Assessment of types of synthetic cannabinoids in narcotic cases assessed by the Council of Forensic Medicine between 2011–2015, Ankara, Turkey

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\textbf{A B S T R A C T}

Synthetic cannabinoids mimic the effects of cannabis and are the largest and fastest growing class of newly appearing designer drugs. Reports have revealed that various types of synthetic cannabinoids are mixed with herbal substances. The present study investigated the herbal substance cases involving synthetic cannabinoids in Ankara and nearby cities in Turkey. Data were collected from the reports of synthetic cannabinoids that were analyzed between January 01, 2011 and December 31, 2015 in the Ankara Narcotic Department of the Council of Forensic Medicine at the request of the judicial authorities. In all, 4610 narcotic reports were obtained and reviewed. Among these narcotic reports during the period, 370 reports (8\%) were related to synthetic cannabinoids. 28 synthetic cannabinoid compounds could be identified in herbas: 5-F-AB-PINACA, 5-F-APK-48, 5-F-NNEI, 5-F-PB-22, AB-CHMINACA, AB-FUBINACA, AB-PINACA, ADB-CHMINACA, ADB-FUBINACA, AKB-48, AM-2201, EAM-2201, JWH-018, JWH-022, JWH-031, JWH-122, JWH-201, JWH-210, JWH-250, JWH-251, JWH-307, MAM-2201, NM-2201, PB-22, RCS-4, THJ-2201, UR-144, XLR-11. The amount of herbas was 30.72 g, 329.22 g, 665.89 g, 4844.7 g, and 5684.3 g in 2011, 2012, 2013, 2014, and 2015, respectively. Generally, herbas contained more than one synthetic cannabinoids. ADB-FUBINACA was the most common synthetic cannabinoid among the herbs determined in this study, which was 3132.43 g, excepting multi-synthetic cannabinoid herbas. The amount and diversity of synthetic cannabinoid compounds have increased dramatically between 2011 and 2015.

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1. Introduction

Synthetic cannabinoids are molecules that mimic $\Delta^2$-THC; they are produced under laboratory conditions to elaborately enhance their cannabinoid effects, in addition to evaluating their medical potential; they are used clinically for their pharmacological properties. In recent years, synthetic cannabinoids are increasingly abused both in Turkey and worldwide, albeit their addictive properties, and are popular among drug addicts as strong psychoactive drugs, marketed in Turkey under the name of “Bonsai”. Synthetic cannabinoids are substances developed to benefit from the therapeutic properties of the endocannabinoid system. However, since early 2000s, synthetic cannabinoids have been dried after synthesizing in laboratories and sold as an alternative to cannabis by spraying on dried plants. SCs are known as “Bonsai and Jamaica” in Turkey, as “Spice” in Europe and as “K2” in the USA.

Synthetic cannabinoid products can be found in the form of an herb mixture containing one or more cannabinoid compounds or in the form of a pill [1,2]. Although synthetic cannabinoids are usually smoked (cigars, cigarettes, e-cigarettes or waterpipes) [3], there are reports on their consumption through vaporizing, by an oral route, or by rectal administration [4]. The dose used of these compounds in herbal products was found to vary in different studies. Lindigkeit et al. [5] reported that the range of the concentrations in 9 different brands was between 3–11 mg/g for CP-47,497-C8 and 6–23 mg/g for JWH-073. In another similar study, it was reported that the dose range of synthetic cannabinoid in 46 herbal products was 1–17 mg/g for CP-47,497-C8 and 2–36 mg/g for JWH-018 [6].

These products especially attract the attention of teenagers because of their cannabis-like effects, easy accessibility through...
the Internet, and the lack of reliable and quantitative toxicological detection methods [1,7]. The first compounds detected with the forensic analysis of botanical materials were JWH-018, JWH-073, and CP 47,497 [8]. In spite of all kind of efforts to control sales, number of new compounds continue to arise worldwide and many compounds are not yet illicit or detectable.

Although psychoactive effects of synthetic cannabinoids are like those of Δ9-THC, the duration of their effects may vary. Their half-lives are usually longer than that of Δ9-THC, and their toxic effects last longer. For example, it was reported that the activity of JWH-018 continues for 1 to 2 h, and the activity of CP-47,497-C8 continues for 5–6 h. This can affect addicts’ preferences and the effects of their use [9].

Cannabinoids can attach to one of the cannabinoid (CB) receptors known to be endogenous compounds in human cells, such as Type 1 (CB1) and Type 2 (CB2) receptors. The CB1 receptor is mainly located in the brain and spine and is typically responsible for the physiological effect of cannabis and partially responsible for its psychotropic effect. The CB2 receptor is mainly located in the spleen and immune cells and is responsible for the immunomodulator effect. Synthetic cannabinoids typically have a full agonist effect on the CB1 receptors, and thus, have a maximal effect even at low doses [10]. As in the case of JWH-200, the affinity of synthetic cannabinoids to the CB1 receptors may resemble that of Δ9-THC [11], or as in the case of AM2201, it can be 105-fold higher than that of Δ9-THC [12].

There are case reports on cardiovascular problems and psychological disorders occurring after use, especially due to synthetic cannabinoid use at high doses. Cerebral hemorrhage, hypertension, cardiac arrests, convulsion, hallucinations, and paranoia can be listed among the clinical symptoms, which can even lead to death [13,14].

The first capture of a synthetic cannabinoid (JWH-018), which is not produced in Turkey and was illegally imported into the country by the police departments was on May 2010. Although limited in number, there are reports of toxicity and death resulting from synthetic cannabinoid use, in addition to the reports on other compounds among the increasing diversity of synthetic cannabinoids in Turkey [15]. The results of the present study, in which the role and frequency of synthetic cannabinoid use in judicial cases as an indicator of their increasing use were investigated, will provide information on the prevalence of synthetic cannabinoid use in Turkey.

2. Materials and methods

2.1. Sampling of herbas

The herbas containing the synthetic cannabinoid that were seized by the police from the user or the dealer were first analyzed by gas chromatography-mass spectrometry (GC–MS) and determined to contain synthetic cannabinoid or not. Narcotics reports were generated for products containing synthetic cannabinoid. In all, 4610 narcotic reports obtained and reviewed between January 01, 2011 and December 31, 2015 in the Ankara Narcotic Department of the Council of Forensic Medicine at the request of the judicial authorities were retrospectively reviewed for synthetic cannabinoids. Among these narcotic reports during the period, reports were evaluated related with synthetic cannabinoids, and those about classical marijuana use were not included. It has been determined that 1.1% (n = 49) products investigated contain cannabis together with synthetic cannabinoids. This study was performed by permission of the Presidency of Scientific Board of Council of Forensic Medicine.

2.2. Sample preparation and gas chromatography–mass spectrometry parameters

The presence of synthetic cannabinoids in the herbas was determined by the method reported by Rossi et al. [16], with the help of GC–MS system. The herbal samples were dissolved in methanol to injection into the GC–MS system. For chemical characterization of the synthetic cannabinoids at unit mass resolution, a GC–MS system consisting of a Thermo Trace 1310 gas chromatograph coupled to a Thermo ISQ LT mass spectrometer was used. Chromatographic separation of the analytes was achieved by split injection (1:5) of 1 μL on a DB-5MS capillary column (30 m; 0.25 mm; film thickness 0.25 μm; Agilent, Waldbronn, Germany). The following temperature program was used: 80°C (2 min), 10°C/min–130°C (2 min), 20°C/min–310°C (25 min). The following MS settings were applied: ionization energy 70 eV, ion source temperature 280°C and interface temperature 290°C. SWGDRUG Mass Spectral Library and Cayman Spectral Library were used [17,18]. Only synthetic cannabinoids identification in herbas was determined by the GC–MS method, synthetic cannabinoids quantification was not performed.

3. Results and discussion

During this 5-year study, 4610 narcotic cases were reported and 370 (8%) of total cases involved synthetic cannabinoids. In herbal products, 28 different synthetic cannabinoid compounds were determined (5-F-AB-PINACA, 5-F-ABK–48, 5-F-NNEI, 5-F-PB-22, AB-CHMINACA, AB-FUBINACA, AB-PINACA, ADB-CHMINACA, ADB-FUBINACA, AKB-48, AM-2201, EAM-2201, JWH-018, JWH-022, JWH-031, JWH-122, JWH-201, JWH-210, JWH-250, JWH-251, JWH-307, MAM-2201, NM-2201, PB-22, RCS-4, THJ-2201, UR-144, XLR-11).

The amounts of herbal products in 2011, 2012, 2013, 2014, and 2015 were 30.72 g, 329.22 g, 665.89 g, 4844.681 g, and 5684.336 g, respectively; the number of cases in these years was 3, 16, 114, 142, and 101, respectively. Synthetic cannabinoid containing herbal product amounts significantly increased over the years (Fig. 1).

Herbal products usually contain more than one synthetic cannabinoid compounds. The synthetic cannabinoid contents of herbal products with the highest synthetic cannabinoid ratios are given in detail in Fig. 2, between 2011 and 2015 by amount; the remaining amounts were categorized as “other” and their synthetic cannabinoid ratios were given in total. Among all synthetic cannabinoids, at 27.11% (3132.399 g), ADB-FUBINACA had the highest ratio, followed by AM-2201, at 19.63% (2267.485 g), and ADB-FUBINACA + AM-2201, at 9.85% (1138.519 g). Table 1 shows in detail the synthetic cannabinoid types herbal products contain. The chemical structures and mass spectra for the 28 synthetic
cannabinoids in this study are shown in Table 2 in Supplementary material.

As could be seen in Table 1, some synthetic cannabinoids constantly appear during the whole study period. It is noteworthy that these were first synthesized synthetic cannabinoids such as JWH-018, AM-2201. There could be several reasons why these are still in use over the years; (a) the fact that users have definite knowledge about both the pharmacological and adverse health effects of these first generation synthetic cannabinoid (b) especially toxic effects of these synthetic cannabinoids are known and predicted in greater detail by users (c) the price of the first synthesized synthetic cannabinoids is getting cheaper.

Synthetic cannabinoids are Designated Substances, use of which is unrestrainedly escalating around the world. This threatens the health of all nations because of constant alterations to their chemical structure done to licit the substances, and because of low cost and easy access to the substances through the Internet. In 2009, 2010, 2011, 2012, 2013, 2014, 2015 and 2016, The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reported 9, 11, 23, 30, 29, 30, 25, 11 and total 169 synthetic cannabinoids, respectively [7]. Death and poisoning cases are reported in many countries of the world depending on the use of synthetic cannabinoids. For instance, during the fall of 2014 in Russia, 15 cases of death were reported due to the use of synthetic cannabinoids [19]. Similarly, during the spring of 2015, 15 cases of death and more than 300 potentially life-threatening intoxication cases were reported due to the use of synthetic cannabinoids in the United States [20].

A brief examination of the change in the diversity of synthetic cannabinoids in countries over the years reveals that, in Japan, 23 synthetic cannabinoids were listed in the Designated Substances category in 2012 [21], whereas, in 2013, a report from Japan identified 35 different synthetic cannabinoids [22]. In 2014, Lewin et al. [23] reported synthetic cannabinoid receptor agonist substances in over 140 different products. In Germany, during the routine analyses between August 2011 and January 2012, at least one of the synthetic cannabinoids (JWH-018, JWH-019, JWH-073, JWH-081, JWH-122, JWH-200, JWH-203, JWH-210, JWH-307, AM-2201 and RCS-4) were found in 227 of 833 original serum samples (27%) [24].

The legislative regulations in Turkey concerning synthetic cannabinoids are summarized below. Based on the recommendation of the Ministry of Health, as of 13.02.2011, active substances such as AM-2201, RCS-4, JWH-201, JWH-302, JWH-018, JWH-019, CP-47, among others, were added to the controlled substances list according to the Law no 2313 [25]. In Turkey, some of the synthetic cannabinoids were declared illegal on 22.05.2013. Turkey has developed a national policy and series of strategies on drugs for 2013–2018. In this new approach many non-scheduled NPS are also controlled and added to the controlled substances list which synthetic cannabinoids, cathinones and piperazines are included. NPS is included in the scope of Law 2313 with generic classification in Turkey. For 2014, 246 different NPS were regulated and controlled by this new strategy [26]. Between 2011 and October 2014, 125 synthetic cannabinoids were included in the list of prohibited substances. With the law amendment on 24 February 2015, synthetic narcotic drugs such as ‘Bonsai’ were included in the scope of the Turkish Criminal Code. In the fourth paragraph of the 188th article of Turkish Criminal Code No. 5237, the description of ‘synthetic cannabinoids and its derivatives’ was added.

In Turkey, the first official operation to confiscate synthetic cannabinoids was on May 2010 [1]. The number of arrests in 2013 was 66-fold higher than the number of arrests in 2011, and the number of suspects increased 182-fold between 2011 and 2013. In 2013, 15,065 suspects from 11,139 synthetic cannabinoid cases were arrested [27]. Gurdal et al. [1] analyzed 1200 herbal components, which were evaluated in the Narcotics Department of the Forensic Medicine Institute, and determined that 98.3% of these herbal components contained synthetic cannabinoids and 99.4% and 65.9% of these synthetic cannabinoids were JWH-01 and JWH-081, respectively. According to Turkish Narcotics Report in 2013, seven cases of synthetic cannabinoid use were determined in the first half of 2012; one of these cases resulted in death attributed to synthetic cannabinoid use. Moreover, in three cases involving death, concomitant use of cannabis and synthetic cannabinoid was determined [15]. The second half of 2012, seven cases related to the use of synthetic cannabinoids have been detected, one of these cases died depending on the use of synthetic cannabinoids [28]. In addition, simultaneous use of cannabis and synthetic cannabinoids has been identified in three other cases resulting in death in 2013 [29]. Furthermore, between 2012 and 2014, of the 197 synthetic cannabinoids poisoning cases (190 (96.4%) male; 7 (3.6%) female) admitted to the emergency department of Ümraniye Training and Research Hospital, Istanbul, Turkey, 2 cases resulted in death and 141 cases were kept under 6–12 h observation [15,27].

According to data of Turkish Monitoring Centre for Drugs and Drug Addiction (TUBIM), the average age of first use is decreased to 14 in Turkey (TUBIM, 2014) [15]. In 2012, a survey conducted in University of Michigan showed that the ratio of synthetic cannabinoid use among high school students was 11.3% for 12th graders, 8.8% for 10th graders, and 4.4% for 8th graders. It is reported that this annual prevalence declined to 3.5%, 3.3% and 2.7% in three years in 2016 [30]. It was reported that these ratios were lower in Europe [7]. In addition, based on data of The American Association of Poison Control Centers (AAPCC), as of May 31, 2017, poison centers received 850 calls about synthetic cannabinoid exposure, and the number of calls in 2013, 2014, and 2015 were 2668, 3682, and 7794 [31]. The studies carried out in different countries over the years show that the diversity of synthetic cannabinoids is increasing. For example, in Bulgaria, JWH-018, JWH-073, JWH-081, RCS-4, JWH-018 + JWH-073, JWH-081 + JWH-073 + JWH-203; 2012 yilinda AM-2201, AM-694, AM-2233, JWH-018, JWH-081, JWH-210, URB-754, AKB-48, URB-754, RCS-4, MAM-2201, STS-135, JWH-081 + CB-3, RCS-4 + JWH-081, AM-694 + AM-2201, AM-2201 + JWH-210, JWH-018 + JWH-081, 4-FMC + JWH-018 + JWH-081, JWH-210 + JWH-203 + 4-FA + RCS-4, JWH-081 + JWH-250 + JWH-073, were detected in 2011 and AM-2201, JWH-018, MAM-2201, UR-144, URB-754, XLR-11, STS-135, AB-PINACA, 5-F-ABK-48, AB-FUBINACA, 5-F-UR-144, UR-144 + URB-754, JWH-018 + JWH-081 + JWH-022 + JWH-210 + AM-2201, JWH-210 + JWH-122, UR-144 + STS-135 + MAM-2201, UR-144 + MAM-2201, 5-F-ABK-48 + URB-754, 5-F-ABK-48 + URB-754 + UR-144, 5-F-ABK-48 + UR-144, URB-754 + 5-F-ABK-48 were detected in different herbal products in 2013 [32].

Fig. 2. Synthetic cannabinoid ratios of herbal products.
<table>
<thead>
<tr>
<th>Year</th>
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Table 1
Synthetic cannabinoids determined in herbal products in Turkey over the years.
of the conclusions of this study was that JWH-018, RCS-4, AM-2201, JWH-210, AKB-48, MAM-2201, JWH-210, JWH-250, XLR-11, AB-PINACA, 5-F-AMB, AB-FUBINACA, JWH-022, and JWH-122, are synthetic cannabinoids for use in both Turkey and Bulgaria. Examples of the variation of the variety of synthetic cannabinoids found in herbal products over the years are also found in countries in different parts of the world such as Taiwan, Korea [33], Germany [34] and England [35]. However, 4-FMC, 4-FA, URB-754, and STS-135 determined in Bulgaria, STS-135 and MDMB-CHMICA determined in England, AB-001, ADBICA, A-834,735, NNEI, and QCICHI determined in Korea were not evaluated in this study.

As can also be seen in this study, chemical compositions of bonsai or bonsai-like products in the market in Turkey vary greatly in terms of amount and content and most of the products usually contain more than one synthetic cannabinoid compound. The most important issue is the constantly changing contents of these herbal products and consequently, not knowing the effects of the substances in their composition. The main cause of this diversity in synthetic cannabinoids is constantly offering new analogs to the market to cheat the law. The diversity of synthetic cannabinoid compounds leads to having difficulties in tracing these substances and complicates their toxicological analysis. Furthermore, some synthetic cannabinoids (Cumyl-4CN-BINACA, etc.) are not registered in any mass spectrometry system and do not have reference standards; therefore, detecting these substances is challenging [36]. The low concentration of the metabolites of some synthetic cannabinoids in urine, such as CP-47 and 497-C8, complicates their detection using standard laboratory analyses. These issues make the detection of synthetic cannabinoids in biological materials, such as blood and urine, difficult.

4. Conclusion

Despite the current legislative regulations by states, the increasing numbers of synthetic cannabinoids worldwide have psychiatric, medical, and social repercussions. The increase in synthetic cannabinoid demand and use, not exactly knowing the effects, offering new compounds that are not within the scope of the relevant law to the market, multiple synthetic cannabinoid compounds in herbal products, and not knowing what substance was used by individuals render synthetic cannabinoid use extremely dangerous. As a consequence of one or more of these issues, many patients are admitted to emergency rooms or psychiatry polyclinics or need to consult with family physicians; the number of death cases is increasing with each passing day. We certainly believe that community education and prevention programs are of top priority in decreasing the use of these substances

Conflict of interest

All of the authors are without declaration of interest, including financial interests, activities, relationships, and affiliations.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.forensic.2017.09.017.

References


