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Synthetic cannabinoids: characteristics, use and clinical implications

Emilio Sánchez Hervás

Summary

Synthetic cannabinoids are chemicals that bind to cannabinoid receptors and produce effects similar to those of tetrahydrocannabinol. Although initially designed as possible pharmacological tools, they are currently among the most important of the so-called new drugs. Some of these cannabinoids are extremely potent and have serious effects on the health of users, who are primarily young people. Their use can affect behavior unpredictably (many users do not really know what they are consuming), and produce more adverse consequences than marijuana. This article reviews the most important characteristics of these substances, the consequences of their consumption and the clinical implications that derive from it.

drug abuse / marijuana / cannabis / synthetic cannabinoids

INTRODUCTION

Marijuana is the most commonly used illegal drug in the world. The plant contains a mind-altering chemical called delta-9-tetrahydrocannabinol (THC). Besides THC, more than 100 cannabinoids are found in the marijuana plant. Some of them (THC and cannabidiol (CBD)) have led to the creation of drugs that may treat various symptoms and diseases, and are even considered in the treatment of addictions [1–3]. Other types of cannabinoids, called endocannaninoids, are produced by animal and human bodies. In addition, scientists as well as manufacturers of illegal drugs have produced several lab-derived cannabinoids (synthetic cannabinoids). Some of these cannabinoids are extremely potent and have caused serious health consequences for people who have abused them [4].

The classification of cannabinoids is based on the chemical structures of the molecules [5–7]. Recently, Shevyrin and colleagues [8] have proposed a classification system divided into the following classes: phytocannabinoids, endocannabinoids and synthetic cannabinoids. Synthetic cannabinoids (SCs) were initially designed as pharmacological tools to study the endogenous cannabinoid system in the search for THC-like compounds that may have therapeutic potential without causing addiction, although they have never passed the clinical trials necessary to prove that they are safe for human consumption.

SCs are included within a group of substances called novel psychoactive substances (NPS), which have appeared in recent years for recreational use. These are hundreds of powerful and harmful psychoactive compounds that are openly sold on the internet or in small shops, taking advantage of a legal vacuum. They are called "new drugs" and they represent an im-

Emilio Sánchez Hervás PhD: Addictive Behaviors Unit of Catarroja, Valencia Regional Health Departament, Av. Rambleta, S/N, 46470 Catarroja, Valencia, Spain.
Correspondence address: esh455k@gmail.com

portant current and potential public health problem [9]. There is some concern about the acute and chronic psychopathological manifestations associated with SCs' ingestion. We searched the most recent literature using the following keywords: drug abuse, marijuana, cannabis, synthetic cannabinoids.

SYNTHETIC CANNABINOIDS

SCs are a group of substances that simulate the effects of THC by binding to the cannabinoid receptors of the organism in the same way THC does. These substances have been used to create a wide variety of products called "legal hallucinogens" which are sold as legal cannabis substitutes. They constitute the largest group of NPS that are subject to surveillance by different international organizations [10].

These compounds are not obtained from the marijuana plant, they are not synthetic marijuana, nor do they contain cannabis, but when they are smoked they cause similar effects. Most SCs used in legal hallucinogenic products are manufactured by chemical companies based in China and are shipped to Europe in bulk powder. Once in Europe they are combined with herbs that are used as a vegetable base for smoking blends – they are mixed or sprayed on the plant material, usually on an industrial scale and using liquid solvents such as acetone or methanol. The resulting mixture is dried and packed. It is then sold on the Internet and in specialist shops [7,10].

In 2008, forensic researchers from Germany and Austria detected for the first time a synthetic cannabinoid known as JWH-018, in a product that was being sold under the brand name of "Spice". Subsequently, several cannabinoids were detected in herbal blends for smoking or in the so-called "environmental incense". These are colorful packages that normally contain between 0.5 and 3 grams of chopped vegetable matter, to which one or more synthetic cannabinoids have been added. Brands like K2, Spice or Smoke are some typical examples. Some of these products share similarities with cannabis in terms of color and texture, and are also used in a similar way, by being mixed with tobacco in a cigarette or smoked in a pipe. In some countries they became very popular thanks to advertising, which described them as "legal and non-dangerous alternatives" to cannabis. Since then, hundreds of new herbal products have been marketed under different trade names [7,11] (Table 1).

Table 1. Cannabinoids: classification, street names and adverse effects of SCs [5–8,10]

Classic classification system	New classification system	Street names of SCs	Adverse effects of SCs
Classical cannabinoids Nonclassical cannabinoids Hybrid cannabinoids Aminoalkylindoles Eicosanoids Others	Phytocannabinoids Endocannabinoids Synthetic cannabinoids	K2, Spice (Gold, Silver, Diamond), Smoke, Black Mamba, Bombay Blue, Fake Weed, Genie, Joker, Kronic, Yucatan Fire, Chill X, Algerian Blend, and others	Tachycardia, agitation, nausea, anxiety, drowsiness, hallucinations, delusions, confusion, psychosis, dizziness, cardiovascular, cerebrovascular, neurological and renal problems

LEGAL STATUS

The number of synthetic cannabinoids, their chemical diversity and the rate at which new ones are produced make their detection and control particularly challenging. When a synthetic cannabinoid is legally controlled, manufacturers have one or more replacement substances prepared for sale. Currently many synthetic cannabinoids have been banned at international level and over the recent years large amounts have been seized. However, producers replace newly criminalized synthetic cannabinoids with new and uncontrolled ones, which allows circumvention of control measures [12]. By 2015, at least 134 synthetic cannabinoid compounds had been discovered throughout Europe [11]. SCs dominate the global NPS market, particularly in the USA where the largest quantities are seized, but Europe also recorded an increase in these substances being seized, in most cases AM-2201 [13]. Con-

sumers of these products generally do not know what chemical components they contain [10].

CHARACTERISTICS OF SCS

SCs are substances whose structural characteristics allow them to be bound to one of the known cannabinoid receptors present in human cells, CB1 or CB2. The CB1 receptor is primarily found in the brain and spinal cord, and is responsible for the psychotropic effects of cannabis, while the CB2 receptor is primarily located in the spleen and in the cells of the immune system.

SCs can comprise a large variety of structurally different compounds [12]. Given their synaptic plasticity, the cannabinoid receptor can recognize multiple classes of these compounds [14]. The potentially more dangerous effects of SCs compared with natural cannabis are probably due to a higher affinity of SCs with the CB1 receptor [15]. SC compounds lack CBD and are similar to high-potency natural cananbis (high THC and low CBD levels). THC is a partial agonist at cannabinoids, while SCs are full agonists with a higher affinity and potency ranging from 40 – to 660-fold higher than cannabis [16]. Since the chemical composition of many SCs is unknown and/or is changing from one batch to another, it is possible that these products contain substances that cause different effects than the consumer expects. Although relatively little is known about the pharmacology and toxicology of various synthetic cannabinoids, several of these substances may have an addictive potential, higher than that of cannabis, could present a greater acute and long-term toxicity [13] and lead to serious adverse effects [12]. The desired and adverse effects are considered to be more intense than those obtained by smoking cannabis, which is explained in part by the full agonist activity of synthetic cannabinoids and a greater affinity with cannabinoid receptors [17].

It is possible that besides being extremely potent, some of these substances also have a long half-life, which could lead to a prolonged psychoactive effect. It appears that at least some of them affect other physiological functions of the body, in addition to their effects on cannabinoid receptors [10].

USE AND EFFECTS OF SCS

Since the mid-2000s (from 2005 in Europe and from 2009 in the United States), "legal hallucinogenic" products containing SCs have been sold in the form of herbal smoking blends. So far, more than 300 SC compounds have been synthesized, and as new compounds appear rapidly it is difficult to study their effects on physical and mental health [18], as well as long-term consequences [19].

There may be considerable variability within the same batch of products and between different batches, both in terms of quantity and the substances they contain. Synthetic additives can vary considerably in quantity and also the types of SCs used. Some of these substances are of high purity, while others are contaminated with synthetic by-products [13]. The risks may be even greater. Due to the manufacturing process, there may be an unequal distribution of the substances within the herbal blend. As a consequence, some products may contain parts in which cannabinoids are highly concentrated [10], which means that in many cases the effects may be unpredictable [20].

There are notable differences in the prevalence of SCs' use between the European and US drug markets. The most recent prevalence data in the European Union indicate a decline in use over the past couple of years among 17 – and 18-year-olds (e.g. in England from 5.8% in 2014 to 0.1% in 2016) [10]. Unfortunately, it is difficult to provide an accurate estimate of the incidence owing to a lack of rapid laboratory confirmation and the variety of SC compouds [19].

RECREATIONAL EFFECTS

SCs produce effects similar to natural cannabis: relaxation, euphoria, disinhibition, disorientation and altered perception. The effects emerge about 5 minutes after inhalation and usually disappear after 2–6 hours [20]. SCs require a shorter time to reach their peak effect and have a shorter duration of action [21,22]. Users are looking for a stronger and/or different effect than that produced by natural cannabis. SCs are not consumed in isolation, but are often combined with other substances, usually alcohol, cannabis and

tobacco [23]. On the other hand, due to rapid development of the effects, users may have difficulties interpreting or integrating their experiences [20].

ADVERSE EFFECTS

Toxic effects depend on the type, mixture and amount of product used [24]. Since SCs' producers often change formulas to avoid detection, users' experience may vary over time [25]. The most common adverse effects include: tachycardia, agitation, nausea, anxiety, irritability, drowsiness, hallucinations, delusions, hypertension, confusion, dizziness, vertigo and chest pain, besides cardiovascular, cerebrovascular, neurological and renal problems [24], some of which may have a lethal outcome [26,27]. Acute SC poisoning can lead to hospitalization. Recent studies have shown a decline in the executive function in SCs' users compared with recreational users of cannabis and non-users [28]; they also present more symptoms of confusion, disorientation and incoherent speech than consumers of natural cannabis [29].

PSYCHOSIS

The relationship between cannabis use and psychosis is well known, with double the occurrence rates of the non-using population [30]. THC is believed to be the active component responsible for this association, while other components of the plant, such as cannabidiol, exhibit anxiolytic and antipsychotic properties. The higher affinity and potency of SCs compared with cannabis suggest that SCs may have a greater association with psychosis and other psychiatric complications [31–33].

SCs' users are more frequently diagnosed with psychotic disorder and require longer hospitalizations than other types of patients, given that the symptoms of psychosis, agitation and irritability persist for many days [18,24]. The use of SCs is associated with psychopathology and with onset or exacerbation of disorders, particularly psychosis [17]. Several studies have shown that the risk of psychosis is greater with SCs than with natural cannabis [16,33]. While the possible long-term consequences are not known, mood and anxiety disorders, as well as exacerbation of pre-existing psychotic symptoms, have been reported in patients with psychiatric disorders [34].

ADDICTIVE POTENTIAL

Tolerance to SCs has been described in the literature; some users feel unable to reduce or stop their intake, and they use the substances for longer periods than originally planned [35,36]. According to clinical case reports, withdrawal symptoms are similar to those seen in users of natural cannabis, but more serious. Some chronic users experience withdrawal symptoms when they reducing doses [37], and report anxiety, headache, limb cramps, chills, anorexia and intense drug cravings [38,39]. In some countries they currently represent an important group of patients who demand hospitalization for detoxification [40]. The data on presentations to emergency treatment services indicate that SCs are significantly more hazardous and pose a greater risk to health than natural cannabis [22].

TREATMENT

Since SCs are rarely identified and physical symptoms of use may be non-specific, standards of care and treatment for patients who have consumed SCs have not yet been established by health agencies [15]. There is no specific antidote for SCs and pharmacological actions on intoxicated patients are not well described, although the use of benzodiazepines and antipsychotics has been reported in a detoxification service [40]. In addition, SCs are often taken along with other recreational drugs or alcohol, which makes it difficult to atribute the observed effects to a specific product. The approach usually consists of symptom management, including patient monitoring, hydration with fluids and observation until clinical improvement occurs. Counseling for participation in social or supportive therapies is advisable. The management of these patients is based on the extrapolation of experience with cannabis [1].

Since the pharmacology of these substances is complex or unknown, benzodiazepines may

possibly be a choice, although they may require frequent dosage adjustment and high doses to achieve a proper sedative effect, and this can be a problem when people have also ingested alcohol; when patients cannot be controlled with only benzodiazepines, antipsychotics may be considered [9,40,41]. Hospital admission to intensive care units will sometimes be necessary [40–42].

CLINICAL IMPLICATIONS

In general, most users prefer natural marijuana over SCs since it tends to be associated with fewer adverse effects [15,22,37], so the majority of SC use is experimental [43].

SCs users report very different reasons for their use than marijuana users. The most common reason for marijuana use is self-medication for a wide variety of health issues such as pain or irritable bowel syndrome, and various psychiatric conditions (depression, anxiety and insomnia) [44]. The reasons for SCs' use are normally their better availability, avoiding positive screening on a drug test and their lower cost [20,45]. However, the frequency of marijuana use appears to increase the likelihood of SCs' use [43].

Epidemiological data suggest that most users are young adults who perceive SCs to be safer than non-cannabinoid illicit drugs, to be easily accessible and an alternative to cannabis as they avoid detection by conventional drug tests [37]. Most SCs' users are young men, many with a history of polysubstance use [24], housing problems or a history of arrests [46]. Recent studies indicate that students using SCs tend to engage in more risky behaviors than students who use marijuana alone [47].

In addition, it has been pointed out that SCs' consumption among homeless and mentally ill people is a growing public health problem, particularly in urban and ethnic minority communities [48]. In a recent study conducted in a psychiatric emergency department of a large urban public hospital in the USA, it was noted that the use of SCs affects individuals with socio-demographic disadvantages and mental illnesses, and might exacerbate already existing psychiatric problems [49].

DISCUSSION

It is possible that easy availability and the false belief that SCs are natural and harmless substances have contributed to their growing popularity among young people in recent years. However, SCs can affect behavior in unpredictable ways (many users do not really know what they are consuming) and produce more adverse consequences than cannabis. In general, there is little information about the consumption of SCs in the population, the data on their effects are limited and much is still unknown about their effects and associated risks. SCs pose a risk to the conventional treatment of other drugs because they are not easily detected by common urinalysis techniques. They are not routinely detected because current drug tests are specific to THC, which is not an active chemical compound in SCs [50,51], so patients may be consuming SCs without clinicians' knowledge.

Some authors have pointed out that given the growing public acceptance of recreational and medical marijuana, along with negative perceptions and increasing regulation of SCs, botanical marijuana is likely to remain the more popular drug [52]. However, the probability of abuse and addiction posed by SCs is a great concern for the scientific community [51].

Since there are currently no effective behavioral or pharmacological therapies for the treatment of addiction to these products [53], the approach mainly involves symptom management and support [24]. Risk reduction has also been proposed for those users who do not quit [20]. Previous studies indicate that SCs' users do not differ from non-users in treatment outcomes [17], so one option would be to use the most effective treatments for cannabis dependence: motivational therapy combined with cognitive–behavioral therapy plus incentives [54].

The most frequent symptoms of SCs are tachycardia, agitation and nausea. Severe adverse events (stroke, seizure, myocardial infarction, rhabdomyolysis, psychosis and hyperemesis) and associated deaths occur less frequently. Precise estimates of their incidence are difficult to calculate due to the lack of rapid laboratory confirmation, the variety of compounds involved and the unknown number of exposed individuals [19].

Given the evidence of the damage caused by SCs and the risk of adverse complications, more epidemiological and clinical studies are needed to investigate the risk factors associated with the abuse of these substances in order to integrate such information into the prevention and treatment programs. In addition, clinicians should be aware of the effects of the use of these substances and their possible complications in order to offer a more appropriate approach to treatment.

REFERENCES

1. Prud'homme M, Cata R, Jutras-Aswad D. Cannabidiol as an intervention for addictive behaviors: a systematic review of the evidence. Substance Abuse Res Treat. 2014; 9: 33–38.
2. Fischer B, Kuganesan S, Gallassi A, Malcher-Lopes R, Van den Brink W, Wood E. Addressing the stimulant treatment gap: a call to investigate the therapeutic benefits potential of cannabinoids for crack-cocaine use. Int J Drug Policy. 2015; 26: 1177–1182.
3. Trigo JM, Lagzdins D, Rehm J, Selby P, Gamaleddin I, Fischer B, et al. Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings. Drug Alcohol Depend. 2016; 161, 298–306.
4. National Institute on Drug Abuse. Marijuana. Available at https://www.drugabuse.gov/publications/drugfacts/marijuana (accessed 10 February 2017).
5. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev. 2002; 54(2): 161–202.
6. Thakur GA, Nikas SP, Makriyannis A. CB1 cannabinoid receptor ligands. Mini Rev Medicinal Chemistry. 2005; 5(7): 631–640.
7. UNODC. Synthetic Cannabinoids In Herbal Products. New York: United Nations Office on Drugs and Crime; 2011.
8. Shevyrin V, Melkozerov V, Endres GW, Shafra, Y, Morzheri Y. On a new cannabinoid classification system: a sight on the illegal market of novel psychoactive substances. Cannabis Cannabinoid Res. 2016; 1(1): 186–194.
9. Schifano F, Orsolini L, Duccio Papanti G. Novel psychoactive substances of interest for psychiatry. World Psychiatry. 2015; 13: 15–26.
10. EMCDDA. Synthetic Cannabinoids in Europe (Perspectives on Drugs). Lisbon: European Monitoring Center for Drugs and Drug Addiction; 2016.
11. EMCDDA. European Drug Report. Lisbon: European Monitoring Center for Drugs and Drug Addiction; 2016.
12. UNODC. Recommended Methods for the Identification and Analysis of Synthetic Cannabinoid Receptor Agonists in Seized Materials. Manual for Use by National Drug Analysis Laboratories. New York: Laboratory and Scientific Section, United Nations Office on Drugs and Crime. 2013.
13. UNODC. World Drug Report. New York: United Nations Office on Drugs and Crime; 2016.
14. Mackie K. Cannabinoid receptors: where they are and what they do. J Neuroendocrinol. 2008; 20 (Suppl 1): 10–14.
15. Debruyn D, Le Boisselier R. Emerging drugs of abuse: current perspectives on synthetic cannabinoids. Substance Abuse Rehabil. 2015; 6: 113.
16. Van Amsterdam J, Brunt T, van den Brink W. The adverse health effects of synthetic cannabinoids with emphasis on psychosis-like. J Psychopharmacol. 2015; 29(3): 254–263.
17. Blevins C, Banes K, Stephens R. Walker D, Roffman RA. A preliminary evaluation of synthetic cannabinoid use among adolescent cannabis users: characteristics and treatment outcomes. Addictive Behaviors. 2016; (63): 114–119.
18. Nia AB, Medrano B, Perkel C, Galynker I, Hurd YL. Psychiatric comorbidity associated with synthetic cannabinoid use compared to cannabis. J Psychopharmacology. 2016; 30(12): 1321–1330.
19. Tait RJ, Caldicott D, Mountain D, Hill SL, Lenton S. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clin Toxicol. 2016; 54(1): 1–13.
20. Kassai S, Pintér JN, Rácz J, Böröndi B, Tóth-Karikó T, Kerekes K, et al. Assessing the experience of using synthetic cannabinoids by means of interpretative phenomenological analysis. Harm Reduction J. 2017; 14: 9.
21. 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 Spectrometry. 2009; 44(5): 832–837.
22. Winstock A, 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; 29(6): 698–703.
23. 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): 106–111.
24. Mills B, Yepes A, Nugent K. Synthetic cannabinoids. Am J Med Sci. 2015; 350(1): 59–62.
25. Brewer TL, Collins M. A review of clinical manifestations in adolescent and young adults after use of synthetic cannabinoids. J Specialist Pediatr Nurs. 2014; 19(2): 119–126.
26. Labay LM, Caruso JL, Gilson TP, Phipps RJ, Knight LD, Lemos NP, et al. Synthetic cannabinoid drug use as a cause or contributory cause of death. Forens Sci Intern. 2016; 260: 31–39.
27. Ford BM, Tai S, Fantegrossi WE, Prather PL. Synthetic pot: not your grandfather's Marijuana. Trends Pharmacol Sci. 2017; 38(3): 257–276.

28. Cohen K, Kapitány-Fövény M, Mama Y, Arieli M, Rosca P, Demetrovics Z, et al. The effects of synthetic cannabinoids on executive function. Psychopharmacol. 2017: 1–14.
29. Chase PB, Hawkins J, Mosier J, Jimenez E, Boesen K, Logan BK, et al. Differential physiological and behavioral cues observed in individuals smoking botanical marijuana versus synthetic cannabinoid drugs. Clin Toxicol. 2016; 54(1): 14–19.
30. Gage SH, Hickman M, Zammit S. Association between cannabis and psychosis: epidemiologic evidence. Biol Psychiatry. 2016; 79: 549–556.
31. Panlilio VL, Goldberg SR, Justinova Z. Cannabinoid abuse and addiction: clinical and preclinical findings. Clin Pharmacol Ther. 2015; 97: 616–627.
32. Campos AC, Fogac MV, Sonego AB, Guimaraes FS. Cannabidiol neuroprotection and neuropsychiatric disorders. Pharmacol Res. 2016; 112: 119–127.
33. Bassir Nia A, Medrano B, Perkel C, Galynker I, Hurd YL. Psychiatric comorbidity associated with synthetic cannabinoid use compared to cannabis. J Psychopharmacol. 2016; 30(12): 1321–1330.
34. Celofiga A, Koprivsek J, Klavz J. Use of synthetic cannabinoids in patients with psychotic disorders: case series. J Dual Diagnosis. 2014; 10(3): 168–173.
35. Every-Palmer S. Synthetic cannabinoid JWH-018 and psychosis: an explorative study. Drug Alcohol Depend. 2011; 117(2–3): 152–157.
36. Vandrey R, Dunn KE, Fry JA, Girlin ER. A survey study to characterize use of Spice products (synthetic cannabinoids). Drug Alcohol Depend. 2012; 120(1): 238–241.
37. 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.
38. Nacca N, Vatti D, Sullivan R, Sud P, Su M, Marraffa J. The synthetic cannabinoid withdrawal syndrome. J Addiction Med. 2013; 7(4): 296–298.
39. Van Hout MC, Hearne E. User experiences of development of dependence on the synthetic cannabinoids, 5f-AKB48 and 5F-PB-22, and subsequent withdrawal syndromes. Int J Ment Health Addiction, 2016; 1–15.
40. Macfarlane V, Christie G. Synthetic cannabinoid withdrawal: a new demand on detoxification services. Drug Alcohol Rev. 2015; 34(2): 147–153.
41. Monte AA, Calello DP, Gerona RR, Hamad E, Campleman SL, Brent J, et al. Characteristics and treatment of patients with clinical illness due to synthetic cannabinoid inhalation reported by medical toxicologists: a ToxIC database study. J Med Toxicol. 2017: 1–7.
42. Kersten BP, McLaughli ME. Toxicology and management of novel psychoactive drugs. J Pharm Pract. 2015; 28(1): 50–65.
43. Palamar JJ, Acosta P. Synthetic cannabinoid use in a nationally representative sample of US high school seniors. Drug Alcohol Depend. 2015; 149: 194–202.
44. Osborn LA, Lauritsen KJ, Cross N, Davis AK, Rosenberg H, Bonadio F, et al. Self-medication of somatic and psychiatric conditions using botanical marijuana. J Psychoact Drugs. 2015; 47(5): 345–350.
45. Lauritsen KJ, Rosenberg H. Comparison of outcome expectancies for synthetic cannabinoids and botanical marijuana. Am J Drug Alcohol Abuse. 2016; 42: 377–384.
46. Miller BL, Stogner JM, Miller JM, Fernandez MI. The arrest and synthetic novel psychoactive drug relationship: observations from a young adult population. J Drug Issues. 2017; 47(1): 91–103.
47. Clayton HB, Lowry R, Ashley C, Wolkin A, Grant AM. Health risk behaviors with synthetic cannabinoids versus marijuana. Pediatrics. 2017; 139(4): e20162675.
48. Joseph AM, Manseau MW, Lalane M, Rajparia A, Lewis CF. Characteristics associated with synthetic cannabinoid use among patients treated in a public psychiatric emergency setting. Am J Drug Alcohol Abuse. 2017; 43(1): 117–122.
49. Manseau MW, Rajparia A, Joseph A, Azarchi S, Goff D, Satodiya R, et al. Clinical characteristics of synthetic cannabinoid use in a large urban psychiatric emergency setting. Subst Use Misuse. 2017; 3: 1–4.
50. Ninnemann AL, Lechner WV, Borges A, Lejuez CW. Synthetic cannabinoids to avoid urine drug screens: implications for contingency management and other treatments for drug dependence. Addict Behav. 2016; 63: 72–73.
51. Le Boisselier R, Alexandre J, Lelong-Boulouard V, Debruyne D. Focus on cannabinoids and synthetic cannabinoids. Clin Pharmacology Therapeutics. 2016; 101: 220–229.
52. Palamar JJ, Barratt MJ. Synthetic cannabinoids: undesirable alternatives to natural marijuana. Am J Drug Alcohol Abuse. 2016; 42(4): 371–373.
53. NIDA. Synthetic cannabinoids. National Institute on Drug Abuse. Available at https://www.drugabuse.gov/publications/drugfacts/synthetic-cannabinoids (accessed 1 March 2017).
54. Gates PJ, Sabioni P, Copeland J, Le Foll B, Gowing L. Psychosocial interventions for cannabis use disorder. Cochrane Database Syst Rev. 2016; Issue 5. Art. No: CD005336.