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Editorial / Editoryal

Synthetic Cannabinoids: Crisis of The Decade

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INTRODUCTION

The Chinese emperor Shen-Nung was first to mention (2737 BC) the benefits of cannabis, noting its properties against malaria and rheumatism (1). Following the isolation of Δ9-tetrahydrocannabinoid (Δ9-THC) in 1964 (2) and discovery of cannabinoid receptors (CB1 and CB2) in the 1980s (3), a large number of cannabinoid receptor agonists have been synthesized for therapeutic purposes (3) while, on the other hand cannabis has become the most widely produced and consumed illicit substance worldwide (4). For many decades there have been few additions to the spectrum of drugs abused. However, in recent years, there has been a huge upsurge in novel psychoactive substances, also known as "legal highs", "designer drugs", "herbal highs" or "research chemicals". Since 1997 more than 200 new psychoactive substances have been identified (5). In 1990s, Huffman et al. (6) synthesized naphthoylindoles, naphthoylpyrroles and related compounds with cannabinoid receptor agonist activity, which have become known as the "JWH compounds" and have become the major component of novel drugs containing synthetic cannabinoids (SCs) afterwards. Since 2004, SCs have become available on the market and they have become popular with those seeking a "legal high" (7). The SCs reported since 2008, belongs to different chemical groups named as naphthoylindoles, cyclohexylphenols, tricyclic terpenoids, phenylacetylindoles, benzoylindoles, naphthoylpyrroles, naphthoylnaphthalenes, adamantoylindoles, quinones and cyclopropylindoles (8).

Products containing SCs are commonly referred as "Spice" in Europe, "K2" in USA, whereas "Bonzai" or "Jamaika" in Turkey. These are "herbal smoking mixtures", typically containing a number of different SCs that are sprayed onto the herbal constituents, which are then smoked by users, similar to cannabis (9,10). These drugs are widely marketed in Europe, the United States, and Japan, and easily accessible from the internet. "Herbal mixtures" of the "Spice"-type are labelled "not for human consumption" and are advertised e.g. as incense or plant growth regulator. These mixtures are declared to be purely herbal, but exhibit strong cannabimimetic effects after smoking because they have been adulterated with SC receptor agonists (10).

Because of the lack of specific regulations and widespread use of products with unknown composition in terms of components and dosages, the growing consumption of SCs as designer drugs of abuse has become a significant trouble for public health institutions (11).

Epidemiology

As the SCs appeared for sale on the Internet and in head shops and marketed as herbal incense, discussions surrounding the highs that could be experienced through smoking these herbal mixtures became increasingly visible on the internet, particularly on 'drug forums', giving rapid momentum to their popularity (12).

In the beginning, SCs were noticed particularly in

Europe, but now reports of the misuse of these compounds appear around the globe (13,14). In the 2008 report of the European Monitoring Centre for Drugs and Drug Addiction (15), JWH-018 was listed as the first non-classical cannabinoid, defining a new class of psychoactive compounds. Since then, the EMCDDA has identified SCs as class of compounds with high growth rates in terms of newly appearing compounds per year (EMCDDA report 2009: 9 compounds; EMCDDA report 2010: 11 compounds) (16,17). Two thirds of the newly notified substances reported in 2011 were SCs or synthetic cathinones and these two groups also represent two thirds of all new substances reported to the early warning system since 2005 (8). In 2011, the Drug Enforcement Administration scheduled a number of specific chemicals commonly used to make it, but chemical variations continue to appear to stay at least one step ahead of legal restrictions (13,14). Most of these substances were synthesized for pharmaceutical purposes and have been described in the scientific literature before, but others originate from clandestine laboratories (18).

The first report of SC-related toxicity was reported in an individual who seemed to develop a chronic dependency to "Spice" after a period of 8 months of use (19). Today the potential harm of "Spice" constitutes a significant public health concern since exposures and anecdotal reports of human fatalities following SC exposure are increasing (20). The American Association of Poison Control Centre (AAPCC) reported the call volume of "Spice" exposure increased exponentially from 53 calls in 2009 to over 13.000 in 2011 (21).

National samples of 45.000 to 50.000 students in three grades (8^{th}, 10^{th} and 12^{th}) were evaluated in "Monitoring the Future" study which was conducted by the University of Michigan to identify the prevalence of drug abuse among American youth. The annual prevalence of SC use was reported to be 11.3% among 12^{th} graders, 4.4% among 8th graders and 8.8% among 10^{th} graders in 2012 and it was mentioned that the prevalence rate has remained this high despite federal and state efforts to reduce its use. Aside from alcohol and tobacco, SC was the second most widely used drug among 10^{th} and 12^{th} graders after marijuana, and the third most widely used among 8^{th} graders after marijuana and inhalants (22).

Hu et al. (23) reported that 8% of college students surveyed used Spice, where the majority of college users were first or second year male students. In this study, concurrent use with hookah tobacco (88%), marijuana (91%) or cigarettes (77%) was also prevalent among college students (23). Co-abuse of Spice and alcohol was observed in 10 out of 11 adolescents (15–19 years old) evaluated at the South Miami Hospital Addiction Treatment Center in Miami-Dade County, Florida (24).

Pharmacology

Cannabinoid receptors are part of the complex endocannabinoid system and two endogenous cannabinoid receptors, CB1 and CB2, are well characterized up to date. CB1 and CB2 are G protein-coupled receptors (GPCRs) that inhibit adenylyl cyclase activity. Activation of GPCRs results in presynaptic hyperpolarization through changes in calcium influx and potassium efflux, ultimately resulting in neuronal hyperpolarization and a decrease in neurotransmitter release. They also inhibit N- and P/Q-type calcium channels and activate A-type and inwardly rectifying potassium channels and mitogen-activated protein kinase (25,26).

CB1 receptors are among the most abundant GPCRs expressed in the brain and play a significant role in the modulation of GABA and glutamate neurotransmission (27). They are densely concentrated in the cortical and subcortical regions, spinal cord in the dorsal root ganglion, and peripheral nervous system areas affecting pain from peripheral organs and tissues (28). They are responsible for most of the psychoactive components of cannabinoids like mood elevation, anxiety, panic reactions and they also induce analgesia, decrease motor function, impair memory and sense of time, and affect auditory and visual cognition (25,29,30).

CB2 receptors are predominantly expressed on marginal zone of the spleen, tonsils and immune cells, especially on macrophages, B cells, natural killer cells, monocytes, T-lymphocytes, polymorphonuclear

neutrophils and astrocytes (26) and are thought to mediate immunosuppression by inducing apoptosis, inhibition of proliferation, and suppression of cytokine and chemokine production (31). CB2 receptor agonists have been the focus of research due to the possibility that they could decrease inflammation pain without the psychoactive effects that the CB1 receptors elicit. Accordingly, it was suggested that synthetic cannabinoid receptor agonists inhibit tumor growth and metastasis of breast cancer (32) and human tumor prostate PC-3 cell growth (33). CB2 receptors were also reported to exist in the brain stem, cortex, or cerebellum, and might play a role in the control of emesis (34).

Cannabinoid receptors are also commonly complexed as heterodimers with other receptors (35) and the interplay between cannabinoid and opioid receptors is a target of pharmaceutical strategies aimed at new, effective pain control (36).

JWH-018, JWH-073, JWH-398, JWH-250; HU-210; CP-47,497 and its homologues; and oleamide, the SCs that have been reported in "Spice" samples in Europe, are lipid-soluble, non-polar, with typically 20–26 carbon atoms, and they are fairly volatile (9). The affinity of the indoles to cannabinoid receptors was explained by a three-point attachment for each compound with regions of the natural ligand Δ9-THC, the three key regions being the naphthalene ring, the carbonyl group and the N-alkyl substituent of the indole moiety (37). It is also claimed that replacement of the naphthalene by a methyl-, methoxy-, fluoro-, chloro- or bromo-substituted phenylacetyl group resulted in an increased selectivity for the CB1 receptor depending on the nature and location of substituent at the aromatic ring (38). Reports on benzoylindoles, pyrroles and indenes with potential cannabimimetic activity are also available (39). The binding affinity of the SCs to the CB1 receptor can range from being similar to the one of Δ9-THC like JWH-200 (40) to 90 times higher as in case of JWH-210 (39). Higher affinity of SCs to endogenous cannabinoid receptors produce a stronger effect than natural cannabis (41).

Little is known about the detailed pharmacokinetic and pharmacodynamic profiles of most SCs in humans. They are primarily smoked (via pipe, cigarette, blunt, or water pipe/bong), though administration via vaporization, oral ingestion and rectal ingestion were also reported (42). Parenteral route of administration have not been reported yet. Due to the instant absorption via the lungs and redistribution into other the organs like brain in a short time, after smoking, onset of action usually occurs within minutes (43). There is a delay in absorption and onset of action following oral consumption due to food intake, digestion activity and variations in the extent of the first pass effect (43). High volumes of distribution can be expected for these lipophilic compounds and as a result after chronic consumption, accumulation in fat containing compartments of the body is very likely (43).

Case reports indicate oral and inhalational bioavailability, but the degree of bioavailability is not entirely known. Despite specific metabolic pathways leading to detoxification (and/or activation) and excretion of SCs remain to be determined, it is generally thought that hepatic cytochrome P450 oxidation is followed by glucuronic acid conjugation and renal excretion (44). Chimalakonda et al. (45) reported UGT1A1, UGT1A3, UGT1A9, UGT1A10 and UGT2B7 as major UDP-glucuronosyltransferases responsible for conjugation. Although the duration of effects in humans compared to Δ9-THC differs, [shorter for JWH-018 (1–2 h), and longer for CP-47,497 or its C8 homologue (5–6 h)] (46), in general SCs have longer half-lives, leading to prolonged toxicological effects (10,25). Excretions of aminoalkylindoles seem to be via urine in the form of various metabolites and an unknown proportion is expected to be excreted via feces (43). In the case of CP-47,497-C8, urine metabolite concentrations are very low, resulting in difficulty to detect consumption by analyzing urine with standard laboratory equipment (43).

Unlike Δ9-THC metabolites, SC metabolites retain varying amounts of biologic activity and can act as agonists, neutral antagonists, or inverse agonists at CB1 receptors. The glucuronic acid conjugate of an omega-hydroxyl metabolite of JWH-018 retains reasonable affinity for CB1 receptors and can act as a neutral antagonist (47) while mono-hydroxylated derivatives of JWH-073 retain intermediate to high affinity for CB1

receptors, acting as partial agonists or neutral antagonists (48). The finding that multiple candidate metabolites of SCs retain high CB1 receptor affinity and exhibit a range of intrinsic activity suggests that biotransformation of SCs may explain the mixed and relatively severe adverse effects of SCs and highlight potential safety concerns (48,49).

SCs with affinity for the CB2 receptors, like JWH-015 and JWH-133 (39,50), may also affect the immune system by modulating chemotaxis of T lymphocytes (51), or inducing thymic atrophy and apoptosis (52). In addition, the presence of CB2 receptors in neurons and glial cells in the brain (53) suggests that these SCs might also affect basic neural cell processes like cell proliferation and survival (54). The chronic exposure of mice to JWH-015 has been associated with increased vulnerability to drug abuse and depression (55,56), while intra-accumbens administration of JWH-133 has been found to dose-dependently decrease the rewarding and locomotorstimulating effects of cocaine in mice (57).

SCs may also interact with non-cannabinoid receptor targets by directly binding noncannabinoid receptors, such as the vanilloid type 1 receptor (TRPV1) (58), or through the formation of heterodimers between CB1 receptors and D2 dopamine, μ-opioid, or orexin-1 receptors (59,60). Pharmacological implications of non-cannabinoid receptor activation by SCs remain to be determined.

Toxicology

Although SCs are accepted to be more potent than natural cannabinoids, human data concerning the induction and duration of adverse effects remains limited. The lack of available reliable detections assays and the dynamic, unpredictable nature of these substances prevent consistent, quality case reporting of abuse in the literature (49). Chronic use of these drugs lead to addiction syndrome, withdrawal symptoms and psychiatric-based symptoms similar to long-term cannabis abuse (9,61). However, unlike cannabis, there are emerging reports of acute toxicity, which seems to be more similar to the acute toxicity seen with the use of stimulant or sympathomimetic drugs (61). When assessing the toxicity of these "Spice drugs" containing SCs it should be considered that they also include fatty acids and their esters (linoleic acid, palmitic acid), amide fatty acids (oleamide, palmitoylethanolamide), plant-derived substances (eugenol, thymol, and flavors like acetyl vanillin), preservatives (benzyl benzoate), additives (alpha-tocopherol) (14,62) and ß2-adrenergic agonist clenbuterol (63), which may contribute to the sympathomimetic-like effects (tremor, tachycardia, anxiety) (64,65). A previous study detailed the analytical detection of 11 different SCs across 40 batches of 16 different incense products in various combinations and proportions from brand to brand and from batch to batch, even within brands (41). Therefore it can be suggested the clinical effects of drugs containing SCs are quite unpredictable.

The duration of clinical effects is shorter than 8 hours in majority of cases with SC intoxication whereas it lasts longer than 24 hours in some cases (7). Reported psychoactive effects of SCs are ranging from pleasant, desirable euphoria to anxiety, agitation, irritability, psychosis, and alterations in cognitive abilities (9,10,24,66,) and acute physical effects are diaphoresis, nausea, vomiting, appetite changes, hypertension/hypotension, chest pain, tachycardia/bradycardia, respiratory depression, confusion, psychomotor agitation or somnolence and sedation (7,19,24,67,68). After consumption of SCs some users report sedation while others relate agitation, sickness, hot flushes, burning eyes and xerostomia along with mydriasis and tachycardia (10,69). Reason of the variability in clinical presentation is unknown, but some SCs may be more likely to be associated with the development of stimulant-like acute toxicity while others are associated with the development of cannabis-like chronic toxicity (61) or it may be due to the Spice compound used, the individual susceptibility to the drug effects, the dose, or may be multi-factorial (70).

The most common clinical effect reported after SC exposure is tachycardia (7,68). Tachycardia is also a common sign found among patients with marijuana intoxication, but Hoyte et al. (7) reported that patients with marijuana intoxicaiton generally presented with decreased psychomotor activity, sedation, and lethargy,

where as agitation and irritability was the second most common clinical effect in SC intoxication. Tremors and palpitations have also been described after consumption SCs (68).

Although the majority of individuals exposured to SCs have only minimal symptoms, some are presented with life-threatening symptoms like seizures or myocardial infarction (MI). Seizures and status epilepticus have been reported in SC intoxication, despite they are not commonly associated with cannabis intoxication (7,71,72). Interaction of the SCs with CB1 receptor or some other unidentified receptor on the central nervous system (7) and inhibition of γ-aminobutyric acid (GABA) neurotransmission in the brain (70) were suggested to be responsible from the seizures. But an alternative explanation is that, other epileptogenic agents such as O-desmethyltramadol, an active metabolite of the synthetic opioid tramadol; eugenol; caffeine; and nicotine found in the preparations of consumed herbal blends may play a role in this phenomenon (63).

Recently, 3 cases of acute ST-elevation MI were reported in teenage patients who smoked products containing SCs, at a single medical center within a 3-month period (73). But in a large nationwide cohort no MI was described and it was suggested that those cases of MI were isolated (7). Two explanations were made to identify these cases; it might be possible that the particular supply of products containing SCs used by these patients was contaminated with an unidentified substance that caused coronary vasospasm, or the products was containing some SCs not yet identified that caused coronary vasospasm as sole agents (7). There have been 1 reported death supposed to be associated with SC consumption, a 58-year-old man with intentional inhalational abuse who was brought to the emergency department in cardiac arrest, but the clinical effects were coded "unknown if related" to the exposure (7).

SCs are also suggested to be dangerous because they are probably associated with hallucinations and dreams that potentially places the user in a position for harm or even death (70). In addition to dramatic reports of intoxications in the recent past, there are increasing numbers of reports on suicides, which are associated with preceding consumption of SCs (20).

Treatment for symptoms related to SC use is suggested to be supportive; benzodiazepines are recommended for controlling agitation and anxiety (74). Combined use of SCs with other psychoactive products such as alcohol, cannabis, or tobacco was also reported (42), which suggest that the clinicians must be aware about it when dealing with an intoxicated patient. Furthermore, because most of the intoxicated patients have increased activity, they are reported to be at high risk for rhabdomyolysis, elevated creatine kinase, and subsequent renal failure (70).

Information about the chronic use and toxicity of SCs are limited, but speculations can be proposed based on the long-term effects of heavy marijuana use. Prolonged cannabis use has been associated with an increased risk of psychosis (75) in younger and heavy users in an age- and dose-dependent manner (76,77). Similarly long-term SC users often experience psychotic symptoms ranging from auditory and visual hallucinations to paranoid delusions, from thought blocking to disorganized speech, from anxiety and insomnia to stupor and suicidal ideation (24,67,68,78,79). It was hypothesized that long term use of SCs may induce significant alterations in emotional processing and cognitive functioning because cannabinoids modulate prefrontal cortex neural functioning by decreasing the release of GABA and increasing glutamate and dopamine levels and they have important effects on emotional processing, sensory perception, and elaboration of incoming sensory information (49). Consumption of the SCs has been reported to be associated with psychosis relapse (67,78) and new-onset psychosis has been described in ten otherwise healthy men who smoked SC more than once (from 4 times over 3 weeks up to daily use over 1.5 years) (79). Taken all together, it can be suggested that similar to cannabis, the use of SCs in individuals who are susceptible to psychosis may precipitate or worsen underlying psychosis (78). Another possible harm of SCs associated with long-term use was suggested as their carcinogenic potential, especially for their metabolites carrying a naphthyl moiety (80).

Development of tolerance and physical abstinence syndrome has been described after protracted use of SCs. It seems that tolerance may develop fairly fast, and arguably this might be associated with relatively high potential to cause dependence. Withdrawal syndrome was described as internal unrest, profuse sweating, drug craving, tremor, headache, nocturnal nightmares, insomnia, irritability, difficulty in concentrating, nausea and depression (19,42).

Laboratory Testing

SCs cannot be identified quickly, so far as not included in any mass spectrum library and because of the lack of reference standards (81). To overcome legal bans, new analogues of cannabimimetics have been continuously introduced in the market (11). For this reason, forensic laboratories are increasingly involved in the analysis of a great number of samples containing both scheduled and not yet identified SCs. The development of rapid and efficient analytical tools for the identification of these compounds is important to confirm drug exposures and to further pharmacokinetic and pharmacodynamic testing of these compounds (11,49).

Because little is known about the metabolism of SCs, it makes difficult to regulate these popular abusive drugs. Matrices like urine, serum, blood, oral fluid and hair have been used for sampling to confirm drug consumption (82-84). While in oral fluid and hair the parent compounds of SCs are analyzed (83), their metabolites are determined in urine analysis (84). Thus far, analysis of body fluids largely relies on the detection of the parent drug, and once the parent drug is metabolized, the consumption of the drug cannot be proven without data on the metabolites (30). Therefore, for analysis of SCs in urine, the main metabolites of the parent compounds have to be identified prior to developing analytical methods (84).

Liquid chromatography–tandem mass spectrometry (LC–MS/MS) method for the quantitation of urinary metabolites of eight JWH-type SCs has been developed and validated (12) but the fast growing number of new compounds makes it difficult to adapt urine analysis methods. Teske et al. (69) published a method for the detection of JWH-018 in 2010 and Dresen et al. (82) added a method recently covering 10 SCs, e. g. JWH-018, JWH-073, JWH-081, JWH-122 and JWH-250 by LC-MS/MS in serum samples. LC-MS/MS method also proved to be suitable for the detection and quantification of the 22 SCs in human hair samples (85). It was also suggested that gas chromatography–flame ionization detection (GC–FID) method might be preferred for the rapid and simultaneous quantification of several SCs (81). On the other hand oral fluid analysis by incorporation of the solid-phase extraction and LC-MS, is becoming more popular as a method for the detection of drugs both in the workplace and by law enforcement to provide non-invasive information on recent drug consumption (70,83).

Studies that have been done on spice products have shown complex matrices and non-psychoactive materials, such as vitamin E, that mask the active components (86), which is an additional trouble for the identification of SCs. Although the identification of some of the SCs has been reported, the detection of a whole range of all related chemicals remains elusive (70) and in order to prove the consumption of SCs, the range of analytes covered by these methods had to be expanded (70,85).

Legal Issues

Herbal blends whose labels do not mention the added SCs, are often legally sold in head shops and smart shops, because of their natural material content. However, their popularity has spread via Internet, allowing for the distribution of these products on the international market, despite, in most instances, differing legislation between the countries of the source company and distribution point (81).

Neither the purported herbal ingredients of 'Spice' and 'Spice'-like products, nor any of the SCs found in them are internationally controlled under the 1961 or 1971 UN drug control conventions (Single Convention on Narcotic Drugs, 1961; Convention on Psychotropic Substances, 1971). Responding to potential health concerns, Austria, Germany, France, Luxembourg, Poland, Lithuania, Sweden and Estonia have recently

taken legal actions to ban or otherwise control 'Spice' products and related compounds (46). The United States Drug Enforcement Administration (DEA) announced the emergency scheduling of some SCs as 'Schedule I' substances in 2010, but only some States have put cannabimimetics under control so far and hence, not so many changes in product composition were seen here (43). In Turkey, the substances that are followed up by Early Warning System (EWS) National Working Group under coordination of TUBIM reported some of the SCs and they are subject to the Law on Supervision of Narcotic Drugs since 2011 (87).

The control status of these compounds differs significantly from country to country, but in the course of time, many countries have banned JWH-018, CP-47,497-C8 and some closely related compounds (43,46). Although the legal regulations usually restrict manufacturing, trading and possession of these compounds, to overcome this ban, new analogues of SCs have been continuously introduced in the market (11,43,46).

An Internet based study have revealed that most of the users were obtaining the drug from retail vendors (e.g. head shops, gas stations/convenience stores), Internet or friends, where as interestingly, only a few of them (2%) were obtaining the drug from an illicit drug dealer (42). Half of the respondents (49%) also reported that these products were not banned by the legal authorities in their living area (42). Although being not illegal is an advantage for drug seekers, Vandrey et al. (42) reported that 1 of every 5 SCs users continued to consume SCs following local legislation banning these products or their constituents.

Despite legislative efforts, legal confusion remains as new SCs emerge within products and Spice drugs are still readily available on the Internet with manufacturers continually making slight structural modifications to continue circumventing legal actions. Broad legislation may seem like a feasible solution but care must be taken since cannabinoids are promising novel therapeutic agents, overregulation could be particularly troublesome for this class of compounds (49).

Conclusions and Future Perspectives

As outlined by Griffiths et al. (88), 'Spice' may be a transient product, but it provides an excellent case study of how globally connected the world in which we now live in is challenging existing models of drug control. The studies showed that the underground synthesis laboratories continue to synthesize new compounds, which involve an even greater risk of intoxication since their potency is most likely much higher than that of other SCs recently identified (18). Moreover, although most of the users recognized that use of SCs carried a risk, most believed the likelihood/severity of potential harm to be low (42).

The wide abuse of SCs highlights the urgent need for further evaluation of SCs to characterize their pharmacology and toxicology better and to delineate drug scheduling and legislation properly (49). Developing treatments for intoxication, and implementing effective deterrents like workplace and athletic monitoring programs are also needed (49). Moreover as there is currently insufficient information on the prevalence of 'Spice' use, further epidemiological research combined with forensic-toxicological investigations would be very helpful to assess the dimension of the problem (43). We need greater funding in this area and better cooperation between the analytical chemists who discover these drugs, the scientists who research them and the clinicians who treat the abusers (5). Appropriate legislation is also necessary to assist in limiting availability as well as efforts to educate local communities, physicians, and those working within the judicial system (49).

DISCUSSION

Although both Δ9-THC and SCs act mainly on CB1 and CB2 receptors they are chemically and pharmacologically different. Δ9-THC is a partial agonist that exhibits a plateau effect, beyond which no additional amount of drug increases the effect. On the other hand SCs are full agonists, so a greater dose leads to a greater effect without any plateau. The duration of

action of the SCs may be longer than for Δ9-THC or shorter, but the effect is more intense (72). SCs exhibit higher potency and affinity for cannabinoid receptors (39) and some have longer half-lives and/or result in the production of active metabolites (48,89). Moreover, compared to Δ9-THC, SCs are associated with an apparently higher prevalence of severe adverse effects, such as hypertension, tachycardia, hallucinations, agitation, seizures and panic attacks that often require immediate medical care (48).

Herbal blends containing SCs are often legally sold in head shops and smart shops, and easily accessible via Internet, offering an attractive feature for the users (81). The promise of a more intense high than cannabis, affordability, easy access, and avoidance of detection in standardized drug tests likely contributes to the growing use of SCs (20).

Because the SCs are chemically distinct from Δ9-THC, they escape detection on drug screens, so that the consumption of SCs seems to be particularly attractive in conditions involving regular urine drug screening, for instance in driver's license recovery or in forensic psychiatry settings (23,85). Thus, SCs seems to be potential crisis of the decade in addiction treatment and forensic psychiatry settings, such as probation, in Turkey as in other countries.

REFERENCES

1. Drummer O, Odell M. The Forensic Pharmacology Of Drugs Of Abuse. London: Arnold, 2001.
2. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc 1964; 86:1646-1647.
3. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie K, Martin BR, Mechoulam R, Pertwee RG. International union of pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 2002; 54: 161-202.
4. UNODC, World Drug Report 2011. United Nation Office on drugs and crime. United Nation Publications, 2011, 175-193.
5. Davidson C. New psychoactive substances. Prog neuropsychopharmacol biol psychiatry 2012; 39:219-220.
6. Huffman JW, Dai D, Martin BR, Compton DR. Design, synthesis and pharmacology of cannabimimetic indoles. Bioorg Med Chem Lett 1994; 4:563-566.
7. 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; 60:435-438.
8. EMCDDA–Europol 2011 Annual Report on the implementation of Council Decision 2005/387/JHA.http://www.emcdda.europa.eu/attachements.cfm/att_155113_EN_EMCDDA-Europol%20Annual%20Report%202011_2012_final.pdf. Accessed Feburary 21, 2013.
9. Vardakou I, Pistos C, Spiliopoulou Ch. Spice drugs as a new trend: Mode of action, identification and legislation. Toxicol Lett 2010; 197:157-162.
10. Auwärter V, Dresen S, Weinmann W, Mueller M, Puetz M, Ferreiros N. 'Spice' and other herbal blends: Harmless incense or cannabinoid designer drugs? J Mass Spectrom 2009; 44:832-837.
11. Merola G, Aturkib Z, D'Oraziob G, Gottardoc R, Macchiaa T, Tagliaroc F, Fanalib S. Analysis of synthetic cannabinoids in herbal blends by means of nano-liquid hromatography. J Pharm Biomed Anal 2012; 71:45-53.
12. de Jager AD, Warner JV, Henman M, Ferguson W, Hall. LC-MS/MS method for the quantitation of metabolites of eight commonly-used synthetic cannabinoids in human urine--an Australian perspective. J Chromatogr B Analyt Technol Biomed Life Sci 2012; 897:22-31.
13. Grigoryev A, Savchuk S, Melnik A, Moskaleva N, Dzhurko J, Ershov M, Nosyrev A, Vedenin A, Izotov B, Zabirova I, Rozhanets V. Chromatography–mass spectrometry studies on the metabolism of synthetic cannabinoids JWH-018 and JWH-073, psychoactive components of smoking mixtures. J Chromatogr B Analyt Technol Biomed Life Sci 2011; 879:1126-1136.
14. Uchiyama N, Kikura-Hanajiri R, Ogata J, Goda Y. Chemical analysis of synthetic cannabinoids as designer drugs in herbal products. Forensic Sci Int 2010; 198:31-38.
15. EMCDDA-Europol 2008 Annual Report on the Implementation of Council Decision 2005/387/JHA. Annex 2: New psychoactive substances reported to the EMCDDA and Europol for the first time in 2008 under the terms of Council Decision, 005/387/JHA. http://www.emcdda.europa.eu/attachements.cfm/att_77263_EN_EMCDDA-Europol_Annual_Report_Art10_2008.pdf. Accessed Feburary 21, 2013.

16. EMCDDA, 2009 Annual report on the state of the drugs problem in Europe. European Monitoring Centre for Drugs and Drug Addiction, Lisbon, 2009. http://www.emcdda.europa.eu/attachements.cfm/att_93236_EN_EMCDDA_AR2009_EN.pdf. Accessed February 19, 2013.

17. EMCDDA, 2010 Annual report on the state of the drugs problem in Europe. European Monitoring Centre for Drugs and Drug Addiction, Lisbon, 2010. http://www.emcdda.europa.eu/attachements.cfm/att_120104_EN_EMCDDA_AR2010_EN.pdf. Accessed February 19, 2013.

18. Moosmann B, Kneisel S, Girreser U, Brecht V, Westphal F, Auwärter V. Separation and structural characterization of the synthetic cannabinoids JWH-412 and 1-[(5-fluoropentyl)-1H-indol-3yl]-(4-methylnaphthalen-1-yl)methanone using GC-MS, NMR analysis and a flash chromatography system. Forensic Sci Int 2012; 220:17-22.

19. Moosmann B, Kneisel S, Girreser U, Brecht V, Westphal F, Auwärter V. Withdrawal phenomena and dependence syndrome after the consumption of "spice gold". Dtsch Arztebl Int 2009; 106:464-467.

20. Fattore L, Fratta W. Beyond THC: The new generation of cannabinoid designer drugs. Front Behav Neurosci 2011; 5:60-66.

21. AAPCC Issues Statement on the Synthetic Drug Abuse Prevention Act. American Association of Poison Control Centre, 2012. http://www.aapcc.org/press/2/. Accessed February 21, 2013.

22. Johnston, LD, O'Malley PM, Bachman JG, Schulenberg JE. The rise in teen marijuana use stalls, synthetic marijuana use levels, and use of 'bath salts' is very low. University of Michigan News Service: Ann Arbor, MI, 2012. htttp://www.monitoringthefuture.org/pressreleases/12drugpr.pdf. Accessed Feburary 21, 2013.

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

24. Castellanos D, Singh S, Thornton G, Avila M, Moreno A. Synthetic cannabinoid use: A case series of adolescents. J Adolesc Health 2011; 49:347-349.

25. Pertwee RG. Pharmacology of cannabinoid receptor ligands. Curr Med Chem 1999; 6:635-664.

26. Ameri A. The effects of cannabinoids on the brain. Prog Neurobiol 1999; 58:315-348.

27. Hájos N, Freund TF. Distinct cannabinoid sensitive receptors regulate hippocampal excitation and inhibition. Chem Phys Lipids 2002; 121:73-82.

28. McCarberg BH, Barkin RL. The future of cannabinoids as analgesic agents: A pharmacologic, pharmacokinetic, and pharmacodynamic overview. Am J Ther 2007; 14:475-483.

29. Ashton JC, Wright JL, McPartland JM, Tyndall JDA. Cannabinoid CB1 and CB2 receptor ligand specificity and the development of CB2-selective agonists. Curr Med Chem 2008; 15:1428-1443.

30. Wintermeyer A, Möller I, Thevis M, et al. In vitro phase I metabolism of the synthetic cannabimimetic JWH-018. Anal Bioanal Chem 2010; 398:2141-2153.

31. Rieder SA, Chauhan A, Singh U, Nagarkatti M, Nagarkatti P. Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. Immunobiology 2010; 215:598-605.

32. Qamri Z, Preet A, Nasser MW, Bass CE, Leone G, Barsky SH, Ganju RK. Synthetic cannabinoid receptor agonists inhibit tumor growth and metastasis of breast cancer. Mol Cancer Ther 2009; 8:3117-3129.

33. Olea-Herrero N, Vara D, Malagarie-Cazenave S, Díaz-Laviada I. Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R(+)-methanandamide and JWH-015: Involvement of CB2. Br J Cancer 2009; 101:940-950.

34. Van Sickle MD, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 2005; 310:329-332.

35. Hojo M, Sudo Y, Ando Y, Minami K, Takada M, Matsubara T, Kanaide M, Taniyama K, Sumikawa K, Uezono Y. mu-Opioid receptor forms a functional heterodimer with cannabinoid CB1 receptor: Electrophysiological and FRET assay analysis. J Pharmacol Sci 2008; 108:308-319.

36. Desroches J, Beaulieu P. Opioids and cannabinoids interactions: Involvement in pain management. Curr Drug Targets 2010; 11:462-473.

37. Aung MM, Griffin G, Huffman JW, Wu M-J, Keel C, Yang B, Showalter VM, Abood ME, Martin BR. Influence of the N-1 alkyl chain length of cannabimimetic indoles upon CB1 and CB2 receptor binding. Drug Alcohol Depend 2000; 60:133-140.

38. Huffman JW, Szklennik PV, Almond A, Bushell K, Selley DE, He H, Cassidy MP, Wiley JL, Martin BR. 1-Pentyl-3-phenylacetylindoles, a new class of cannabimimetic indoles. Bioorg Med Chem Lett 2005; 15:4110-4113.

39. Huffman JW, Padgett LW. Recent developments in the medicinal chemistry of cannabinomimetic indoles, pyrroles and indenes. Curr Med Chem 2005; 12:1395-1411.

40. Huffman JW, Mabon R, Wu MJ, Lu J, Hart R, Hurst DP, Reggio PH, Wiley JL, Martin BR. 3-Indolyl-1-naphthylmethanes: New cannabimimetic indoles provide evidence for aromatic stacking interactions with the CB(1) cannabinoid receptor. Bioorg Med Chem 2003; 11:539-549.

41. Hudson S, Ramsey J, King L, Timbers S, Maynard S, Dargan PI, Wood DM. Use of high resolution accurate mass spectrometry to detect reported and previously unreported cannabinomimetics in "herbal high" products. J Anal Toxicol 2010; 34:252-260.

42. Vandrey R, Dunn KE, Fry JA, Girling ER. A survey study to characterize use of Spice products (synthetic cannabinoids). Drug Alcohol Depend 2012; 120:238-241.

43. UNODC, Synthetic cannabinoids in herbal products. United Nations Office on Drugs and Crime, 2011. http://www.unodc.org/documents/scientific/Synthetic_Cannabinoids.pdf. Last accessed February 19, 2013.

44. Gronewold A, Skopp G. A preliminary investigation on the distribution of cannabinoids in man. Forensic Sci Int 2011; 210:7-11.

45. Chimalakonda KC, Bratton SM, Le VH, Yiew KH, Dineva A, Moran CL, James LP, Moran JH, Radominska-Pandya A. Conjugation of synthetic cannabinoids JWH-018 and JWH-073, metabolites by human UDP-glucuronosyltransferases. Drug Metab Dispos 2011; 39:1967-1976.

46. EMCDDA, Understanding the 'Spice' phenomenon. European Monitoring Centre for Drugs and Drug Addiction, Lisbon, 2009. http://www.emcdda.europa.eu/attachements.cfm/att_80086_EN_Spice%20Thematic%20paper%20%E2%80%94%20final%20version.pdf. Last accessed February 19, 2013.

47. Seely KA, Brents LK, Radominska-Pandya A, Endres GW, Keyes GS, Moran JH, Prather PL. A major glucuronidated metabolite of JWH-018 is a neutral antagonist at CB1 receptors. Curr Res Toxicol 2012; 4:825-827.

48. Brents LK, Gallus-Zawada A, Radominska-Pandya A, Vasiljevik T, Prisinzano TE, Fantegrossi WE, Moran JH, Prather PL. Monohydroxylated metabolites of the K2 synthetic cannabinoid JWH-073 retain intermediate to high cannabinoid 1 receptor (CB1R) affinity and exhibit neutral antagonist to partial agonist activity. Biochem Pharmacol 2012; 83:952-961.

49. 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; 39:234-243.

50. Uchiyama N, Kikura-Hanajiri R, Goda Y. Identification of a novel cannabimimetic phenylacetylindole, cannabipiperidiethanone, as a designer drug in a herbal product and its affinity for cannabinoid CB1 and CB2 receptors. Chem Pharm Bull 2011; 59:1203-1205.

51. Ghosh S, Preet A, Groopman JE, Ganju RK. Cannabinoid receptor CB2 modulates the CXCL12/CXCR4-mediated chemotaxis of T lymphocytes. Mol Immunol 2006; 43:2169-2179.

52. Lombard C, Nagarkatti M, Nagarkatti P. CB2 cannabinoid receptor agonist, JWH-015, triggers apoptosis in immune cells: Potential role for CB2-selective ligands as immunosuppressive agents. Clin Immunol 2007; 122:259-270.

53. Onaivi ES, Ishiguro H, Gong JP, Patel S, Perchuk A, Meozzi PA, et al. Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. Ann N Y Acad Sci 2006; 1074:514-536.

54. Fernández-Ruiz J, Romero J, Velasco G, Tolón RM, Ramos JA, Guzmán M. Cannabinoid CB2 receptor: A new target for controlling neural cell survival? Trends Pharmacol Sci 2007; 28:39-45.

55. Onaivi ES, Ishiguro H, Gong JP, Patel S, Meozzi PA, Myers L, Perchuk A, Mora Z, Tagliaferro PA, Gardner E, Brusco A, Akinshola BE, Hope B, Lujilde J, Inada T, Iwasaki S, Macharia D, Teasenfitz L, Arinami T, Uhl GR. Brain neuronal CB2 cannabinoid receptors in drug abuse and depression: From mice to human subjects. PLoS One 2008; 3:1640.

56. Onaivi ES, Ishiguro H, Gong JP, Patel S, Meozzi PA, Myers L, Perchuk A, Mora Z, Tagliaferro PA, Gardner E, Brusco A, Akinshola BE, Liu QR, Chirwa SS, Hope B, Lujilde J, Inada T, Iwasaki S, Macharia D, Teasenfitz L, Arinami T, Uhl GR. Functional expression of brain neuronal CB2 cannabinoid receptors are involved in the effects of drugs of abuse and in depression. Ann N Y Acad Sci 2008; 1139:434-449.

57. Xi ZX, Peng XQ, Li X, Song R, Zhang HY, Liu QR, Yang HJ, Bi GH, Li J, Gardner EL. Brain cannabinoid CB2 receptors modulate cocaine's actions in mice. Nat Neurosci 2011; 14:1160-1166.

58. Di Marzo V, De Petrocellis L, Fezza F, Ligresti A, Bisogno T. Anandamide receptors. Prostaglandins Leukot Essent Fatty Acids 2002; 66:377-391.

59. Hudson BD, Hébert TE, Kelly ME. Ligand- and heterodimer-directed signaling of the CB(1) cannabinoid receptor. Mol Pharmacol 2010; 77:1-9.

60. Milligan G, Smith NJ. Allosteric modulation of heterodimeric G-protein-coupled receptors. Trends Pharmacol Sci 2007; 28:615-620.

61. Wood DM, Dargan PI. Novel psychoactive substances: How to understand the acute toxicity associated with the use of these substances. Ther Drug Monit 2012; 34:363-367.

62. Zuba D, Byrska B, Maciow M. Comparison of "herbal highs" composition. Anal Bioanal Chem 2011; 400:119-126.

63. 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; 45:1186-1194.

64. Simmons J, Cookman L, Kang C, Skinner C. Three cases of "Spice" exposure. Clin Toxicol 2011; 49:431-433.

65. Simmons JR, Skinner CG, Williams J, Kang CS, Schwartz MD, Wills BK. Intoxication from smoking "Spice". Ann Emerg Med 2011; 57:187-188.

66. Müller H, Sperling W, Köhrmann 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; 118:309-310.

67. Every-Palmer S. Warning: Legal synthetic cannabinoid-receptor agonists such as JWH018 may precipitate psychosis in vulnerable individuals. Addiction 2010; 105:1859-1860.

68. Schneir AB, Cullen J, Ly BT. "Spice" girls: Synthetic cannabinoid intoxication. J Emerg Med 2011; 40:296-299.

69. Teske J, Weller JP, Fieguth A, Rothämel T, Schulz Y, Tröger HD. Sensitive and rapid quantification of the cannabinoid receptor agonist naphthalen-1-yl-(1-pentylindol-3-yl) methanone (JWH-018) in human serum by liquid chromatography–tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 2010; 878:2659-2663.

70. Harris CR, Brown A. Synthetic cannabinoid intoxication: A case series and review. J Emerg Med 2013; 44:360-366.

71. Reece AS. Chronic toxicology of cannabis. Clin Toxicol 2009; 47:517-524.

72. Jerry J, Collins G, Streem D. Synthetic legal intoxicating drugs: The emerging 'incense' and 'bath salt' phenomenon. Cleve Clin J Med 2012; 79:258-264.

73. Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. Pediatrics 2011; 128:1622-1627.

74. Rosenbaum CD, Carreiro SP, Babu KM. Here today, gone tomorrow and back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones bath salts), Kratom, Salvia divinorum, methoxetamine, and piperazines. J Med Toxicol 2012; 8:15-32.

75. McGrath J, Welham J, Scott J, Varghese D, Degenhardt L, Hayatbakhsh MR, Alati R, Williams GM, Bor W, Najman JM. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. Arch Gen Psychiatry 2010; 67:440-447.

76. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. BMJ 2002; 325:1212-1213.

77. D'Souza DC, Sewell RA, Ranganathan M. Cannabis and psychosis/schizophrenia: Human studies. Eur Arch Psychiatry Clin Neurosci 2009; 259:413-431.

78. Every-Palmer S. Synthetic cannabinoid JWH-018 and psychosis: An explorative study. Drug Alcohol Depend 2011; 117:152-157.

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

80. Lin CY, Wheelock AM, Morin D, Baldwin RM, Lee MG, Taff A, Plopper C, Buckpitt A, Rohde A. Toxicity and metabolism of methylnaphthalenes: Comparison with naphthalene and 1-nitronaphthalene. Toxicology 2009; 260:16-27.

81. Gregori A, Damiano F, Bonavia M, Mileo V, Varani F, Monfreda M. Identification of two cannabimimetic compounds WIN48098 and AM679 in illegal products. Science and Justice 2012 (inpress).

82. Dresen S, Kneisel S, Weinmann W, Zimmermann R, Auwärter V. Development and validation of a liquid chromatography-tandem mass spectrometry method for the quantitation of synthetic cannabinoids of the aminoalkylindole type and methanandamide in serum and its application to forensic samples. J Mass Spectrom 2011; 46:163-171.

83. Coulter C, Garnier M, Moore C. Synthetic cannabinoids in oral fluid. J Anal Toxicol 2011; 35:424-430.

84. Hutter M, Broecker S, Kneise Sl, Auwärter V. Identification of the major urinary metabolites in man of seven synthetic cannabinoids of the aminoalkylindole type present as adulterants in 'herbal mixtures' using LC-MS/MS techniques. J Mass Spectrom 2012; 47:54-65.

85. Hutter M, Kneisel S, Auwärter V, Neukamm MA. Determination of 22 synthetic cannabinoids in human hair by liquid chromatography–tandem mass spectrometry. Journal of Chromatography B Analyt Technol Biomed Life Sci 2012; 903:95-101.

86. Möller I, Wintermeyer A, Bender K, et al. Screening for the synthetic cannabinoid JWH-018 and its major metabolites in human doping controls. Drug Test Anal 2011; 3:609-620.

87. 2011 National report (2010 data) to the EMCDDA. "TURKEY" New Development, Trends and in-depth information on selected issues. Reitox National Focal Point, 2012. http://www.emcdda.europa.eu/attachements.cfm/att_191577_EN_Turkey_2011.pdf. Last accessed Feburary 18, 2013.

88. Griffiths P, Sedefov R, Gallegos A, Lopez D. How globalization and market innovation challenge how we think about and respond to drug use: 'Spice' a case study. Addiction 2010; 105:951-953.

89. Brents LK, Reichard EE, Zimmerman SM, Moran JH, Fantegrossi WE, Prather PL. Phase I hydroxylated metabolites of the K2 synthetic cannabinoid JWH-018 retain in vitro and in vivo cannabinoid 1 receptor affinity and activity. PLoS One 2011; 6:21917.