Mini Review
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How present synthetic cannabinoids can help predict symptoms in the future

Abstract

New synthetic cannabinoids appear regularly in the illicit drug market, often in response to legal restrictions. These compounds are characterized by increasing binding affinities (Ki) to CB1 and CB2 receptors. Increasing affinity to CB receptors can occur by substitution of a halogen on the terminal position of the pentyl chain of the classical synthetic cannabinoids. Fluorination of the aliphatic side chain of established cannabinoid agonists is a popular pathway of modifying existing active drugs and synthesizing novel drugs to increase potency. Biological impacts of these compounds that have been reported include seizures, body temperature losses that may lead to cardiac distress, as well as cases reporting delirium and severe neural incapacities. These symptoms have been reported in case reports with evidence that like their cannabinoid counterparts, these compounds distribute post-mortem into a variety of tissues, especially adipose tissue. Researchers have detected and identified certain synthetic cannabinoid compounds on botanicals using a variety of separation and detection systems such as GC-FID and GC-MS, as well as LC-MS/MS and NMR. Researchers have utilized a variety of chromatographic methods including LC MS/MS, to identify the parent compounds, their metabolites and structural analogs in biological samples such as urine and blood. The aim of this review is to spotlight the newer generations of synthetic cannabinoids with a more powerful affinity towards the cannabinoid receptors to continue to help researchers and clinicians further predict symptoms as well as future compounds and treatments.

Keywords: synthetic cannabinoids, chminaca, tissue culture, lcms/ms, tof, gc-ms, gc-fid, case reports

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Abbreviations: SCs, synthetic cannabinoids; Δ-9-THC, delta-9-tetrahydracannabinol; UHPLC, ultra high performance liquid chromatography; DAD, photodiode array; MS, mass spectrometry; GC, gas chromatography; DART, direct analysis in real time; TOF, time of flight spectrometry; NMR, nuclear magnetic resonance; ATR, attenuated total resonance; FTIR, fourier transform infrared spectrometry; TIC, total ion chromatogram; LC-MS/MS, liquid chromatography tandem mass spectrometry; CNS, central nervous system; LOD, limit of detection; LOQ, limit of quantitation; ULOL, upper limit of linearity; DUID, driving under the influence of drug; HLM, human liver microsomes; HPM, human pulmonary microsomes; CES 1, carboxylesterase 1

Introduction

Synthetic cannabinoids (SCs) are synthetic compounds sprayed on herbal products and have spread worldwide since 2004. Many of these compounds, more specifically l-valinamides and l-tert-leucinamides, are often characterized as part of the third, fourth and fifth generation of synthetic cannabinoids. There are many street names for herbal like compounds which are sprayed with these compounds, referred to as "Spice" such as Spice Diamond, Spice Gold, Spice Arctic Energy, Magic, Voodoo and Yucatan Fire. Such drugs are easily obtainable via the Internet, in smoke shops, and street markets. To evade law enforcement, these herbal incense products are often labeled "not for human consumption". Despite this, many countries have entered many synthetic cannabinoids to schedule 1.[1,2]

Initial reports of synthetic cannabinoids (SCs) in Unites States were in November 2008. In December 2008, German forensic laboratories initially identified JWH–018 and cannabicyclohexanol (CP–47,497 C8 homologue). The synthetic cannabinoids are frequently applied on plant material and inhaled. In January 2010, the popularity of these cannabinoids and their associated products appeared to have increased in the United States.[3] Numerous SCs have been identified as adulterants, which have been seized by law enforcement. JWH–018, JWH–073, JWH–200, CP– 47,497, and CP–47,497 C8 homologues were the first SCs identified as being abused. New generations of synthetic cannabinoids quickly emerged to evade law enforcement. After various laws were passed in the United States, different generations of SCs emerged varying only by slight modifications in structure. Some recent SCs include AB–CHMINACA and AB-PINACA. These substances are commonly marketed under the guise of being a "legal high" with a disclaimer of "not for human consumption". Law enforcement, public health officials, and clinicians are encountering cases in which there has been abuse of these substances,[4] requiring up to date information of the drug legislation, chemistry of the compounds and their detection, as well as the toxicology to be able to help identify these compounds when they present clinically.

After the passage of the Synthetic Drug Abuse Prevent Act of 2012 in the United States, a third and fourth generation of SCs including UR-144, XLR11, and AKB-48 emerged. In early 2013, a fifth generation including PB-22 and AB-FUBINACA emerged. These 5th generation synthetic cannabinoids including ABCHMINACA, AB-PINACA and THJ-220 were temporarily placed in Schedule I in December of 2014.[4] Drug legislation in other countries also attempted to combat

the use of these synthetic cannabinoids. For example, Japan reported the emergence of SCs before 2007. This was combated with the passage of the Pharmaceutical Affairs Law Amendment allowing for the control of designated substances prohibiting their advertisement, sale, supply, and production. Also, several European countries not only detected SCs but also began banning early generations in 2009. The difficulty of legislation of these drugs is once certain SCs are scheduled another generation of cannabinoids often emerges.

The slight variations that occur between the different generations of SCs are predominantly changes to the linking group, secondary structure, or tail group. These variations are often characterized by continually increasing binding affinities to the CB1 and CB2 receptors. This ensures the continued popularity of these drugs by offering continued increased potency when compared to delta-9-tetrahydracannabinol (Δ-9-THC), the active component of marijuana.[5] The chemistry of these compounds remains an integral part of determining potency and how changes to chemical structure changes biochemical activity.

Chemistry

Synthetic cannabinoids are composed of four sub-structures and the new compounds are often grouped based upon changes to these groups. The four substructures are: the core indole or imidazole ring; which is attached by a linking group to a secondary structure with a tail substitute on the core group. Synthetic cannabinoids are prepared in large batches and sprayed over botanical material and then marketed in small packages.

As governments start to prohibit the use of more classical synthetic cannabinoids, structurally variable indole synthetic cannabinoids have started to be present in forensic samples that had not been seen in the literature previously.[6] As governments continue to outlaw specific structural moiety changes to the napthyl ring a class of compounds was created called adamantoylindoles. These compounds were created by replacing a napthyl ring with an adamantyl ring; and were titled third generation synthetic cannabinoids.[6] This name arose as the United States changed the federal scheduling to include certain cannabinoids like JWH-018 into Schedule 1.[6] The name has persisted into future generations including the third, fourth, and fifth generation compounds that are the focus of this review.

Halogenation of the aliphatic side chain is a popular way of modifying one of the established cannabinoid receptor agonists to increase their potency and create a structural analog to evade law enforcement detection.

This has prompted blends of compounds that include the parent compound, its halogenated counterpart, and in some cases earlier synthetic cannabinoids. For example, PINACA compounds appear on the market as APINACA (AKB-48) and ADB-PINACA together within a mixture alongside the 5-fluoropentyl analogs.[7–11]

PB-22 and 5F-PB-22 were first reported as the drugs in a 2009 patent filed by the pharmaceutical manufacturer Pfizer.[12] ADB-PINACA was first encountered by law enforcement following reports of serious events in both Georgia and Colorado.[13]

This review will attempt to spotlight the third, fourth, and fifth generation synthetic cannabinoids including the ones featured in Figure 1-12.

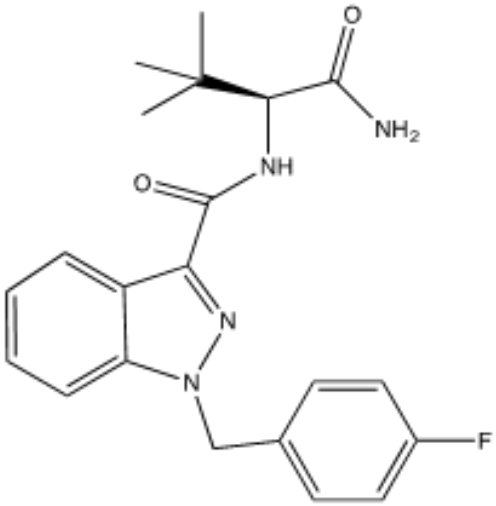

Figure 1 AB-Fubinaca.

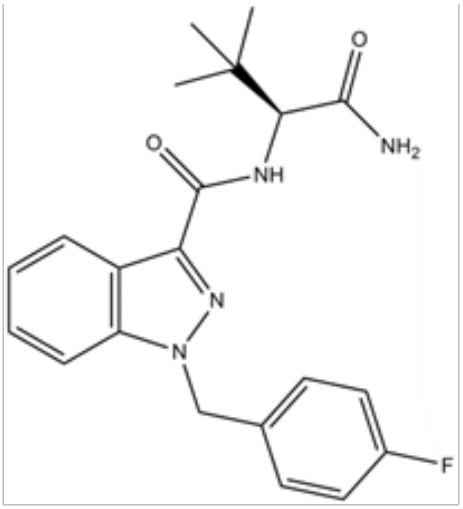

Figure 2 ADB-Fubinaca.

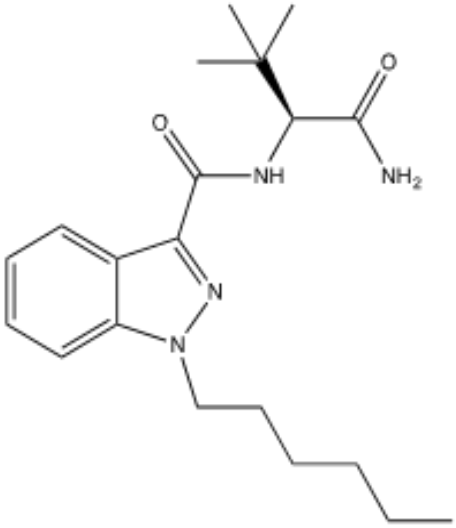

Figure 3 AB-Pinaca.

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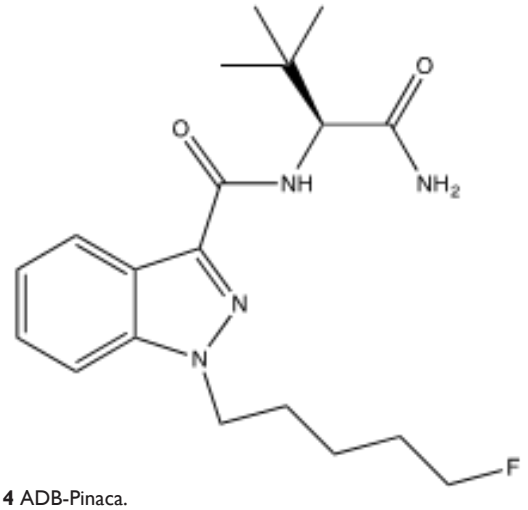

Figure 4 ADB-Pinaca.

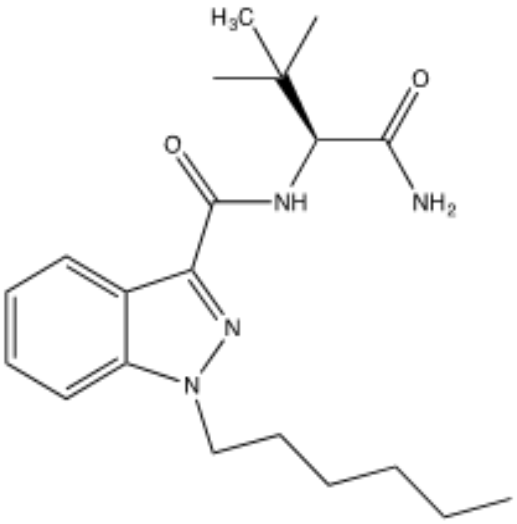

Figure 5 5F-AB-Pinaca.

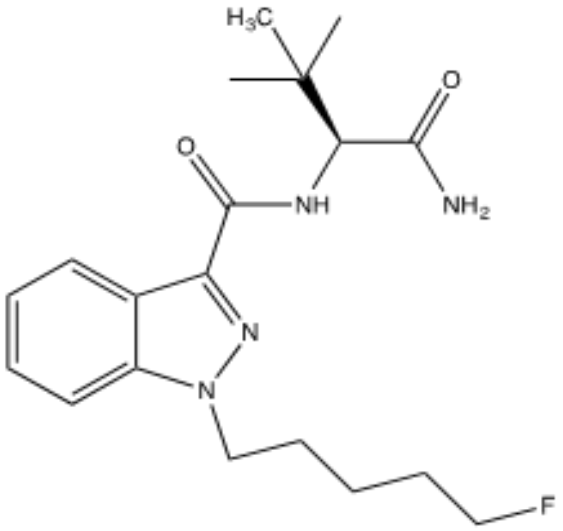

Figure 6 5F-ADB-Fubinaca.

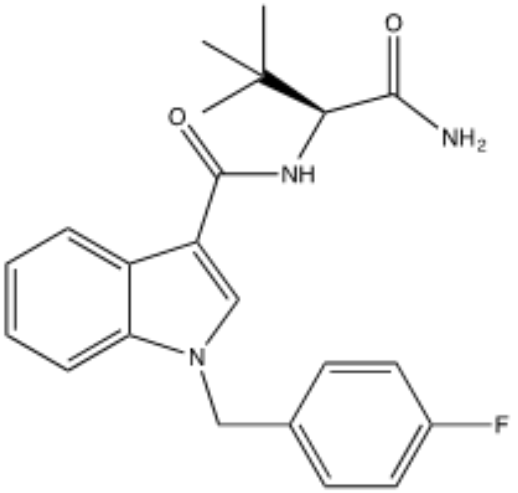

Figure 7 AB-Fubica.

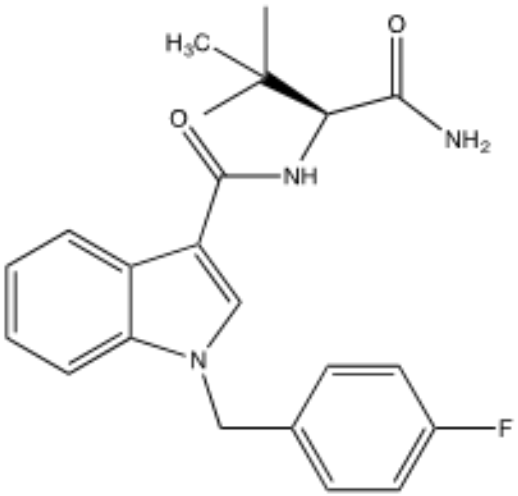

Figure 8 ADB-Fubica.

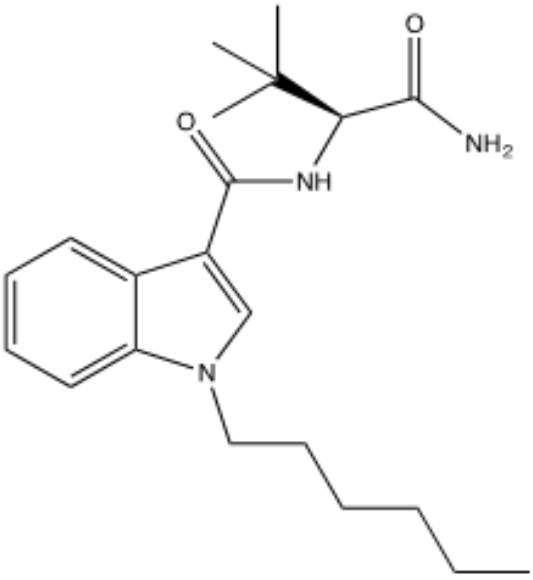

Figure 9 AB-Pica.

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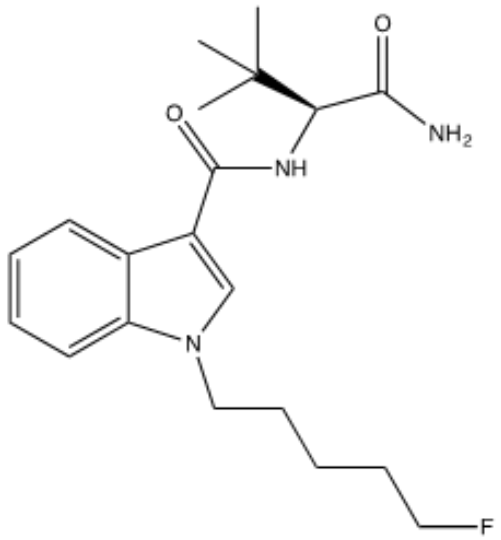

Figure 10 ADBica.

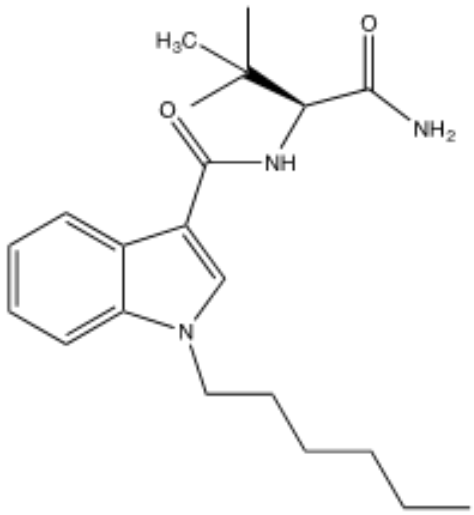

Figure 11 5F-AB-Pica.

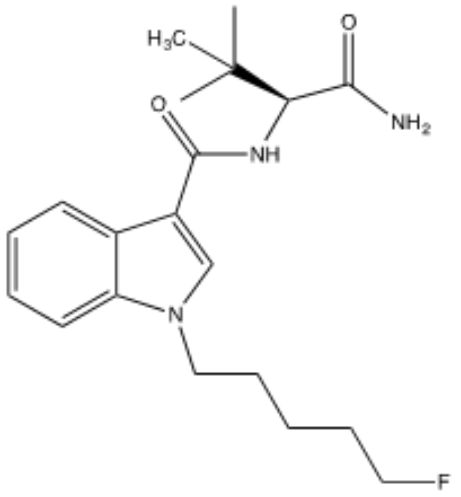

Figure 12 5F-ADBica.

Uchiyama et al.[14] published the identification of two synthetic cannabinoids APICA and APINACA that were illegally produced and sold. The identification used a variety of instrumentation including ultra high performance liquid chromatography with photodiode array and mass spectrometry detection (UHPLC-DAD-MS). Gas chromatography with mass spectrometry (GC-MS), positive mode direct analysis in real time –time of flight spectrometry (DART-TOF) and nuclear magnetic resonance (NMR) were used to overcome the problem of structural similarity.[14] This successful identification supports the idea that new synthetic cannabinoids can be identified using classical forensic technology, allowing for laboratories to maintain casework proficiency.

Veress et al.[15] examined herbal mixtures of AKB-48, AB-PINACA, AB-FUBINACA, PB-22, AB-CHMINACA, 5F-PB-22, and AM-2201 that were seized on the Hungarian black market. The examination was conducted using Attenuated Total Resonance (ATR) Fourier Transform Infrared Spectrometry (FTIR), and confirmation with GC-MS. The authors examined different solvents including n-hexane, methanol, chloroform, and acetone to determine the most efficient one. The upper clear liquid phase was used for FTIR analysis. After evaporation of the solvent and examination of the results of the residues, it was noted that the best spectra for residues were obtained after application of acetone. Data was collected between 4000/cm and 6000/cm with a resolution of 4/cm for 32 scans. The results were confirmed using GC-MS.[15]

Hasegawa et al.[16] was the first to state that the presence of AB-CHMINACA, 5F-fluoro-AMB and diphenidine were found in herbal incense (Super Lemon). This compound caused the death of a 30-year-old male. Using GC-MS and comparing it to the spectral library the total ion chromatogram (TIC) showed two distinct peaks, leading to the conclusion that one would be the SCs, and the other diphenidine after comparing mass spectral patterns to an established library.[16]

The more information that is collected and maintained about these compounds allows for scientists and clinicians to know how to start investigations when new compounds may arise from the black market (Figure 1-12).

Pharmacology and toxicology

Not unlike more classical synthetic cannabinoids, these generations of cannabinoids affects the cardiovascular system by decreasing heart rate. A case report linked ADB-PINACA to 59% of patients who experienced tachycardia, and to one patient who experienced a myocardial infarction.[17] The third and fourth generation synthetic cannabinoids show effects on the central nervous system (CNS), and in one case report 22 patients were admitted to the emergency room after confirmed use of ADB-PINACA. Some patients reported significant CNS effects including confusion/disorientation, somnolence/unresponsiveness and aggression.[18] Although these symptoms may appear to be minor, they can have a negative impact on an individual's ability to perform daily tasks; this impairment has also been studied in relation to driving.[19,20]

Gurney et al.[12] wrote a comprehensive review explaining many of the pharmacological and toxicological effects of classical synthetic cannabinoids. This reported receptor-binding study to determine binding affinities to CB1 and CB2 receptors. For example delta-9-tetrahydracannabinol binds to both receptors, AB-FUBINACA has a 100-fold increase in binding affinity to the CB1 receptor that

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can lead to an increased abuse potential.[12] The review also reported information on the efficacy of classical synthetic cannabinoids, as well as reporting that a single atom substitution of a halogen has a dramatic effect on binding affinity both positively and negatively. Finally, it also reported various physiological effects including kidney damage, tachycardia, and serious CNS effects after exposure to ADB-PINACA. The literature that documents these effects can be helpful to predict the effects of new generations of synthetic cannabinoids, as the trend has been the effects are all similar to marijuana exposure. This review will turn the focus to indazole carboxamide derivatives, sometimes known as third, fourth, and fifth generation synthetic cannabinoids.

A variety of different studies have been conducted involving the metabolism, pharmacology, and adverse effects of these synthetic cannabinoids. This review aims to explain the most recent advancements and discoveries of the newer generation synthetic cannabinoids to help better understand metabolic pathways, which will only assist in determining not only the cause of certain symptoms clinically, but also post-mortem distribution to help future exploration of compounds that arise from the black market.

Hasegawa et al.[16] reported a fatal case of drug poisoning of a 30 year old man, who was found dead in his car, with herbal incense (Super Lemon) containing multiple compounds including AB-CHMINACA, 5F fluoro-AMB, and diphenidine. Samples for toxicology examinations were taken from femoral vein blood, heart blood, urine, and eight solid tissues including adipose tissue. This report was the first to state the presence of AB-CHMINACA, 5F fluoro-AMB, and diphenidine in postmortem human specimens. Different extraction procedures were used for the urine, blood, and solid tissue samples. Standard addition was used to overcome matrix effects and increase accuracy. Liquid chromatography tandem mass spectrometry (LC-MS/MS) was used for the analysis. This was the first report of the postmortem distribution of these compounds. This report showed that these three drugs were distributed post-mortem to adipose and other fatty tissue using a validated method that could be expanded to newly emerging synthetic cannabinoids.

Hasegawa et al.[16] also reported the post mortem distribution of MAB-CHMINACA. In this case report, MAB-CHMINACA was reported in the highest concentration in pericardial blood and whole blood specimens. The highest concentration in solid tissues was found in the liver, then the kidney and pancreas. The method was identical to what was previously reported, but standard addition was used to overcome the matrix effects that were experienced. The group reported that the time between administration and cardiac arrest prevented the compound from accumulating in adipose tissue. It was also interesting to see the drug was accumulating in the kidney, possibly in an effort to remove it from the system.[21]

Freijo et al.[22] used a simple approach to detect and quantify many classical synthetic cannabinoids as well as AB-FUBINACA using LC-MS/MS. In this research they spiked drug-free urine samples with various synthetic cannabinoids and their metabolites. Urine samples from patients and known users were hydrolyzed with β-glucuronidase, and then separated and detected. Analytical figures of merit including a low limit of detection (LOD), limit of quantitation (LOQ), upper limit of linearity (ULOL), precision and accuracy were all determined. The screening method was difficult to use for the determination of metabolites due to matrix effects.[22]

Scheidweiler et al.[23] developed and validated a highly useful novel method for 47 synthetic cannabinoid metabolites from 21 synthetic cannabinoids in urine samples utilizing a LC-QTOF method. The hydrolysis and extraction procedures were optimized and analytical figures of merit determined. SWATH MS data were acquired in positive electrospray mode. While the method was sensitive, it was often difficult to get baseline resolution, lowering selectivity in authentic specimens. Limits of detection (LOD) were measured as 0.25-5μg/L (N=10 unique fortified urine samples). Using SWATH allowed for increased selectivity versus normal non-targeted acquisitions. These measurements also need to be taken with caution because there was such analytical variation in the case reported on.[23]

Peterson and Couper[24] also reported that synthetic cannabinoids appear to have an impact on impaired driving behavior. In their study, it was observed that with exposure to AB-CHMINACA and AB-PINACA, horizontal gaze nystagmus was present in 50-60% of the cases, and blood pressure was lowered in 80% of the cases. This reiterates the cardiovascular effects previously reported in this paper. This study also reported consistent results of the determination of impairment using the field sobriety test.[24]

Karinen et al.[25] reported the concentrations of APINACA, 5-APINACA and UR-144, in whole blood samples collected from driving under the influence of drug (DUID) cases. UR-144 was found in two cases, 5F-APINACA in one case, and concurrent findings of both APINACA and 5F-APINACA in three cases. The analyses were performed using an ultra-performance liquid chromatography-tandem mass spectrometer (UPLC-MS-MS). APINACA and 5F-APINACA were found in concentrations ranging from 0.24 to 24.5mg/L and 0.9 to 6.6mg/L, respectively.[25] This study confirms impairment found in previous studies.

While investigating how these compounds are broken down in the human body remains difficult with such little sample volume, groups have used other in vivo and in vitro methods to characterize pharmacological and toxicological effects. As the research advances, case reports have made this research more applicable.

Gandhi et al.[26] was the first study to report the metabolic profile of AKB-48 (APINACA) by incubating 10μM with human hepatocytes (1.3×10^6cells/mL) in 20-mL glass scintillation vials, constant shaking in an incubator set at 37°C. The samples were removed in a time course of zero, one, and three hours and the reaction was stopped with an equal volume of acetonitrile to precipitate proteins. Analysis was performed using UHPLC-MS/MS. Seventeen AKB-48 metabolites were identified based upon a predefined filtering criterion. Major metabolites were identified which included monohydroxylated, dihydroxylated, trihydroxylated, and mono- and dihydroxylated glucuronide conjugates, and dihydroxylated with ketone formation at the N-pentyl side chain.[26]

Thomsen et al.[27] studied the metabolism of two indazole carboxamide derivatives, AB-PINACA and AB-FUBINACA, by incubation with human liver microsomes (HLM), and human pulmonary microsomes (HPM). The major metabolites were the carboxylic acid derivatives of both synthetic cannabinoids. Other major metabolic pathways were mono-hydroxylation of the N-pentyl chain in AB-PINACA and mono-hydroxylation of the 1-amino-3-methyl-1-oxobutane moiety in AB-FUBINACA. This group indicated based on binding affinity, esterase inhibition assays and UPLC-MS analysis that carboxylesterase 1 (CES1) was the major enzyme responsible for the amide hydrolysis in human hepatic and enzymatic cells.[27]

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Banister et al.[28] further narrowed the chemistry to compounds based on the indole and indazole scaffolds to investigate the pharmacology and chemistry of these compounds. This study not only synthesized these compounds, but also investigated the activity at the CB1 and CB2 receptors by comparing activity to that of Δ-9-tetrahydracannabinol. Using murine neuroblastoma cells, the group showed an effect on hyper polarization in these cells. The group determined that even the least potent synthetic cannabinoid studied was still 1,000 times more potent than Δ-9-tetrahydracannabinol. The group also determined a dose dependent hypothermic effect while also causing the heart of the rat to beat irregularly. These effects could be reversed by the use of a CB1 antagonist, confirming case reports in humans.[28]

Takayama et al.[29] performed an important experiment about ADB-FUBINACA, AB-FUBINACA, AB-PINACA, QUPIC, and 5F-QUPIC, by using liver microsomes in 2014. Dimethyl sulfoxide (DMSO) was dissolved with 2μL of 5mM parent substrate (ADB-FUBINACA, AB-PINACA, AB-FUBINACA, QUPIC 5 F-QUPIC), and combined with freshly prepared solutions of the NADPH regeneration system solutions. The identification of the metabolites derived from ADBFUBINACA, AB-FUBINACA, AB-PINACA, QUPIC, and 5 F-QUPIC, were determined by comparison of the MS data, selected ion chromatograms (SICs), and MS/MS product ion spectra before and after the metabolism reaction by the human liver microsomes.[29]

Debruyne & Le Boisselier[30] reviewed information from clinical professionals and found that as a general rule, the synthetic cannabinoids that acted as agonists show little selectivity between the two receptors, while those that act as antagonists are highly selective in vitro. In mice, the group also described agonistic binding to CB1 receptors resulting in euphoria, anxiety, or alteration of memory. Based on case reports, the group reported effects beginning only a few minutes from inhalation and lasting approximately 2-6 hours. Case reports also showed that neurological and cardiovascular effects occur. This review also showed the extensive metabolism not only of these compounds but all synthetic cannabinoids is prevalently hydroxylation and glucuronidation. It is important to note that CYP enzymes appear to be responsible for the oxidative metabolism, specifically CYP3A4. Diagnostically, the group stressed clinicians to look for signs consistent with cannabis use and a negative cannabinoid screen to suspect synthetic cannabinoid use and abuse.[30]

Chen et al.[31] narrowed the scope to one compound, AB-FUBINACA. The group looked at the oxidative fate of the compound in Wistar rats as well as the effect on genetic expression in the liver and the heart. Using LC-TOF/MS, the group determined after a time course, that excretion was readily detected three hours after injection and the excreted produced decreased gradually but was approximately 50% of the concentration at three hours, demonstrating slow degradation. The group also concluded that two derivatives were increasing with time in urine, consistent with the previously reported hydroxylated metabolites.[31] In gene expression, seventeen genes were up regulated and eleven down regulated in the liver while thirteen were up regulated and three down regulated in the heart after treatment. Treatment with AB-FUBINACA was concluded to have an effect on the cellular response. The study also concluded that there was a 2-fold decrease of HaO2 gene expression. In rats, it was considered an ideal gene for regulating systolic blood pressure and has a potential link to hypertension. The study showed decreased levels of HaO2 mRNA after treatment suggesting AB-FUBINACA has a potential to regulate blood pressure and heart disease.[31]

As LC-TOF/MS methods improve, more information about the pharmacology of specific compounds is being revealed. Vikingsson et al.[32] used HLM as well as authentic urine samples to determine oxidative metabolites of APINACA and its halogenated analog 5F-AKB-48. The group identified four standout metabolites, one mono-hydroxylated metabolite, one diadamantyl hydroxylated metabolite, one adamantyl-pentyl-hydroxylated metabolite and one diadamantyl-hydroxylated metabolite. The metabolites identified in the halogenated analog were a dihydroxylated and keto-metabolite, a 5F-monohydroxylated metabolite, and a 5F-dihydroxylated metabolite. Although the group found many similarities with the HLM and case subjects, variation appears to be dose dependent, as well as varied by metabolic activity.[32]

New generations of synthetic cannabinoids are emerging and it is imperative as toxicologists that we remain aware of emerging compounds but also emerging technologies. Westin et al.[33] reported the emergence of another similar synthetic cannabinoid named MDMB-CHMICA. The group used LC-QTOF-MS and the compound was determined in the serum sample from a patient that was found unconscious with an unknown brown powder. The serum sample contained the compound, and compared to the tested splenic tissue, the group determined an overdose of MDMB-CHMICA was likely the cause of death.[33]

Conclusion

As synthetic cannabinoids continue to change to avoid detection it remains important to elicit data to be able to predict these compounds activity. As clinicians continue to see patients that have a negative cannabinoid screen, it is important to remain aware of new technologies to determine these drugs. Also, the important information that can be determined about the metabolism, pharmacology and toxicology allows researchers to continue the studies further into phase II metabolism as well as to lessen the variation in pharmacokinetic studies. Method development only increases the chances for clinicians to be able to treat synthetic cannabinoid exposure more effectively. More development is needed to improve the screening process to allow for high throughput screening of sprayed botanical material and powders as well as biological matrices. As many of the symptoms of synthetic cannabinoid abuse mimic marijuana use, more understanding of the metabolism, affinities to either the CB1 or CB2 receptor, and how changes to the chemical structures affect biochemical activity will allow researchers and clinicians to plan for future emerging synthetic cannabinoid exposures.

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.

References

1. Administration. Spice, Bath Salts and Behavior Health. *SAMHSA*. 2014;13(2):4.
2. General, NAAG. Education and prevention initiatives as necessary tools to combat drug abuse. *NAAGazette*. 2014;8:5.
3. *Rules and Regulations*. USA: Federal Register; 2014.
4. *Federal Register*. In: Register F, editor. USA: Federal Register; 2014.
5. Seely KA, Lapoint J, Moran JH, et al. Spice Drugs are more than harmless herbal blends: A review of the pharmacology and toxicology of synthetic cannabinoids. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;39(2):234–243.

6. Presley BC, Jansen–Varnum SA, Logan BK. Analysis of Synthetic Cannabinoids in Botanical Material: A Review of Analytical Methods and Findings. *Forensic Sci Rev*. 2013;25:27.
7. Cox AO, Daw RC, Mason MD, et al. Use of SPMEHS–GC–MS for the analysis of herbal products containing synthetic cannabinoids. *J Anal Toxicol*. 2012;36(5):293–302.
8. Jankovics P, Tolgyesi L, Lohner S, et al. Detection and identification of the new potential synthstic cannabinoids 1–pentyl–3–(2–iodobenzoyl) indole and 1–pentyl–3–(1–adamantoyl)indole in seized bulk powders in Hungary. *Forensic Science International*. 2011;214(1–3):27–32.
9. Logan BK, Reinhold LE, Xu A, et al. Identification of synthetic cannabinoids in herbal incense blends in the United States. *J Forensic Sci*. 2012;57(5):1168–1180.
10. Nakajima J, Takahashi M, Nonaka R, et al. Identification and quantitation of a benzoylindole (2–methoxyphenyl) (1–pentyl–1H–indol–3–yl) methanone and a naphthoylindole 1–(5–fluoropentyl–1H–indol–3–yl)–(naphthalene–1–yl)methanone (AM–2201) found in illegal products obtained via the Internet and their cannabimimetic effects evaluated by *in–vitro* [35S]GTPγS binding assays. *Forensic Toxicol*. 2011;29(2):132–141.
11. Nakajima J, Takahashi M, Nonaka R, et al. Identification and quantitation of two benzoylindoles AM–694 and (4–methoxylphenyl)(1–pentyl–1H–indol–3–yl)methanone, and three cannabimimetic naphthoylindoles JWH–210, JWH–122, and JWH–019 as adulterants in illegal products obtained via the Internet. *Forensic Toxicol*. 2011;29(2):95–110.
12. Gurney SM, Scott KS, Kacinko SL, et al. Pharmacology, Toxicology, and Adverse Effects of Synthetic Cannabinoid Drugs. *Forensic Sci Rev*. 2014;26(1):53–78.
13. Administration DE. *Schedules of Controlled Substances: Temporary Placement of Four Synthetic Cannabinoids into Schedule I*. In: Justice DO, editor. USA: Department of Justice: Federal Register; 2014.
14. Uchiyama N, Kawamura M, Kikura–Hanajiri R, et al. Identification of two new–type synthetic cannabinoids, N–(1–adamantyl)–1–pentyl–1H–indole–3–carboxamide (APICA) and N–(1–adamantyl)–1–pentyl–1H–indazole–3–carboxamide (APINACA) and detection of five synthetic cannabinoids, AM–1220, AM–2233, AM–1241, CB–13 (CRA–13) and AM–1248 as designer drugs in illegal products. *Forensic Toxicol*. 2012;30(2):114–125.
15. Veress T, Julia N. Fast and Simple Procedure for Preliminary Investigation of Synthetic Cannabinoids in Plant Matrix Using Infrared Attenuated Total Reflectance Spectroscopy. *Eur J Forensic Sci*. 2015;2(1):21–25.
16. Hasegawa K, Wurita A, Minakata K, et al. Postmortem Distribution of AB–CHMINACA, 5–fluoro–AMB, and diphenidine in body fluids and solid tissues in a fatal poisoning case: usefulness of adipose tissues for detection of the drugs in unchanged forms. *Forensic Toxicol*. 2015;33(1):45–53.
17. Drenzek C, Steck A, Arnold J, et al. *Notes from the Field: Severe Illness Associated with Synthetic Cannabinoids Use–Brunswick, C.F.D. Control*. Georgia; 2013. 939 p.
18. Drugs, A.C.o2014.t.M.o. *New psychoactive substances review: report of the expert panel*. 2014.
19. Musshoff F, Madea B, Kernbach–Wighton G, et al. Driving under the Influence of Synthetic Cannabinoids ("Spice") A Case Series. *Int J Legal Med*. 2014128(1):59–64.
20. Yeakel JK, Logan BK. Blood Synthetic Cannabinoid Concentrations in Cases of Suspected Impaired Driving. *J Anal Toxicol*. 2013;37(8):547–551.
21. Hasegawa K, Wurita A, Minakata K, et al. Postmortem distribution of MAB–CHMINACA in body fluids and solid tissues of a human cadaver. *Forensic Toxicol*. 2015;33(2):380–387.
22. Freijo TD Jr, Harris SE, Kala SV. A Rapid Quantitative Method for the Analysis of Synthetic Cannabinoids by Liquid Chromatography–Tandem Mass Spectrometry. *J Anal Toxicol*. 2014;38(8):466–478.
23. Scheidweiler KB, Jarvis MJ, Huestis MA. Non–targeted SWATH Acquisition for Identifying 47 Synthetic Cannabinoid Metabolites in Human Urine by Liquid Chromatography–High Resolution Tandem Mass Spectrometry. *Anal Bioanal Chem*. 2015;407(3):883–897.
24. Peterson BL, Couper FJ. Concentrations of AB–CHMINACA and AB–PINACA and Driving Behavior in Suspected Impaired Driving Cases. *J Anal Toxicol*. 2015;39(8):642–647.
25. Karinen R, Tuv SS, Oiestad EL, et al. Concentrations of APINACA, 5F–APINACA, UR–144 and its degradant Product in Blood Samples From Six Impaired Drivers Compared to Previous Reported Concentrations of Other Synthetic Cannabinoids. *Forensic Sci Int*. 2015;246:98–103.
26. Gandhi AS, Zhu M, Pang S, et al. The First Characterization of AKB–48 Metabolism, a Novel Synthetic Cannabinoid, Using Human Hepatocytes and High–Resolution Mass Spectrometry. *AAPS J*. 2013;15(4):1091–1098.
27. Thomsen R, Nielsen LM, Holm NB, et al. Synthetic cannabimimetic agents metabolized by carbxylesterases. *Drug Test Analysis*. 2015;7(7):565–576.
28. Banister SD, Moir M, Stuart J, et al. Pharmacology of Indole and Indazole Synthetic Cannabinoid Designer Drugs AB–FUBINACA, ADB–FUBINACA, AB–PINACA, ADB–PINACA, 5F–AB–PINACA, 5F–ADB–PINACA, ADBICA, and 5F–ADBICA. *ACS Chem Neurosci*. 2015;6(9):1546–1559.
29. Takayama T, Suzuki M, Todorokia K, et al. UPLC/ESI–MS/MS based determination of the metabolism of several new illicit drugs, ADB–FUBINACA, AB–FUBINACA, AB–PINACA, QUPIC, 5–QUPIC, and alpha–PVT by human liver microsome. *Biomedical Chromatography*. 2014;28(6).
30. Debruyne D, Le Boisselier R. Emerging drugs of abuse: current perspectives on synthetic cannabinoids. *Substance Abuse and Rehabilitation*. 2015;6:113–129.
31. Hsin–Hung Chen M, Dip A, Ahmed M, et al. Detection and Characterization of the effect of AB–FUBINACA and its metabolites in a Rat Model. *J Cell Biochem*. 2015;117(4):1033–1043.
32. Vikingsson S, Josefsson M, Green H. Identification of AKB–48 and 5F–AKB–48 Metabolites in Authentic Human Urine Samples Using Human Liver Microsomes and Time of Flight Mass Spectrometry. *J Anal Toxicol*. 2015;39(6):426–435.
33. Westin AA, Frost J, Brede WR, et al. Sudden Cardiac Death Following Use of the Synthetic Cannabinoid MDMB–CHMICA. *J Anal Toxicol*. 2015;40(1):86–87.

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