



A New Synthetic Cannabinoid Substance, AB-CHMINACA: Review Article

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Abstract

The synthetically new illicit drugs which are called New psychoactive substances (NPS) are the calamity of the modern era. Their danger is much more than the natural drugs of abuse and at the same time, they cannot be detected on regular drug screens making diagnosis very difficult. The number of NPS is growing very fast making their detection more complicated. Another challenge is that their health effects are not well studied and cannot be predicted. Synthetic cannabinoids (SCs) are the most prevalent group in all available NPS. One recent member of the SCs group is AB-CHMINACA. This review article summarizes the available data about AB-CHMINACA. The obtained data were summarized under the following subtitles; historical background, chemical structure, classification, physical characters, pharmacokinetics and pharmacodynamics, toxicity, methods of detection, the magnitude of the problem, and the situation in Egypt. The reviewed studies reveal that AB-CHMINACA like other SC substances are considered toxic with high liability for dependence. Most of the available studies are case reports. The available literature is lacking in specific organ pathology and well-structured toxicity studies.

Keywords: AB-CHMINACA, Cannabinoids, NPS

Introduction

New psychoactive substances (NPS) are considered a major health threat and a medico-legal challenge all over the world. Although they are gaining the attention of health workers and police authorities, still the information about their health hazards is insufficient. Another challenge is the speed at which new substances appear making researchers take

the responsibility of evaluating the risk and detecting new substances. This helps authorities banning their trading and consumption^[1]. Classification of NPS is based on their effects compared to the old drugs of abuse. They include Synthetic cannabinoids, Synthetic Cathinones, Synthetic opioids, benzodiazepine analogs, and many others.^[2]

Synthetic cannabinoids (SCs) are substances that are created in the lab to give the same psychoactive action as tetrahydrocannabinol (THC), the main active substance in Cannabis. Cannabis is the most widely used substance of abuse worldwide, which is legally banned in most countries. SCs may have chemical structures related to THC, but most of them have different structures making them undetectable by usual screening methods.^[3] They emerged in the drug market as first, second, and most recent third-generation substances.^[4]

Material and methods

Searching the available literature for all types of articles: review articles, observational studies, and experimental studies. The used search engines were google scholar and Egyptian Knowledge Bank. The used keywords: AB-CHMINACA, synthetic cannabinoids, THC, and Strix in Egypt. The revised data were summarized and arranged under the following subtitles: historical background, chemical structure, classification, physical characters, pharmacodynamics and pharmacokinetics, toxicity, methods of detection, the magnitude of the problem, and the situation in Egypt.

Historical background

The plant cannabis Sativa is the most popular plant for recreational purposes for many centuries. There are many active substances isolated from this plant, the major one is tetrahydrocannabinol (THC).^[3] Cannabis is banned in most countries including Egypt. However, a small number of countries still have legal use of cannabis as medicine for example Canada, Netherlands, Spain, Israel, and some states in the United States. The only legally prescribed cannabinoid medications are Nabilone, Dronabinol, and THC-cannabidiol mixture. They are pre-

scribed for selected cases as those with severe vomiting associated with anticancer chemotherapy, severe chronic pain, spasticity, and control marijuana withdrawal symptoms. However, these medications still have abuse potential that makes their use very limited [5and6] Many researchers tried to synthesize substances that act on the cannabinoid receptors without the side effects of Δ^9 -THC. The beginning was in the late 1970s and early 1980s.^[7] The results of the research showed that these substances have adverse effects, and they never found their way to a commercial drug.^[8]

In the early 2000s, new illicit substances emerged in the form of herbal mixtures. A few years later chemical analysis showed it was a mixture of new SC substances. These substances were added to schedule I for drug control this stimulated the factories of the illicit drug market to create other new substances going around in a circle of banning and synthesizing new drugs.^[9]

In 2009, the UNODC stated that SCs are the most reported NPS in the illicit drugs market. The number of SC substances that were reported in 2009 was 31. The number increased to reach 154 in 2013. As a result of the rapid emergence of new substances, synthetic cannabinoids are still the most reported substance in the NPS group.^[10]

AB-CHMINACA is a new SC substance. It was reported by Pfizer as a trial for a commercial drug, but the project failed due to the development of side effects.^[11] In 2013, AB-CHEMINACA was first detected in ER cases of acute intoxication as a new illicit drug.^[12]

Chemical structure and Classification

Chemical structure is shown in Figure (1). AB-CHMINACA is an abbreviation

for its chemical name “N-[(2S)-1-amino-3-methyl-1-oxo-2-butanyl]-1-(cyclohexyl-methyl) -1H- indazole-3-carboxamide”^[13].

According to structural relation to THC, AB-CHMINACA is an SC that has a chemical structure not related to THC. So, it is considered non-classical in its chemical structure.^[3] classification according to its relation to the SC family, AB-CHMINACA is an Indazole carboxamide derivative of the group Naphthylmethylindoles.^[13] Regarding its emergence in the illicit drug market, AB-CHMINACA is a third-generation SC.^[4, 14]



Figure (1): chemical structure of AB-CHMINACA^[13].

Physical characters

Available preparations: AB-CHMINACA and other cannabinoids are prepared in the lab as crystal or powder substances. The substance is dissolved in organic solvent then the solution is sprayed over other herbs that may be inactive substances or upon cannabis itself to give stronger effects. The herbs and the substance upon it are usually smoked to give effects like cannabis. Packages are commonly labeled as herbal incense, not for human use Figures (2), this is the commonest form.^[3] Another form is the c-liquid for an electronic cigarette.^[9] Also,

the pure form itself is sold as it is and reported cases that had been found to have the substance in their stomach suggesting oral administration^[15] Other rare preparations are soaked paper and letters with the substance that was reported as a drug-smuggling method for prisoners in the UK.^[16]



Figure (2): Different packages of SC labelled as not for human consumption^[36].

Pharmacokinetics

The most common route of administration is inhalation via water pipe, bong, cigarette, or blunt. Other routes have been also recorded as vaporized administration, oral and even rectal administration.^[17]

Theoretically, the effect can be obtained as small as 0.5-1 mg if smoked. The dose is larger if ingested due to decreased oral bioavailability.^[18] However, the real consumption dose is highly variable as there is no precise amount is applied to each package and the amount received peruse cannot be predicted. The absorption across alveolar membranes is assumed to be very rapid that the onset of action begins within few minutes.^[19]

AB-CHMINACA is rapidly distributed to different body organs as Pancreas, ad-

ipose tissue, kidney, liver, heart muscles, brain, lung, and spleen. It has a high affinity to adipose tissue.^[20] AB-CHMINACA also can be detected in the hair of abusers.^[21and22]

AB-CHMINACA is rapidly metabolized.^[23] In vitro and in vivo studies showed 26 metabolites of AB-CHMINACA shown in Figure.(3) The main metabolic reaction is hydroxylation by cytochrome p450. Another pathway is carboxylation by amidase and glucuronidation.

The parent drug is lipophilic, so it is present to a lower extent in the urine. Most metabolites of AB-CHMINACA are detected in urine.^[14]

Although studies are limited, there is evidence of obstetric complications and fetal affection on the use of synthetic cannabinoids during pregnancy. Eclampsia, craniofacial anomalies, and withdrawal symptoms in the newborn were reported.^[24and 25]

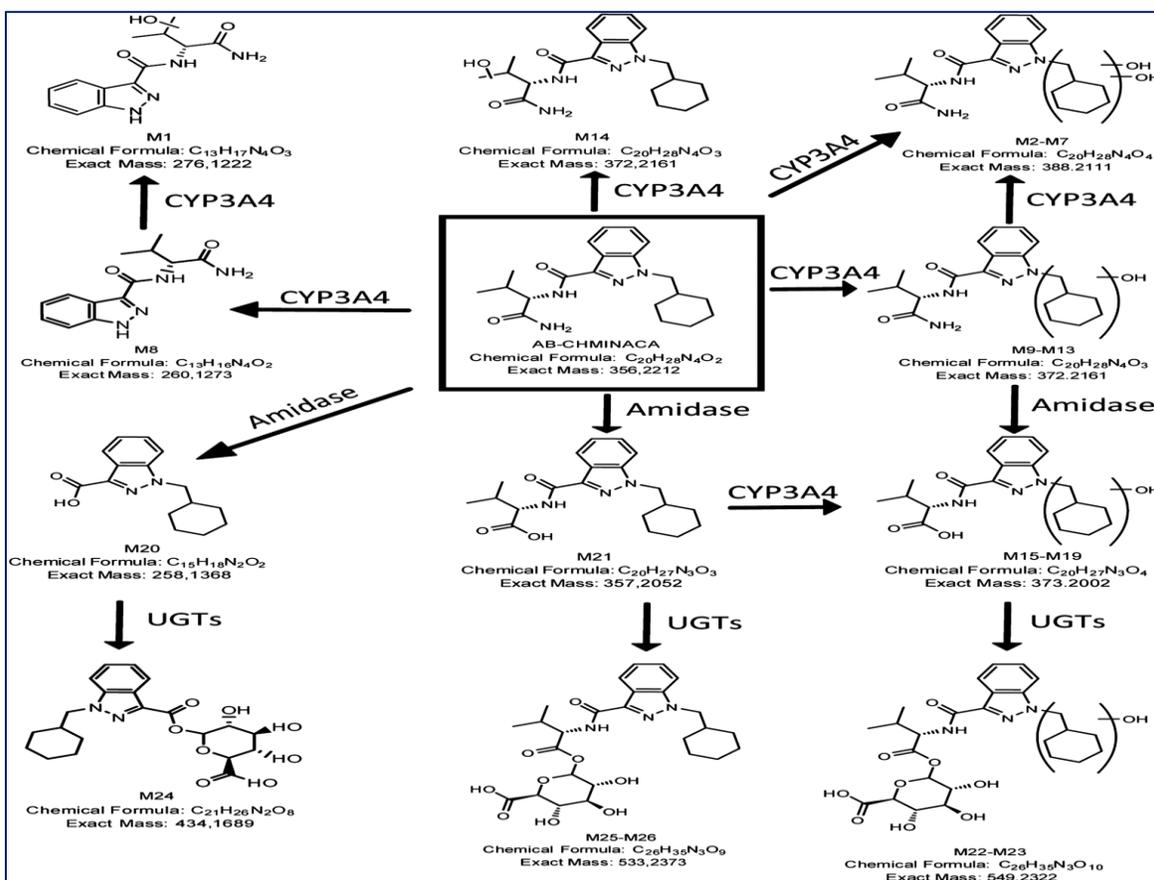


Figure (3): Metabolic pathways of AB-CHMINACA ^[15].

Pharmacodynamics

AB-CHMINACA acts through the ordinary cannabinoid receptors, CB1 and CB-2. CB1 receptors are primarily found in the central and peripheral nervous systems. CB1 is also found at a lower extent

in other tissues as immune cells, testes, heart, and blood vessels. On the other hand, CB2 receptors are present outside the nervous system, mainly in cells of the immune system and to a lesser extent

in hematopoietic cells and CNS.^[7] However, other receptors are involved but to a lesser degree.^[3] These other receptors are responsible for the non-CB1/CB2 actions of cannabinoids. However, the minor actions by other receptors are not evoked by all types of cannabinoids.^[26]

Although THC and other SCRA all are acting through the same receptors, there are differences in their actions due to the presence of multiple ligands and pathways of intracellular signaling on stimulation of cannabinoid receptors.^[27] This is a promising research area, still a window to develop an SCRA that has desired medical action without the undesired side effects.^[28]

Potency

In general, SCs are far more potent than THC. THC is considered a partial agonist while most SCs are full agonists.^[29] In vitro, AB-CHMINACA was tested for binding to CB1 receptors, and it was found to be a full agonist. Also, it was found that AB-CHMINACA has potency 11 to 58 times more than THC in the different components of the mouse tetrad test.^[30]

Pharmacological actions and toxicity

Acting on the same receptors, SCs have actions like THC. CB1 receptors are responsible for the anti-nociceptive effects that control neuropathic pain and the psychotropic effects of THC as well. While CB2 receptors are responsible for immune response mediated by THC.^[31and 32]

The clinical picture of acute toxicity of AB-CHMINACA is like other SCs. Many studies and case reports are available describing the acute toxic effects observed in ER patients. The most common presentation is neuropsychiatric abnormalities and the most serious is cardiop-

ulmonary complications. Also, GIT manifestations are very common. Other system affection includes acute kidney injury and acute liver failure. Clinical presentation includes excitation, depression, agitation, psychosis, convulsions, hyperemesis, hypotension or hypertension, infarction, stroke, respiratory depression or tachypnea, lung edema, visual disturbance, suicidal behavior, and even death from direct toxicity to body organs.^[9and33] The toxic dose in humans is unknown. Even animal studies are inadequate regarding toxicity. There is no available data about the LD50 of AB-CHMINACA. However, LD50 of THC and other cannabinoids suggesting low lethality.

There is no specific treatment is known till now, only symptomatic, and supportive measures according to the case or treatment of associated consumption.^[15] Regarding the abuse potential, no studies are evaluating the potential liability of AB-CHMINACA to produce dependence and withdrawal symptoms on discontinuation of the drug. Studies on other synthetic cannabinoid substances proved the development of withdrawal symptoms in abusers mainly anxiety and tachycardia. Administration of THC did not relieve the symptoms probably due to adulteration or co-ingestion. There are no specific measures to control the withdrawal symptoms, but they can be calmed using benzodiazepines.^[34]

Manner of death and intoxication

Most cases are accidental overdoses in patients with a history of drug abuse.^[35] Less frequent are suicidal cases with associated depression or other problems.^[15]

Methods of detection

Because of different chemical structures, Synthetic cannabinoids cannot be cross-

reacting with THC detection kits. Chromatography techniques are preferred for the identification and detection of many drugs.[36] AB-CHMINACA and its metabolites were successfully detected in urine, blood, hair, and different tissue samples using Gas-chromatography mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), liquid chromatography time of flight mass spectrometry (LC-TOFS).[37and38]

Magnitude of the problem

It is difficult to estimate the total consumption of synthetic cannabinoids all over the world because not all countries have a good surveillance system. However, some countries have annual reports on the consumption of drugs of abuse. As mentioned by United Nations Office on Drug and Crime (UNODC), from data collected from 29 countries, the cross-sectional analysis represents the problem at interval time between 2016-2018, half of the reported new psychoactive substance (NPS) was synthetic cannabinoids and opioids together while Synthetic cannabinoids (Synthetic cannabinoid receptor agonists or SCRA) were a little bit higher than opioids.[39]

The situation in Egypt

As a part of the global problem, Egypt suffers the same growth rate of NPS consumption. There is no national surveillance to estimate the actual total number of NPS abusers. However, there are few separate epidemiologic studies on different population groups indicating that the problem is present and growing up.

Hashim et al., made surveillance in five different faculties at Cairo University to evaluate the prevalence of NPS among students. Their study showed that three fourth of abusers are male students, 6.8% consumed stox and 0.5% consum-

ed voodoo. Also, there was a strong relationship between tobacco and hashish smoking and strong usage.[40]

In another study, the emergency cases admitted to Ain-Shams University hospital, a poison control center were assessed for SC exposure in the interval of 18 months from the beginning of the year 2018. The total number of cases was more than five hundred patients and 96% of them were males. Strix consumption was the most prevalent, 70% of cases, followed by voodoo, then other substances.[41]

Regarding legislation, drugs with abuse potential are categorized into five schedules. These schedules are arranged from I to V according to the abuse potential of the contained drugs. Schedule I drugs have the highest liability of abuse while schedule V drugs have the least. Also, drugs of schedule I have no medical role and their trade is illegal. However, drugs in schedules from II to V have medical uses that can be legal in certain situations. In Egypt, AB-CHMINACA was added to schedule I controlled substances by the Controlled Substance Act 440, 2018.[42]

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