ORIGINAL ARTICLE

Synthetic cannabinoids abused in South Korea: drug identifications by the National Forensic Service from 2009 to June 2013

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Abstract The rapid increase in the number of new psychoactive substances and their abuse is the most recent drug abuse issue worldwide. Although abuse of synthetic cannabinoids is highly restricted in South Korea, the rapid increase in the number of new substances is forcing the legal regulation authority to continuously improve the drug regulation act. As a result of drug screening by the National Forensic Service from 2009 to June 2013, 26 species of synthetic cannabinoids were identified in materials seized mainly by the Police Agency and the Prosecutor's Office in South Korea. One of the most remarkable trends in synthetic cannabinoids is the increase in halogenated derivatives and new substances, including UR-144 and A-836,339 originally developed as analgesics by Abbott Laboratories. The *N*-pentyl fluorinated analog of UR-144 (XLR-11) has become the most frequently found synthetic cannabinoid in 2013 since its first appearance in 2012, whereas abuse of A-836,339 analogs has been little reported despite their abuse potential. Until early 2011, nicotine was the most frequently found active coingredient with synthetic cannabinoids. However, various psychoactive substances such as Δ^9-tetrahydrocannabinol, α-pyrrolidinobutiophenone, α-pyrrolidinovalerothiophenone, and *N*,*N*-diallyl-5-methoxytryptamine have often been found as coingredients in herbal highs since late 2011. These coingredients should also be systematically regulated, because they can cause unexpected side effects. It is suggested that authorities in different countries share information about synthetic cannabinoids and their coingredients.

Introduction

The recent increase in the abuse of new psychoactive substances (NPSs) has become a remarkable worldwide trend. These NPSs are traded and abused in the forms of "legal highs" or "research chemicals" via the Internet or international mailing services. Their chemical structures are continuously being modified to avoid legal regulations [1, 2]. The NPSs are classified as synthetic cannabinoids, cathinones, phenethylamines, tryptamines, and amphetamine derivatives. Among them, synthetic cannabinoids are most frequently abused because their structure–activity relationships are well known from previous studies, which make it easy to modify their chemical structures. Synthetic cannabinoids were first identified in herbal incense in 2008 [3, 4], and their abuse is increasing continuously all over the world [5–7]. The psycho activity of synthetic cannabinoids increases as their CB_1 receptor affinity increases. Most of the classical synthetic cannabinoids such as JWH-018 or JWH-073 have CB_1 receptor affinity and psychotropic effects higher than Δ^9-tetrahydrocannabinol (THC) [8, 9], which is the active ingredient in cannabis. CB_2 selective agonists show greater analgesic effects than psychotropic effects, and have been developed for medical use [10–12]. However, some of the CB_2 selective agonists such as UR-144 have been found in herbal highs intended for recreational use [13]. Classical synthetic cannabinoids

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such as JWH-series indole compounds and CP-47,497 homologs were synthesized based on previous studies including pharmacology [14–16]. However, recently identified synthetic cannabinoids include new substances that lack pharmacological information, and therefore pose a real risk of severe toxicity or even fatal intoxication [17, 18]. Some of the NPSs imported to South Korea are interdicted by customs, while others are seized by the Police Agency and the Prosecutor's Office during drug trafficking. The National Forensic Service (NFS) identifies psychoactive substances seized mainly by the Police Agency and some by the Prosecutor's Office, and this collection may reflect the regional status of NPS abuse in South Korea. Thus, we report on the trends of synthetic cannabinoids identified by the NFS from 2009 to June 2013, along with the legal regulation status in South Korea to reduce widespread use of these NPSs.

Materials and chemicals

We used 140 species of seized materials containing synthetic cannabinoids, which were composed of dried leaves ($n = 97$), powder ($n = 11$), tablets ($n = 13$), and ashes in smoking apparatus ($n = 19$). Although the materials were separated in different packages and had different evidence numbers, they were considered one sample if their appearance, logos, and identified ingredients were the same. The materials were seized mainly by the National Police Agency and some by the Prosecutor's Office of South Korea from 2009 to June 2013 and were sent to the NFS for forensic identification. All solvents used were of analytical grade. JWH-018, JWH-122, JWH-210, and AM-2201 reference materials were obtained from TRC (Toronto, ON, Canada). MAM-2201, RCS-4, UR-144, A-836,339, and the CP-47,497-C8 homolog were obtained from Cayman Chemicals (Ann Arbor, MI, USA). JWH-019, JWH-073, and JWH-250 were purchased from Lipomed (Arlesheim, Switzerland). Standard stock solutions of the reference materials (100 mg/l in methanol) were used to identify the synthetic cannabinoids in the seized materials, and were stored at −20 °C when not in use.

Drug identification of the seized materials

Preliminary drug screening on the seized articles was carried out using gas chromatography–electron ionization mass spectrometry (GC–EI-MS). Each analyte was identified through comparison of mass spectra and retention times with those of commercial standards and MS libraries. The GC–MS analysis was performed on an Agilent 5975C mass selective detector equipped with an Agilent 7890A gas chromatograph (Santa Clara, CA, USA) and an HP-5MS capillary column (30 m × 0.25 mm i.d., film thickness 0.25 μm). The injector was operated in the splitless mode, and the injection volume was set to 0.2–1.0 μl. Inlet temperature and helium flow rate were set to 260 °C and 1.0 ml/min, respectively. Oven temperature was initially 80 °C for 3 min, increased to 290 °C at a heating rate of 20 °C/min, and held at that temperature for 16 min. The source and transfer line temperatures were set to 260 and 280 °C, respectively. The MS was operated in the scan mode, and the acquisition range was set to m/z 40–550. Sample preparation procedures are described below.

Dried leaves

About 0.1 g of dried leaves was extracted in 1 ml of methanol under ultrasonication for 10 min or shaking for 30 min. After extraction, the extracts were centrifuged at 3,000 rpm for 5 min, and the methanol extracts were diluted further with methanol to a suitable concentration, if necessary, before GC–MS analysis.

Powder

About 0.01 g of powder was dissolved in 1 ml of methanol. The extracts were centrifuged at 3,000 rpm for 5 min, and the supernatant was diluted with methanol to a suitable concentration, if necessary, before GC–MS analysis.

Tablets

Each tablet sample was crushed to powder with a mortar and pestle and then extracted using the same process described for powder samples.

Ashes in smoking apparatus

Ashes remaining in various types of smoking apparatus were extracted with an appropriate volume of methanol, and diluents of the extracts were used as samples for GC–MS analysis. In cases of unreported compounds, additional structural elucidations were performed on unknown compounds by nuclear magnetic resonance and liquid chromatography–time-of-flight–mass spectrometry [13, 19]. When necessary, the synthetic cannabinoids in the samples were quantified using the GC–MS method developed in the previous study [20].

Results and discussion

Synthetic cannabinoids identified by the NFS from 2009 to June 2013

Table 1 Active coingredients identified in the herbal highs ($n = 97$) containing synthetic cannabinoids

Coingredient	No. of occurrences				
	2009 ($n = 8$)	2010 ($n = 14$)	2011 ($n = 22$)	2012 ($n = 22$)	June 2013 ($n = 31$)
Nicotine	4	5	3	4	
Caffeine				1	
THC			1	1	1
Guaifenesin				2	
Phenazepam			1		
5-MeO-DALT			2	3	3
α-PBP					4
α-PVT					4

5-MeO-DALT N,N-diallyl-5-methoxytryptamine, *α-PBP* α-pyrrolidinobutiophenone, *α-PVT* α-pyrrolidinovalerothiophenone, *THC* Δ^9-tetrahydrocannabinol

Synthetic cannabinoids were identified mainly in the form of dried leaves, and others were identified in tablets, powders, or ashes in smoking apparatus. Powder is generally used to prepare homemade herbal highs by mixing or spraying solutions on commercially available herbs. Since a herbal incense containing JWH-018 was first identified in Korea, 26 species of synthetic cannabinoids have been identified by the NFS in 140 samples related to 88 cases investigated by the Police Agency and the Prosecutor's Office. The seized dried leaf materials contained one to three species of synthetic cannabinoids and some of them also contained active coingredients (Table 1). Until early 2011, the major coingredients of herbal highs were nicotine and caffeine, which were considered natural ingredients of the base herbs used for the preparation of homemade herbal highs. However, since N,N-diallyl-5-methoxytryptamine (5-MeO-DALT), THC, and phenazepam were first identified in material seized in late 2011, various psychoactive coingredients have been identified in seized materials. In particular, since 2013, new psychoactive substances such as α-pyrrolidinovalerothiophenone (α-PVT) and α-pyrrolidinobutiophenone (α-PBP) have often been found in herbal highs seized in South Korea, and there was even a herbal incense product containing only α-PVT without synthetic cannabinoids. THC and oxycodone were also found in ashes of smoking apparatus, which means that they were abused together with the synthetic cannabinoids. Various NPSs such as phenethylamines, tryptamines, and amphetamines were identified as coingredients in tablets, whereas synthetic cannabinoids were only found in small amounts. Administration of several of these drugs could induce a drug interaction or synergistic effect, which could result in severe intoxication. However, there is insufficient toxicological information about the toxicological effect that may be caused by multidrug administration of these new psychoactive substances.

The synthetic cannabinoids identified by the NFS were classified into ten basic categories (Table 2), which were categorized into two classes according to their literature base and year of first appearance. Class 1 included classical synthetic cannabinoids, naphthoylindoles, phenylacetylinoles, benzoylindoles, and CP-47,497 homologs, which are generally produced based on previous scientific literature including studies by Huffman et al. [14–16]. In contrast, class 2 compounds are those with new basic moieties such as cyclopropylindoles, aminocarbonylindazoles, adamantylindoles, adamantylindazoles, quinolinylindoles, and cyclopropylthiazoles, which include research chemicals developed as pharmaceuticals. Class 1 synthetic cannabinoids including the JWH-series naphthoylindoles prevailed until early 2012, but class 2 analogs replaced them in late 2012 (Fig. 1). Similar phenomena were observed with the increase in fluorinated analogs. Fluorinated analogs have increased continuously since AM-2201 was first identified in 2011, and fluorinated modifications of existing compounds have become a general synthetic cannabinoid trend (Fig. 2). It may be because halogenation of the N-pentyl side chain increases CB_1 affinity of synthetic cannabinoids [21]. Another reason may be to avoid legal regulation in the countries where only compounds with designated structures are controlled. The evolution of synthetic cannabinoids forces government regulatory authorities to legislate systemized regulation of possible analogs. The characteristic patterns since 2012 also include the appearance of CB_2 selective agonists developed as analgesics in herbal highs. Their representatives are UR-144, A-836,339, and their analogs, which were developed by Abbott Laboratories as analgesics but are less psychoactive than other synthetic cannabinoids [22–24]. The low CB_1 agonist activity makes it difficult to classify them as narcotics, and UR-144 and its N-pentyl fluorinated derivative XLR-11 have become one of the most frequently encountered synthetic cannabinoid types in herbal highs. A-836,339 was first identified along with XLR-11 in a herbal incense product seized by the Police Agency of South Korea in 2012 (Fig. 3); Uemura et al. [25] have also reported the identification of A-836,339 in a dubious product very recently. Unlike UR-144 and its analog, A-836,339 analogs have not been indentified in herbal highs as yet. However, A-836,339 has quite different basic moieties from other synthetic cannabinoids, and its analogs may be abused in the near future to avoid recent worldwide drug regulation of synthetic cannabinoids.

Table 2 Synthetic cannabinoids identified in the seized materials by the National Forensic Service from 2009 to June 2013

Table 2 continued

Basic structure	Identified compounds
Naphthoylindoles	JWH-018 (R_1: C_5H_{11}, R_2: H)[a]
	JWH-019 (R_1: C_6H_{13}, R_2: H)[a]
	JWH-022 (R_1: C_5H_9, R_2: H)[c]
	JWH-073 (R_1: C_4H_9, R_2: H)[a]
	JWH-122 (R_1: C_5H_{11}, R_2: CH_3)[a]
	JWH-210 (R_1: C_5H_{11}, R_2: C_2H_5)[a]
	AM-2201 (R_1: $C_5H_{10}F$, R_2: H)[a]
	MAM-2201 (R_1: $C_5H_{10}F$, R_2: CH_3)[a]
	EAM-2201 (R_1: $C_5H_{10}F$, R_2: C_2H_5)[c]
Phenylacetylindoles	JWH-203 (R_1: C_5H_{11}, R_2: Cl)[a]
	JWH-250 (R_1: C_5H_{11}, R_2: OCH_3)[a]
Benzoylindoles	RCS-2 (R_1: C_5H_{11}, R_2: OCH_3, R_3: H, R_4: H)[b]
	RCS-2-butyl (R_1: C_4H_9, R_2: OCH_3, R_3: H, R_4: H)[b]
	RCS-3 (R_1: C_5H_{11}, R_3: OCH_3, R_2: H, R_4: H)[b]
	RCS-4 (R_1: C_5H_{11}, R_4: OCH_3, R_2: H, R_3: H)[a]
	AM-694 (R_1: $C_5H_{10}F$, R_2: I, R_3: H, R_4: H)[c]
Cyclopropylindoles	UR-144 (R_1: C_5H_{11})[a]
	XLR-11 (R_1: $C_5H_{10}F$)[b]
Adamantylindoles	APICA (R_1: C_5H_{11})[b]
	5F-APICA (R_1: $C_5H_{10}F$)[b]

| Basic structure	Identified compounds
Adamantylindazoles	APINACA (R_1: C_5H_{11})[b]
	5F-APINACA (R_1: $C_5H_{10}F$)[b]
Aminocarbonylindazoles	AB-PINACA (R_1: C_5H_{11}, R_2: isopropyl)[b]
	ADB-FUBINACA (R_1: 4-fluorobenzyl, R_2: *tert*-butyl)[b]
Quinolinylindoles	5F-QUPIC (R_1: $C_5H_{10}F$)[b]
Cyclopropylthiazoles	A-836,339 (R_1: C_3H_7O)[a]
CP-47,497 homologs	CP-47,497-C8 (R_1: C_7H_{15})[a]

[a] Synthetic cannabinoids identified by comparison with reference materials

[b] Synthetic cannabinoids identified by structural elucidation using nuclear magnetic resonance analysis

[c] Synthetic cannabinoids identified from previous literature data
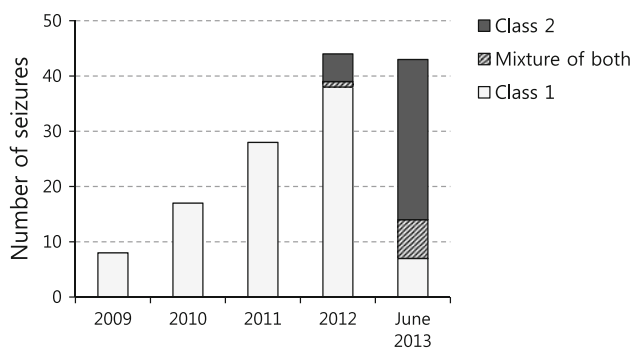
Fig. 1 Number of seizures in which synthetic cannabinoids were detected by the National Forensic Service from 2009 to June 2013. Class 1 includes the classical synthetic cannabinoids such as naphthoylindole, phenylacetylinole, benzoylindole, and CP-47,497 derivatives; class 2 includes new substances with cyclopropylindole, cyclopropylthiazole, aminocarbonylindazole, adamantylindole, adamantylindazole, and quinolinylindole structures
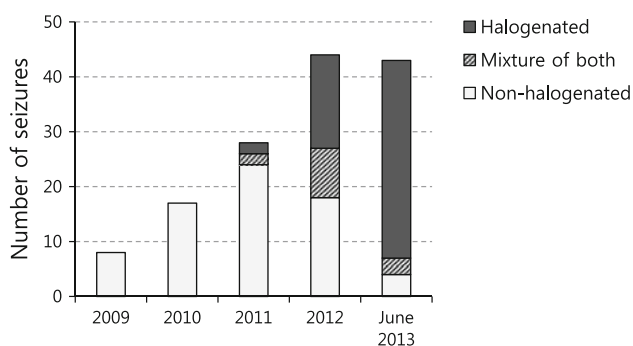
Fig. 2 Synthetic cannabinoids as a function of halogenated derivatization identified in materials seized by the National Forensic Service from 2009 to June 2013. Halogenated compounds include AM-2201, AM-694, MAM-2201, EAM-2201, XLR-11, 5F-APICA, 5F-APINACA, and ADB-FUBINACA

Legal regulation of new psychoactive substances in South Korea

The numbers of chemical species and abuse cases of NPSs have increased rapidly in South Korea since 2010, and the Korean Food and Drug Administration (KFDA) added analogs of major NPSs to the list of narcotics controlled by law in February 2011 based on the Canadian analog system [26] and included analogs of JWH-018 and JWH-073, JWH-250, CP-47,497, methcathinone, and phencyclidine. The present narcotics control act regulates the analogs of classical cannabinoids, such as naphthoylindoles, phenylacetylindoles, and CP-47,497 homologs. However, some of the recent synthetic cannabinoids with new basic moieties are not included in the list, and this will force the legal regulatory authority to prepare a more detailed and expanded analog list for regulation. The rapid increase in the range of NPSs also forces the monitoring of NPSs that have abuse potential. Thus, the KFDA also applied the
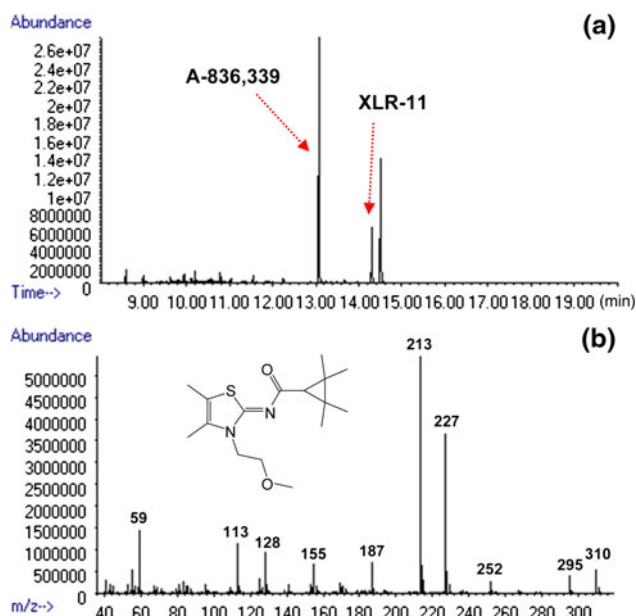

Fig. 3 Total ion chromatogram of a herbal high extract containing N-[3-(2-methoxyethyl)-4,5-dimethyl-1,3-thiazol-2-ylidene]-2,2,3,3-tetramethylcyclopropane-1-carboxamide (A-836,339) and XLR-11 (a) and the electron ionization mass spectrum of A-836,339 (b)

temporary drug designation act in June 2011 to reduce the interval required to legislate the drug regulation act. Since methylenedioxypyrovalerone (MDPV) was first placed on the list on November 2011, 40 species of NPSs have been added to the temporary drug designation list until June 2013, and most of them are being added to the drug regulation act afterward. As a result, regulations on analogs and the temporary drug designation act have contributed to the suppression of expansion of NPSs in South Korea, which was reflected in the decreased number of synthetic cannabinoid compounds identified by the NFS in 2012 (Fig. 4). However, the number increased again in 2013, and the number of seized cases has increased continuously (Figs. 1, 2). The results suggest that trade and abuse of NPSs cannot be reduced only by regional regulation, and it is impossible to block all legal highs sold via the Internet and international mailing services. Thus, international cooperation and information sharing are necessary to efficiently regulate the NPSs without the balloon effect.

Conclusions

The number of species and the amounts of NPSs are increasing rapidly every year, and new substances with no toxicological information are causing unexpected side effects or even fatal intoxication of drug abusers. The evolution of synthetic cannabinoids has been much faster than for other NPSs, and some reports are now available on the side effects and intoxication induced by synthetic
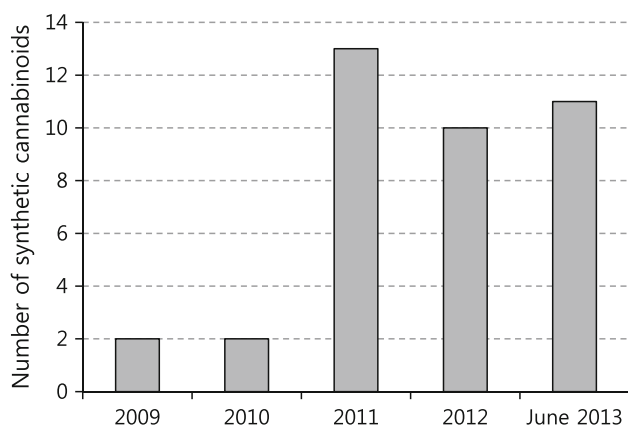
Fig. 4 Number of synthetic cannabinoid species in seized materials identified by the National Forensic Service from 2009 to June 2013

cannabinoids. The most efficient ways to regulate NPSs may include a rapid legislation system and extensive regulations of the analogs of possible abuse. The regulatory system should be improved to cope with the continuous and endless evolution of NPSs worldwide.

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

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