic disorder) agitation, required restraints, profuse sweating	HR 95, BP 150/90	Self-report / "K2"	Restrained, midazolam IM / >10 days
Ukaigwe [57] /	1: ♂, age 38	Nausea, vomiting, severe	HR 89, BP 115/73, RR 16, WBC 14	Self-report / "K2"	IV fluids, Ondansetron / > 72

USA		abdominal pain (compulsion for hot showers)	k/µL, serum electrolytes low (e.g. K 3.4 mmol/L), creatinine 4.78 mg/dL		hours
Van der Veer [67] / USA	3: ♂, age 20-30	All - psychotic symptoms a) (history of PTSD), aggression and suicidality, b) (history brief psychotic episodes) aggression, paranoia & delusions, c) (no psychiatric history) Capgras delusion & suicidality	(Symptoms persisted – required ≥ 2 weeks hospitalization)	Self-report / "Spice" "Spike 99"	a) risperidone / ≥ 2 weeks b) haloperidol / ≥ 2 weeks c) haloperidol / ≥ 2 weeks
Vearrier [107] / USA	1: ♀, age 17	Agitated and intoxicated	HR 120, BP 135/85, hypokalaemia (2.9 mmol/L)	Self-report / SC ("JWH-018")	Lorazepam 2 mg IV / NR
Young [108] / USA	1: ♂, age 17	Chest pain, dyspnoea, light-headed	HR 140, BP 136/78: 11 hours subsequently bradycardia HR 48, BP 121/59	GC-MS / JWH-018, -073	Nitro-glycerine / 3 days
Zimmerman [75] / Germany	1: ♂, age 20	Withdrawal (craving, sweating, nightmares, nausea, tremor)	HR 125, BP 180/90 (day 4)	Self-report / "Spice"	Zociplone 3.75-7.5 mg, promethazine 25mg, clonidine 0.175 mg, pramipexole 0.175-0.35 mg (off label)/ 21 days

ADHD = attention deficit hyperactivity disorder: BGC = blood glucose concentration: BP = blood pressure: BZD = benzodiazepines: CKMB = creatine kinase myocardial band: CSF = cerebrospinal fluid: EEG = electroencephalogram: DAMA = discharged against medical advice: GC-MS Gas chromatography mass spectrometry: GCS = Glasgow coma score: GTC = Generalized tonic-clonic: HR = heart rate: IM = intramuscular: IV intravenous: K = Potassium: LC-ESI-T-MS = Liquid chromatography-electrospray ionization-tandem mass spectrometry: LC-TOFMS = liquid chromatography, time-of-flight mass spectrometry: LC-QTOFMS = liquid chromatography, quadruple time-of-flight mass spectrometry: LC-T-MS = liquid chromatography-tandem mass spectrometry: MRI = magnetic resonance imaging: NA = not applicable: NR = not reported: PCO = partial pressure of carbon dioxide: RR = respiration rate: TLC = thin layer chromatography: WBC = white blood cell count

[a] Also reports on police samples from suspects - not eligible for review – no ED data

Online Supplementary Data

Online Supplementary Data 1

Search syntax - Ovid Medline

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE (R) <1996 to October 10, 2014

1 synthetic cannabis.mp. (11)
2 synthetic cannabinoid.mp. (558)
3 synthetic cannabinoids.mp. (457)
4 1 or 2 or 3 (899)
5 emergency department.mp. or Emergency Service, Hospital/ (57833)
6 Poison Control Centers/ or Poisoning/ or poison centre.mp. (7808)
7 Substance-Related Disorders/ (46684)
8 Drug Overdose/ (6311)
9 5 or 6 or 7 or 8 (115670)
10 4 and 9 (93)

Online Supplementary Data 2

Studies excluded after inspection of full text (n=31)

Study	Reason for exclusion
Bebarta [1]	Abstract subsequently published - included [2]
Bottei [3]	Abstract subsequently published – included [4]
Chan [5]	Main substance benzofuran (SC mentioned at low concentration)
Corkery [6]	Review – did not identify types of adverse event
Every-Palmer [7]	Forensic psychiatry unit interviews
Forrester [8]	Patterns of use
Forrester [9]	Combined synthetic cannabinoid and synthetic cathinone use
Forrester [10]	Comparison of synthetic cannabinoid and MDMA use
Forrester [11]	Patterns of use
Gunderson [12]	Primary care / research study – description of use
Hermanns-Clausen [13]	Report of synthetic cannabinoid events but frequency not specified.
Hunt [14]	Not synthetic cannabinoids
Iwanicki [15]	Synthetic cannabinoid events not separated from other drug adverse events
Jerry [16]	Review – did not identify new adverse events
Khullar [17]	Not synthetic cannabinoids
Kithinji [18]	Reported patterns of use and exposure
Kleinschmidt [19]	405 cases that overlap with Forrester [20] (n=464)
Lapoint [21]	Abstract subsequently published – included [22]
Locatelli [23]	Did not separate outcomes by drug type.
Lonati [24]	Includes cases reported by elsewhere [25]
Lonati [26]	Did not separate outcomes by drug type.
Maxwell [27]	Review – did not identify types of adverse event
McGuiness 2012 [28]	University health clinic
McKeever [29]	Abstract subsequently published – included [30]
Murphy [31]	Included as CDC in Table 1[32]
Musshoff [33]	From police data
Pierre [34]	Review – did not identify new adverse events
Plumb [35]	Sub set of Plumb 2012 [36]
Rodgman [37]	Insufficient data to extract (psychiatric cases)
Tuv [38]	Review – did not identify new adverse events
Yeakel [39]	From police data

MDMA = methylenedioxymethamphetamine

Online Supplementary Data 3

Conference abstracts synthetic cannabinoids

Reference / country	Series n: sex, age	Effects	Signs & symptoms	Analysis / compounds	Treatment / length of stay
			Case Series (≥ 10 cases)		
Bulbena-Cabre [40] / USA	50: (typically ♂, 18-25)	Psychiatric ED – agitation, disordered thoughts aggression		Self-report SC	Stabilization / NR
Cookman [a 41] / USA	60: 80% ♂, mean age 22	NR	Tachycardia 50%, altered mental state 42%, agitation 33% emesis 30%	Self-report SC	IV fluid 38%, benzodiazepines 15% anti emetics 8% / NR
Fernandez [a,b 42] / USA	328: 75%, ♂	Lethargy 18%, agitation 18%, vomiting 17%, hallucinations 11%,	Tachycardia 38%, hypertension 11%	Self-report SC	NR / NR
Hermanns-Clausen [43] / Germany	13: 92% ♂, median 17.5 years	Thoracic pain, hallucinations, agitation, somnolence, seizures, psychosis	Tachycardia, dyspnoea, hypokalaemia	LC-T-MS / JWH-018, -081, 122,-250	NR / NR
Hermanns-Clausen [44] / Germany	35: 91% ♂, median age 17.5	Emesis 66%, somnolence 57%, agitation 17%, seizures 6%, aspiration n=1	Tachycardia 74%, hypokalaemia 40%, hypoxemia n=1	LC-ESI-T-MS / JWH-018, -081, 122, -203, -210, AM-2201, RCS-4	NR / Most symptoms ceased within hours
Hermanns-Clausen [45] / Germany	21: 86% ♂, age 13-30	Emesis 52%, somnolence 52%, hyperglycaemia 43%, syncope 19%, dyspnoea 14%, seizures n=2	Tachycardia 57%, hypokalaemia 19%, elevated CK/ CK-MB	LC-ESI-T-MS / JWH-018, -019, -081, 122, -200, -210, -310, MAM-122, 2201 RCS-4, UR-144	NR / NR
Hill [a 46]/ UK	53: 74% ♂, age 13-52	Death n=1 agitation 19%, confusion 19%, collapse 19%, dizziness 15%	Low GCS/ drowsiness 23%, tachycardia 21%	Self-report / SC "Black mamba" 53%	NR / NR
Ide [47] / Japan	20: 80% ♂, median age 24.9	Disturbance of consciousness 50%, hallucinations 25%, seizure n=1	Tachycardia 50%, hypertension 30%, tachypnea 20%, rhabdomyolysis n=1	GC-MS / JWH -122, 203, -210, AM-694, 2001	NR / NR
Iwanicki [15]/USA	76: 72% ♂, age 23-35	Altered mental state 68%, agitation 42%, seizures 14%	Median HR 100, elevated creatinine 34%, hyperthermia 12%, intubation required 9%	Spectrophotometry / ADB-PINACA	42% benzodiazepines, 14% antipsychotics, 3% ketamine / NR
Locatelli [a 25] /	17: (sex not	Agitation 71%, confusion 47%,	Tachycardia 77%	Self-report + 11 laboratory	Symptomatic care:

Italy	reported), 14-55 years	mydriasis 41%, hallucinations 29%, coma n=2, seizure n=2.		analysis / JWH-018, -022, -250	benzodiazepines / 1 day
Lonati [a 48] / Italy	32: (age & sex not reported)	Agitation 50%, confusion 41%, mydriasis 38%, hallucinations 19%, coma n=4, seizure n=2	Tachycardia 66%	Self-report + 19 laboratory tested / JWH-018, -073, -122, -250	Typically just symptomatic care / discharge usually 24-36 hours
Obafemi [49] / USA	11: 45% ♂, age 20-57	Memory impairment 91%, light-headedness,	HR > 100 18%, BP 140/90 36%,	Analysis method NR / AM2201	NR / <10 hours
Plumb [a 36] / USA	67: 66% ♂, age 11-19 (paediatric study)	Lethargy 28%, anxiety, 25%, emesis 21%, confusion, 16%, chest pain 13%, seizures 15%, hallucinations 9%	(Of 46 with data) tachycardia 75%, hypokalaemia 7%: n=1 for pneumomediastinium, atrial fibrillation, rhabdomyolysis	Self-report / SC "Spice"	Naloxone, BZD, potassium, oxygen, antiarrhythmic meds, alkalinization of urine, IV fluids /NR
Rosenbaum [a 50] / USA	78: 79% ♂, age 12-46	Agitation 47%, emesis / nausea 18%, hallucinations 10%, suicide n=1	Median HR 122	LC-T-MS / JWH-018, -073,-081	NR / NR
Westerbergh [a 51]/ Sweden	214:78% ♂, 96% < 25 years	Drowsiness 36%, muscular symptoms 26%, emesis 12%	Tachycardia 51%, hypertension 13%, all cases mild or moderate severity	NR / CRA13, JWH-018, -015, -081, -210, -250	NR / NR

Case Studies (< 10 cases)

Reference / country	**Case(s) n: sex, age**	**Effects**	**Signs & symptoms**	**Analysis / compounds**	**Treatment / length of stay**
Banerji [a 52] / USA	9: 100% ♂, median age 19	Anticholinergic toxidrome 44%, agitation 44%, tremor 44%, confusion 33%,	Tachycardia 67%, hypertension 22%	Self-report / SC	Symptomatic & supportive care: benzodiazepines n=3 / NR
Besli [53] / Turkey	5: 80% ♂, age 12-17	3 unconscious, 2 euphoric / confused, 5 vomiting	Sinusal tachycardia,	NR / SC	NR / NR
Brickman [54] / Germany	1: ♂, age 17	Nausea, vomiting, respiratory insufficiency	NR	MS: JWH-210	Intubation, ventilation / NR
Butler [55] / USA	1: ♂, age 46	Seizures	HR 140, BP 177/119, RR 10	Family report SC "Blackjack wild"	Midazolam 4 mg, diazepam 10 mg, rocuronium 100 mg, etomidate 20 mg, intubation / 1 day
Canning [56] / USA	1: ♂, age 18	Nausea, persistent vomiting, tremor, blurred vision	HR 93, BP 120/65, RR 18	GC-MS + LC-T-MS / JWH-018	NR / NR

Gerona [57] / USA	2: (age & sex not reported)	Nausea, vomiting, altered mental state	Tachycardia	LC-TOFMS / JWH-007, -015, -018, -073, -122, -210-398.	NR / NR
Grossenbacher [58] /France	1: ♂, age 34	Dizziness	HR 100, BP 120/70	Self-report SC	NR / NR
Gunja [59] / Australia	1: ♂, age 29	Chest pain, agitation	HR 110, BP 170/95, RR 20, other tests normal ranges	NMR-MS / 5-fluoro-AKB48	IV saline, IV midazolam 4mg + 1mg, diazepam 5 mg
Korya [60] / USA	1: ♀, age 28	Garbled speech, left side paralysis	MRI: multiple embolic stokes right middle cerebral artery	Self-report / "K2"	NR / NR
Locatelli [61] / Italy	1: ♂, age 20	Chest pain, dyspnoea	Tachycardia 150, BP 160/80BGC 160 mg/dL,	Self-report / "synthecaine", GC-MS / SC MAM-2201, cocaine, benzoylecgonine	IV fluids, 10 mg diazepam / 12 hours
Loschner [62] / USA	1: ♂, age 19	Respiratory failure, unresponsive	GSC 8 (Diffuse alveolar haemorrhage)	Self-report /"Spice" (Urine test BZD and cannabinoids)	Mechanical ventilation, methylprednisolone / >2 days
McCain [63] / USA	6: (age & sex not reported)	Confusion 66%, agitation 50%, hallucinations 33%, emesis 33%	Tachycardia 100% hypokalaemia 100%	Lab test / JWH-018, -073	BZD, anti-emetics, potassium, IV fluids / all $\leq$ 1 day
McKeever [30] / USA	1: ♂, age 16	Sub-sternal chest pain, dyspnoea, nausea, vomiting	HR 82, BP 127/57, RR 22, peak troponin 8.29 ng/mL, peak CKMB 33.9 ng/mL. Sub-endocardial MI.	Self-report / "K2"	Nitro-glycerine, aspirin morphine / >4days
Morris [64] / USA	1: ♂, age 20	Uncontrolled movements, spasms, altered mental state	(post-operative care unit withdrawal symptoms) HR 120-130	Self-report / "Spice"	IV ativan, midazolam, fentanyl
Moti [65] / USA	1: ♂, age 17	Seizure, confusion	NR	Self-report / "K2"	NR / NR
Remane [66] / Germany	1: ♂, age 25	Dead on arrival	congestion and oedema - lung, brain: congestion - heart, liver, spleen, and kidneys	LC-T-MS / JWH-018, -081, -122, -210, -250	NA / NA
Rosenbaum [67] /USA	1: ♀, age 16	Agitation, seizures, vomiting	Tachycardia	Self-report / "Spice"	Supportive care / NR
Seifert [68] / USA	1: ♂, age 18	Seizure, acute kidney failure	Serum creatinine 1.8 mg/dL, rhabdomyolysis (CK peak 2789)	GC-MS / XLR-11, 4-OH JWH-018, 5-OH JWH-018, Carboxy UR-144, 5-OH UR-144	Keppra / $\geq$ 6 days
Smith [69] / USA	1: ♀, age 24	Extreme agitation	HR 140, BP 127/58, RR 30, CPK peak 68744, AST/ALT peak	Self-report / injected SC	BZD, supportive care / 3

			572/154		days then psychiatric care
Streich [70] / USA	1: ♂, age 49	Asytolic cardiac arrest, died post admission	ECG ST elevation in VL, V2, V3 depression in II, III, VF and V4	NR / JWH-018 UR-144 N- (5-hydroxypentyl), UR-144 N-pentanoic acid	Therapeutic hypothermia protocol, ventilation, vasopressor support / 3 days
Werner [71] / USA	1: ♂, age 26	Severe sub-sternal chest pain	HR 100, BP 124/87, RR 23. Troponin 16.3,	Self-report / "K2"	Standard acute coronary care / NR
Yen [72] / USA	1: ♀, age 22	Left-sided weakness slurred speech, cerebrovascular accident	(Non-contrast head CT, MRI, CT angiogram)	Self-report / SC "K2"	Hyperosmolar therapy mannitol / NR

AST/ALT = aspartate transaminase–alanine transaminase ratio: BGC = blood glucose concentration: BP = blood pressure: CK creatine kinase: CKMB = creatine kinase myocardial band: CPK creatine phosphokinase: EEG = electroencephalogram: GC-MS Gas chromatography mass spectrometry: GCS = Glasgow coma score: HR = heart rate: LC-QTOFMS = liquid chromatography, quadruple time-of-flight mass spectrometry: LC-T-MS = liquid chromatography-tandem mass spectrometry: LC-ESI-T-MS = liquid chromatography-electrospray ionization-tandem mass spectrometry : MI = myocardial infarction: NMR = Nuclear magnetic resonance: RR = respiration rate:

[a] Poison Centre data are received from various sources but are evaluated by the poison centre staff who are trained nurses, pharmacists, or physicians.
[b] Overlapping cases with Forrester [20]

References

1. Bebarta VS, Varney S, Sessions D, Barry D, Borys D. Spice: A new "Legal" herbal mixture abused by young active duty military personnel. Clin Toxicol 2010;48:632.
2. Bebarta VS, Ramirez S, Varney SM. Spice: A new "legal" herbal mixture abused by young active duty military personnel. Subst Abus 2012;33:191-94.
3. Bottei E. First report of drug concentrations of the synthetic cannabinoid 5F-PB-22 found on post-mortem testing. Clin Toxicol 2014;52:750.
4. Behonick G, Shanks KG, Firchau DJ, Mathur G, Lynch CF, Nashelsky M, et al. Four postmortem case reports with quantitative detection of the synthetic cannabinoid, 5F-PB-22. J Anal Toxicol 2014;38:559-62.
5. 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;9:278-81.
6. Corkery J, Schifano F, Corazza O. Consideration of the novel psychoactive substances (‘legal highs’). London: Advidory Council on the Misuse of Drugs; 2011.
7. Every-Palmer S. Synthetic cannabinoid JWH-018 and psychosis: An explorative study. Drug Alcohol Depend 2011;117:152-7.
8. Forrester MB, Haywood T. Geographic distribution of synthetic cannabinoid exposures reported to Texas poison centers. Am J Drug Alcohol Abuse 2012;38:603-08.
9. Forrester MB, Kleinschmidt K. Combined synthetic cannabinoid-synthetic cathinone exposures reported to poison centers. Clin Toxicol 2012;50:610.
10. Forrester MB, Leung L, Kleinschmidt K. Comparison of synthetic cathinone and methylenedioxymethamphetamine (MDMA) exposures. Clin Toxicol 2012;50:706.
11. Forrester MB, Kleinschmidt K, Gardner M. A Comparison of synthetic cannabinoid exposures near the Mexican border vs. those distant from the border. Clin Toxicol 2012;50:613.
12. Gunderson EW, Haughey HM, Ait-Daoud N, Joshi AS, Hart CL. “Spice” and “K2” herbal highs: A case series and systematic review of the clinical effects and biopsychosocial implications of synthetic cannabinoid use in humans. Am J Addict 2012;21:320-26.
13. Hermanns-Clausen M, Sauer O, Gerber G, Faerber E, Koch IE, Hentschel H, et al. New "Herbal drugs" of abuse: Spice and smoke. Clin Toxicol 2009;47:452.
14. Hunt N. Reasoning and restricted choices within recreational repertoires. Int J Drug Policy 2001;12:425-28.
15. Iwanicki JL, Cao DJ, Hoppe J, Hoyte CO, Bronstein AC, Lavonas EJ, et al. Novel synthetic cannabinoid outbreak causing severe illness. Clin Toxicol 2014;52:402.
16. Jerry J, Collins G, Streem D. Synthetic legal intoxicating drugs: the emerging 'incense' and 'bath salt' phenomenon. Cleve Clin J Med 2012;79:258-64.
17. Khullar V, Jain A, Sattari M. Emergence of new classes of recreational drugs - Synthetic cannabinoids and cathinones. J Gen Intern Med 2014;29:1200-04.
18. Kithinji J, Auwarter V, Szabo B, Hermanns-Clausen M. Acute intoxications by new psychoactive substances: Patterns of use and circumstances of exposure EU Project SPICE II Plus. Clin Toxicol 2014;52:359.
19. Kleinschmidt K, Forrester MB. A comparison of ingested versus inhaled synthetic cannabinoids. Clin Toxicol 2011;49:530-31.
20. Forrester MB, Kleinschmidt K, Schwarz E, Young A. Synthetic cannabinoid exposures reported to Texas poison centers. J Addict Dis 2011;30:351-58.
21. Lapoint J, Le V, Lackey F, Radominski-Pandya A, Moran CL, James LP, et al. Seizures following ingestion of the synthetic cannabinoid JWH-018. Clin Toxicol 2011;49:199.
22. Lapoint J, James LP, Moran CL, Nelson LS, Hoffman RS, Moran JH. Severe toxicity following synthetic cannabinoid ingestion. Clin Toxicol 2011;49:760-4.
23. Locatelli CA, Lonati D, Buscaglia E, Papa P, Petrolini VM, Vecchio S, et al. Prevalence of analytically confirmed intoxications by new psychotoxic substances in Italy: Data from Pavia Poison Centre and National Early Warning System. Clin Toxicol 2014;52:366.
24. Lonati D, Giampreti A, Petrolini V, Vecchio S, Papa P, Valli A, et al. Clinical identification and analytical confirmation of new synthetic cannabinoids poisonings in Italy: Role of the Pavia Poison Centre in the National Early Warning System for Drugs of Abuse. Clin Toxicol 2011;49:199.

25. Locatelli CA, Lonati D, Giampreti A, Petrolini V, Vecchio S, Rognoni C, et al. New synthetic cannabinoids intoxications in Italy: Clinical identification and analytical confirmation of cases. J Emerg Med 2011;41:220.
26. Lonati D, Buscaglia E, Papa P, Petrolini VM, Vecchio S, Giampreti A, et al. Prevalence of intoxication by new recreational drugs: Preliminary data by the italian network of emergency departments involved in the national early identification system. Clin Toxicol 2012;50:344.
27. Maxwell JC. Psychoactive substances--some new, some old: a scan of the situation in the U.S. Drug Alcohol Depend 2014;134:71-7.
28. McGuinness TM, Newell D. Risky recreation: Synthetic cannabinoids have dangerous effects. J Psychosoc Nurs Ment Health Serv 2012;50:16-18.
29. McKeever RG, Vearrier D, Jacobs D, LaSala G, Okaneku J, Greenberg MI. K2-Not the spice of life; synthetic cannabinoids and ST elevation myocardial infarction: A case report. J Med Toxicol 2014;52:362-3.
30. McKeever RG, Vearrier D, Greenberg MI. K2-not the spice of life: Synthetic cannabinoids and ST elevation myocardial infarction: A case report. Clin Toxicol 2014;52:362-63.
31. Murphy TD, Weidenbach KN, Van Houten C, Gerona RR, Moran JH, Kirschner RI, et al. Acute kidney injury associated with synthetic cannabinoid use - Multiple States, 2012. Morb Mortal Wkly Rep 2013;62:93-98.
32. Centers for Disease Control. Acute kidney injury associated with synthetic cannabinoid use--multiple states, 2012. Morb Mortal Wkly Rep 2013;62:93-8.
33. Musshoff F, Madea B, Kernbach-Wighton G, Bicker W, Kneisel S, Hutter M, et al. Driving under the influence of synthetic cannabinoids ("Spice"): A case series. Int J Legal Med 2103;128:59-64.
34. Pierre JM. Cannabis, synthetic cannabinoids, and psychosis risk: What the evidence says. Curr Psychiatry 2011;10:49-57.
35. Plumb J, Caravati EM, Anderson KT, McDonnell WM. Spicing things up: Pediatric exposures to synthetic cannabinoids. Acad Emerg Med 2011;1:S74.
36. Plumb J, McDonnell W, M., Anderson KT, Crouch BJ, Caravati EM. Adverse effects from pediatric exposures to spice (cannabinoid agonists). Clin Toxicol 2012;50:708.
37. 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.
38. Tuv SS, Strand MC, Karinen R, Oiestad EL, Christophersen AS, Vindenes V. [Effect and occurrence of synthetic cannabinoids]. Tidsskr Nor Laegeforen 2012;132:2285-8.
39. Yeakel JK, Logan BK. Blood synthetic cannabinoid concentrations in cases of suspected impaired driving. J Anal Toxicol 2013;37:547-51.
40. Bulbena-Cabre A, Dunn NR, Swift RG. Synthetic cannabis "K2" intoxication and psychiatric manifestations. CNS Spectrums 2013;18 (6):344-45.
41. Cookman L, Skinner CG, Von Derau K, Miller M. A retrospective review of poison center calls with patients exposed to ‘spice’ products. Clin Toxicol 2011;49:531.
42. Fernandez M, Roth B, Villarreal C. Fake marijuana causing real problems in Texas. Clin Toxicol 2011;49:212-13.
43. Hermanns-Clausen M, Kneisel S, Auwärter V. New drugs of abuse: Acute intoxication by smoking herbal products containing synthetic cannabinoids. Clin Toxicol 2011;49:199.
44. Hermanns-Clausen M, Kneisel S, Auwarter V. Acute intoxications by herbal blends containing synthetic cannabinoids. Clin Toxicol 2012;50:340.
45. Hermanns-Clausen M, Kneisel S, Szabo B, Auwarter V. Intoxications by synthetic cannabinoids - Current trends. Clin Toxicol 2013;51:340.
46. Hill SL, Cooper GA, Jackson G, Lupton DJ, Bradberry S, Thomas SHL. What’s on the ‘Spice’ rack? Synthetic cannabinoid receptor agonist toxicity reported to the UK National Poisons Information Service. Clin Toxicol 2013;51:345.
47. Ide A, Ide T, Kamijo Y, Nishikawa T, Yoshimura K, Mekari M, et al. A case series of acute intoxication with new psychoactive drugs in Japan: A vicious spiral of "Law" and "Market". Clin Toxicol 2013;51:345.
48. Lonati D, Buscaglia E, Vecchio S, Giampreti A, Petrolini VM, Mazzoleni M, et al. Cannabinoidi e catinoni sintetici: aspetti clinici. 16th Congresso Società Italiana Tossicologia; 2012; Messina, Itally. 2012.

49. Obafemi AI, Goto C, Drew F, Kleinschmidt K. Synthetic cannabinoid laced brownies. Clin Toxicol 2012;5:638.
50. Rosenbaum CD, Scalzo AJ, Long C, Weber JA, Jenkins A, Lopez GP, et al. K2 & spice abusers: A case series of clinical and laboratory findings. Clin Toxicol 2011;49:528.
51. Westerbergh J, Hulten P. Novel synthetic cannabinoids, CRA13, JWH-015, JWH-081 and JWH-210 - Detected in a case series. Clin Toxicol 2011;49:222.
52. Banerji S, Deutsch C, Bronstein A. Spice ain't so nice. Clin Toxicol 2010;48:632.
53. Besli GE, Ozumut S, Yildirim S. Acute intoxication due to synthetic cannabinoids in adolescents: A case series. Pediatr Crit Care Med 2014;1:134.
54. Brickmann C, Leonhardt A, Auwarter V, Sassen MC. Respiratory insufficiency due to synthetic cannabinoid consumption. [German] Respiratorische insuffizienz durch konsum synthetischer cannabinoide. Padiatrische Praxis 2013;81:267-75.
55. Butler K, Hayes BD, Howell F. Status epilepticus following use of synthetic marijuana. Clin Toxicol 2012;50:708.
56. Canning J, Ruha A-M, Pierce R, Torrey M, Reinhart S. Severe GI distress after smoking JWH-018. Clin Toxicol 2010;48:618.
57. Gerona RRL, Birsdall E, Wu AH. Non-targeted analysis of synthetic cannabinoids in two intoxication cases involving herbal incense products. Am J Clin Pathol 2011;136 (3):474-75.
58. Grossenbacher F, Souille J, Djerrada Z, Passouant O, Gibaja V. Exposure to 5f-P22, 5 IAI and diclazepam: A case report. Clin Toxicol 2014;52:365.
59. Gunja N, Kuligowski K, Paul PG, Collins M, Anderson R, Kwan J. Acute agitation and chest pain from 5-fluoro-AKB48: A novel synthetic cannabinoid. Clin Toxicol 2014;52:364.
60. Korya D, Kapoor A, Labiner D. Ischemic stroke in a 28-year-old woman after smoking synthetic THC Neurology 2013;80:P06.250.
61. Locatelli CA, Lonati D, Buscaglia E, Vecchio S, Giampreti A, Petrolini VM, et al. "Synthe-tic co-caine" as legal cocaine hides synthetic cannabinoids. Clin Toxicol 2013;51:346-47.
62. Loschner A, Cihla A, Jalali F, Ghamande S. Diffuse alveolar hemorrhage: Add "greenhouse effect" to the growing list. Chest 2011;140:149A-49A.
63. McCain KR, Moran JH, James LP, Foster HR. Adverse effects and confirmatory testing of JWH-018 and JWH-073 following synthetic cannabinoid use. Clin Toxicol 2011;49:519.
64. Morris SR, Sattari R, Dorian R. Terror in the PACU. J Pain 2012;1:S47.
65. Moti D, Ahmed M. First use of K2, first seizure. J Investig Med 2014;62 (2):538.
66. Remane D, Auwarter V, Werner R, Schermer J, Drobnik S, Mall G, et al. Fatal poisoning involving the synthetic cannabinoids JWH-122 and JWH-210. Rechtsmedizin 2012;22 (4):286.
67. Rosenbaum C, Ward J, Boudreaux E, Burstein S, Boyer E. JWH-018, JWH-073, and Spice. Clin Toxicol 2010;48:307.
68. Seifert SA, Eugenia M, Brazwell EM, Smeltzer C, Gibb J, Logan BK. Seizure and acute kidney injury associated with synthetic cannabinoid use. Clin Toxicol 2013;51:667.
69. Smith SK, Christian MR, Aks SE. Prolonged, severe agitation and rhabdomyolysis after intravenous injection of a synthetic cannabinoid. Clin Toxicol 2012;50:707.
70. Streich HT, Rushton WF, Charlton NP. Death by spice: A case report of mortality following synthetic cannabinoid use. Clin Toxicol 2014;52:365.
71. Werner RB, Chowdhury N, Smalligan RD. When adding spice can threaten life. J Gen Intern Med 2013;28:S422.
72. Yen M, Berger RE, Roberts J, Ganetsky M. Middle cerebral artery stroke associated with use of synthetic cannabinoid K2. Clin Toxicol 2012;50:673-4.