

Cannabinoids and the challenges of new synthetic derivatives

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Abstract

Of all illicit psychoactive substances, cannabis is the most widely consumed drug (4% of the world's population, annually). Since 2004, we have been dealing with a new major international problem, represented by cheap synthetic cannabinoids with an extremely diverse chemical structure that are not regulated by law. In recent years, a new chapter dedicated to semi-synthetic cannabinoids has appeared in response to legislative reforms in the US. HHC, HHC-O, HHC-P and H4CBD are only some of the drugs in this new class. The "Dream Factory" file (over 100,000 vaping devices and edibles that contained semi-synthetic cannabinoids sold to the general population in Romania) is an excellent example of legal and regulatory deficiencies regarding new psychoactive substances consumption. From the studies available and anecdotal reports from consumers, HHC provides the sensation of pleasure and relaxation, similar to the natural analogue (THC-like effects). In vitro testing of the affinity of Δ9-THCP (semi-synthetic cannabinoid) for CB1 demonstrated a 30-fold higher value than Δ9-THC, which means a higher potency and risk of adverse effects. The use of synthetic cannabinoids is correlated with a higher incidence of psychotic disorders (acute/transient, persistent/chronic "spiceophrenia" or relapses/exacerbations of pre-existing psychotic disorders). Like other new psychoactive substances, semi-synthetic and synthetic cannabinoids cannot be detected using standard toxicology tests. Only liquid or gas chromatography mass spectrometry can be used for these drugs (LC-MS/ GC-MS). The treatment of intoxication is nonspecific, supportive and symptomatic, preferably multidisciplinary. Taking into account the availability and consumption trends in Romania, the identification and monitoring of semi-synthetic and synthetic compounds represents a legal, pharmacological and toxicological challenge. Sustained efforts to investigate HHC and related semi-synthetic and synthetic compounds are needed to better describe these molecules and to be able to train medical personnel to address the disorders caused by these new substances. The health risks are still unknown, and severe adverse effects, accidents and fatal overdoses can occur.

Keywords: cannabis, synthetic cannabinoids, semi-synthetic cannabinoids, psychotic disorders, "Dream Factory" file, treatment of intoxication

Rezumat

Dintre toate substanțele psihoactive ilicite, canabisul este cel mai consumat drog (4% din populație la nivel mondial, anual). În ultimii ani a apărut un nou capitol dedicat cannabinodelor semisintetice, ca răspuns la reformări legislative în SUA, unde s-a decis cultivarea de cânepă la nivel industrial. Derivații semisintetici (care respectă structura de bază a THC-ului și sunt prezenți în mod natural și pot fi, de asemenea, sintetizați în laborator) pot fi produși din CBD extras din plantele de canabis cu conținut scăzut de THC („light cannabis”). Se explică, astfel, apariția dosarului „Fabrica de vise” – comercializarea de dispozitive electronice de vapat și diverse dulciuri (prăjituri, jeleuri, drajeuri) care conțineau canabinoizi semisintetici (HHC, HHC-P, HHC-O, H4CBD, THC-P) și canabinoizi naturali (THC). Canabinoizii sintetici prezintă, pe lângă efectul euforizant asemănător THC, și o predispoziție către tulburări psihotice, manifestate în special prin simptome pozitive (delir, halucinații și gândire sau comportament dezorganizat). Intensitatea simptomatologiei este dependentă de doza utilizată. Ca și celelalte substanțe psihoactive noi, canabinoizii semisintetici și sintetici nu pot fi detectați utilizând testele uzuale toxicologice. Pentru identificarea lor, se poate utiliza doar spectrometria de masă prin cromatografie lichidă sau cu gaz (LC-MS/ GC-MS). Tratamentul intoxicației este nespecific, de tip suportiv (cu susținerea funcțiilor vitale și a echilibrului hidroelectrolitic) și simptomatic, de preferat multidisciplinar. În contextul actual și luând în considerare particularitățile disponibilității și trendului de consum în România, identificarea și monitorizarea compușilor semisintetici și sintetici reprezintă o adevărată provocare legală, farmacologică și toxicologică. Sunt necesare eforturi susținute pentru investigarea HHC și a compușilor înrudiți semisintetici și sintetici, pentru a descrie mai bine aceste molecule și pentru a putea instrui personalul medical asupra abordării tulburărilor provocate de aceste noi substanțe. Riscurile pentru sănătate sunt încă necunoscute, putând apărea efecte adverse severe, accidente și supradoze cu efect letal.

Cuvinte-cheie: canabis, canabinoide semisintetice, canabinoizii sintetici, tulburări psihotice, dosarul „Fabrica de vise”, tratamentul intoxicației

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Cannabis, semi-synthetic and synthetic cannabinoids

Of all illicit psychoactive substances, cannabis is the most widely consumed drug (4% of the world's population, annually). Cannabinoids are chemical compounds that interact with CB1 and CB2 receptors⁽¹⁾. The human body is capable of synthesizing its own cannabinoids called endocannabinoids (anandamide and 2-arachidonoylglycerol; 2-AG) and together with the two receptors form the endocannabinoid system⁽²⁾.

Cannabis, a naturally occurring drug, comes in the form of dried leaves or buds from the *Cannabis sativa* plant⁽¹⁾. This plant has over 500 chemical compounds, with over 100 cannabinoids identified. Due to the need to meet safety standards with full description of the active substance with pharmacokinetics, pharmacodynamics properties, therapeutic dose, toxic dose, beneficial effects, adverse effects and drug interactions, marijuana has never been accepted by the FDA. In contrast, the pure cannabinoid compounds Δ9-THC (Δ9-tetrahydrocannabinol) and CBD (cannabidiol) as well as synthetic analogues that respect their chemical structure (dronabinol, nabilone) are FDA-approved in the treatment of various disorders (Table 1)⁽²⁾.

Δ9-THC, first identified in the early 1960s by Raphael Mechoulam, is the main cannabinoid compound responsible for psychoactive effects. CBD is the constitutional isomer of Δ9-THC that is inert psychoactive (or weakly psychoactive) and is the second most abundant cannabinoid after Δ9-THC in *Cannabis sativa*⁽³⁾.

Table 1

FDA approved cannabinoids in the treatment of various disorders

Purified THC/CBD	Therapeutic effects (FDA approved)
Dronabinol (synthetic THC)	Chemotherapy-induced nausea and vomiting Orexigenic (for patients with AIDS)
Nabilone (synthetic THC)	Chemotherapy-induced nausea and vomiting
Nabiximols (purified ~1:1 THC/ CBD)	Spasticity in multiple sclerosis
Epidiolex (purified CBD)	Lennox-Gastaut and Dravet syndrome

After the identification of Δ9-THC as the main psychoactive component in cannabis, the chemical and pharmacological industry searched for more potent analogues. These synthetic compounds (over 250 currently) are produced in illegal laboratories and sold recreationally. Their use carries major risks compared to the natural analogue Δ9-THC which must be consumed in very high doses to produce severe adverse effects⁽³⁾.

Synthetic cannabinoids are preferred by young males, who choose these substances over the natural analogue due to low cost, legal status, increased avail-

ability of the substance and the lack of detection with standard drug tests⁽⁴⁾. This category of substances is used especially by homeless people and inmates⁽⁵⁾.

Since 2004 we have been dealing with this major international problem, cheap synthetic cannabinoids with an extremely diverse chemical structure that are not regulated by law. In recent years, a new chapter dedicated to semi-synthetic cannabinoids has appeared in response to legislative reforms in the USA⁽⁶⁾. In 2018, the US approved the bill to legalize cannabis with a low THC content (maximum 0.3%, also known as "light cannabis") which is a legal substitute for cannabis with a high THC content ("skunk")⁽³⁾.

This is the starting point for a new category of legal drugs: semi-synthetic cannabinoids. Unlike the synthetic cannabinoid agonists found in "Spice" or "Shop" products, semi-synthetic derivatives (THC-like structure, naturally occurring, and which can also be synthesized in the laboratory) can be produced from CBD extracted from light cannabis⁽⁷⁾.

The EMCDDA 2023 report reveals that, last year, in the category of new psychoactive substances (930 currently monitored), synthetic cannabinoids represent approximately 60% of new substances introduced to the market (24 new synthetic cannabinoids out of a total of 41 new psychoactive substances in 2022). From the category of synthetic cannabinoids, there are first reports of semi-synthetic cannabinoid derivatives (Table 2)⁽⁸⁾.

Table 2

Semi-synthetic cannabinoid derivatives

HHC	Hexahydrocannabinol
HHC-O	Hexahydrocannabinol-acetate
HHC-P	Hexahydrocannabiphorol
H4CBD	Tetrahydrocannabidiol

In the 15-34 years old age group, Romania has the highest prevalence of new psychoactive substance users in Europe (5.1%). The EMCDDA issued a warning (in 2021) about the presence of cannabinoids in food products (especially sweets with cannabis extract) that can be consumed by the general population without restrictions, including children⁽⁸⁾.

On 19 September 2023 it took place the operation known as the "Dream Factory", where several people who constituted an organized criminal group responsible for the production and distribution of new psychoactive substances in 23 counties in Romania were detained. It is estimated that, over a period of approximately one year, the company responsible for these acts, which was based in Iași County, produced over 100,000 electronic vaping devices and various sweets (cakes, jellies) that contained semi-synthetic cannabinoids (HHC, HHC-P, HHC-O, H4CBD, THC-P) and natural cannabinoids (THC)⁽⁹⁾.

Although the compounds have been present on the drug market for over a year, Romania has not yet

adopted a clear legal attitude towards semi-synthetic cannabinoids, unlike other countries in Europe that have banned HHC starting in mid-2023.

This is one of the most important moments in the history of legal drugs since the introduction of “Spice” 15 years ago. The consumption and availability are probably much higher than those reported by the EMCDDA⁽⁷⁾.

Like THC, HHC provides the sensation of pleasure and relaxation sought by consumers. Researching the few studies currently available and anecdotal reports from consumers, HHC appears to have effects similar to the natural analogue (data in the literature is not yet sufficient to confirm this and extrapolations from synthetic analogues will be made)⁽¹⁰⁾.

In Europe, there is an increased interest in this semi-synthetic derivative both from “old” cannabis users and from inexperienced users, due to the effects, the uncertain legal status, the increased availability, and the attractive price. From an organoleptic, visual and olfactory point of view, cannabinoids are identical⁽⁷⁾.

Cannabimimetics were synthesized with the aim of analyzing the endocannabinoid system, the most famous compound being JWH-018 (AM-678, component of “Spice”), named after the chemist John W. Huffman, for the purpose of toxicological detection of Δ^9 -THC (military personnel, performance athletes).

Natural and designer HHC was first described and synthesized by Adams in 1940, entering the illegal drug market in the US and Europe in late 2021^(11,12). It can be consumed by inhalation, ingestion (“edibles”) or sublingually, representing a legal, undetectable and cheap alternative to THC^(13,14).

HHC is the first semi-synthetic cannabinoid derived from CBD reported in the European Union and monitored as a new psychoactive substance (from 21 October 2022). There are currently few data on the pharmacological properties of HHC and the prevalence of use⁽³⁾.

HHC has cannabimimetic effects, but with a lower potency than Δ^9 -THC⁽¹⁴⁾. Through the cyclization process, CBD is transformed into a mixture of Δ^8 -/ Δ^9 -THC. The next step is catalytic hydrogenation by which racemic HHC is obtained consisting of two epimers, (9R)-HHC and (9S)-HHC^(6,14).

Using a hydrogen atom transfer reduction model, (9R)-HHC is obtained as the major product. The catalytic hydrogenation process results in variable proportions between the two diastereomers⁽¹²⁾.

(9R)-HHC (“equatorial” methyl isomer) and (9S)-HHC (“axial” methyl isomer) thus represent derivatives of Δ^9 - and Δ^8 -THC. These two compounds are still poorly studied and occur naturally in hemp seeds in small amounts. Like THC, HHC is a partial agonist at CB1 and CB2 cannabinoid receptors^(12,15).

Preclinical studies demonstrate that the receptor affinity and potency of the (9R)-HHC diastereoisomer is similar to that of Δ^9 -THC. (9R)-HHC exhibits THC-like pharmacological properties, compared to

the (9S)-HHC diastereoisomer which exhibits a lower potency. (9R)-HHC is 17 times more potent at the CB1 receptor and nine times more potent at the CB2 receptor than (9S)-HHC. The higher the diastereomeric ratio between the two compounds, the more pronounced are the psychoactive effects. Given that the purity of new psychoactive substances cannot usually be tested, there is a marked variability in the psychoactive effects of different HHC users^(6,12).

To test the cannabimimetic characteristics of a compound, the quadruple pharmacological test is used with the following parameters: spontaneous activity testing, catalepsy (immobility index), analgesic effect, and changes in rectal temperature. Cannabimimetic activity is suggested by decreased locomotor activity, catalepsy, analgesia and hypothermia^(3,16). This quadruple pharmacological test for cannabimimetic effects reveals that (9R)-HHC causes reduction in spontaneous activity (hypolocomotion), analgesia and hypothermia⁽³⁾. A recently discovered synthetic analogue of Δ^9 -THC, Δ^9 -THCP (Δ^9 -tetrahydrocannabiphorol), also exhibits the ability to induce hypomotility, analgesia, catalepsy, and rectal temperature reduction^(3,16). The potency of HHC in producing the tetrad of effects is lower than Δ^9 -THC or Δ^9 -THCP⁽³⁾.

The essential element for the biological activity of cannabinoids at the CB1 receptor is the length of the alkyl (unsaturated, “-R”) side chain⁽¹⁶⁾.

Basically, the potency of a cannabimimetic compound is dependent on the length of the side chain of the molecule (potency and side chain length are directly proportional). Thus, synthetic analogues such as Δ^9 -THCP, which has a 7-carbon side chain, will result in superior cannabimimetic effects than Δ^9 -THC (which has only five carbon atoms on the alkyl side chain in its structure). This fact increases the receptor affinity of Δ^9 -THCP for CB1 and, thus, the potency of the synthetic analogue. Studies have shown that Δ^9 -THC-O (Δ^9 -tetrahydrocannabinol acetate) is also more potent than Δ^9 -THC^(16,17). *In vitro* testing of the affinity of Δ^9 -THCP for CB1 demonstrated a 30-fold higher value than Δ^9 -THC. Δ^9 -THCP is at least as biologically active as Δ^9 -THC, but at lower doses⁽¹⁶⁾. Multiple homologues of Δ^8 -THC have also been synthesized that have more than five carbon atoms on the side chain and, implicitly, they have a much higher potency than Δ^9 -THC⁽¹⁶⁾.

Synthetic cannabinoids act not only on the endocannabinoid receptor system, but also on serotonin, acetylcholine, glycine and glutamate receptors. It is possible that the psychoactive effect of these compounds is also achieved through these secondary actions⁽⁴⁾.

Clinical, laboratory testing and treatment

ICD10-CM classifies these synthetic cannabinoids as other psychoactive substances without a clear definition (F19). ICD11 has a distinct chapter for synthetic cannabinoids (6C42, Table 3) which are described as various chemical compounds which exhibit potent agonistic ac-

tivity on the endocannabinoid receptor system⁽¹⁸⁾. Besides the THC-like euphoric effect, synthetic cannabinoids show a predisposition to psychotic disorders manifested mainly by positive symptoms (delirium, hallucinations and disorganized thinking or behavior). The symptoms of synthetic cannabinoid intoxication are similar with those of cannabis intoxication, presenting the same manifestations but with a higher prevalence for delirium and acute psychotic disorder (Table 4)^(5,18). The intensity of symptoms is dose-dependent. The effects desired by consumers are euphoria, tranquility, relaxation, perceptual distortions (“geometric/fractal figures”, “trailing”), hallucinations, altered state of consciousness, disinhibition, anxiolytic, sedative and antidepressant effects^(4,5).

Table 3

Symptoms of synthetic cannabinoid intoxication

Code	Diagnosis
6C42.0	Episode of harmful use of synthetic cannabinoids
6C42.1	Pattern of harmful use of synthetic cannabinoids
6C42.2	Synthetic cannabinoid addiction syndrome
6C42.3	Synthetic cannabinoid intoxication
6C42.4	Synthetic cannabinoid withdrawal
6C42.5	Delirium induced by synthetic cannabinoids
6C42.6	Psychotic disorder due to the use of synthetic cannabinoids
6C42.70	Affective disorder due to the use of synthetic cannabinoids
6C42.71	Anxiety disorder due to the use of synthetic cannabinoids
6C42.Y	Other specified disorders due to the use of synthetic cannabinoids
6C42.Z	Unspecified disorders due to the use of synthetic cannabinoids
6C41	Catatonia due to the use of substances or drugs

The adverse effects experienced by users are more intense with synthetic cannabinoids than natural cannabis, and there are also more emergency departments presentations⁽⁵⁾.

Psychotic disorders induced by synthetic cannabinoids can be acute/transient, persistent/chronic (“spiceophrenia”) or relapses/exacerbations of preexisting psychotic disorders⁽⁴⁾.

Vaping liquid can contain various substances, including synthetic and semi-synthetic cannabinoids ($\Delta 8$ -THC, $\Delta 10$ -THC, HHC), and vaping products and e-cigarettes can cause EVALI (E-cigarette or vaping use-associated lung injury)⁽¹⁹⁾.

Cannabimimetic compounds may also have therapeutic benefits. If $\Delta 9$ -THC is responsible for the psychoactive effects of cannabis, CBD is an antioxidant, anti-inflammatory and anticonvulsant compound, counteracting the negative effects of $\Delta 9$ -THC^(3,16). CBD is also thought to have neuroprotective, analgesic, anxiolytic and antipsychotic effects⁽¹¹⁾. Synthetic can-

nabinoids usually do not contain CBD and, therefore, they lack the protective effects of this compound^(4,5).

Natural, semi-synthetic and synthetic cannabinoids exhibit anti-tumoral properties through an anti-angiogenic (VEGF inhibitor) mechanism. Angiogenesis is an important regulatory step in tumor growth and dissemination. The mechanism is indirect through the peripheral cannabinoid receptors (CB2) which are located almost exclusively in the immune system⁽²⁰⁾.

Table 4

Synthetic cannabinoids disorders included in ICD-11 chapter

Domains	Signs and symptoms
Neuropsychiatry	Euphoria, memory and attention disorders, impaired judgment and reasoning, suicidal ideation, disorganized thinking, delusional (paranoid) ideation, perceptual distortions (sensation of floating, altered temporal perception), hallucinations, diminished social intelligence, affective disorders, dysarthria and psychomotor slowness, anxiety, psychomotor agitation, aggression and violence, increased appetite. Paraesthesia, vertigo, pallor, tinnitus, diaphoresis, tremor, ataxia, dysmetria, myoclonus, somnolence, syncope, nystagmus, convulsions, altered state of consciousness, confusional episodes, catatonia, coma.
Cardiovascular/cerebrovascular	Tachycardia, hypertension, hypotension, angina pectoris, arrhythmias, palpitations, myocardial ischemia, myocardial infarction, stroke.
Renal	Acute kidney injury.
Others	Conjunctival erythema, hypertonia, myalgia, rhabdomyolysis, hyperglycemia, hypoglycemia, dyspnea, mydriasis, respiratory acidosis, nausea, vomiting, serotonin syndrome.

Currently, HHC is being studied in the treatment of ocular hypotony and colon cancer⁽¹²⁾.

Like other new psychoactive substances, semi-synthetic and synthetic cannabinoids cannot be detected using standard toxicology tests. There are still no rapid immunoanalytical detection methods for these compounds^(3,6). Only liquid or gas chromatography mass spectrometry can be used to identify semi-synthetic and synthetic cannabinoids (LC-MS/GC-MS)⁽¹³⁾.

Drugs containing synthetic cannabinoids usually contain several types of substances from the same class or even substances from other pharmacological classes, which can lead to the risk of interaction between different psychoactive substances with a synergistic effect, abuse and alteration of the user's somatic status⁽⁴⁾.

The treatment of intoxication is nonspecific, supportive (vital functions and hydroelectrolytic parameters) and symptomatic, preferably multidisciplinary. There is no

antidote for synthetic cannabinoid intoxication⁽⁵⁾. For mild and moderate intoxication, patient's monitoring and adequate hydration are sufficient. Benzodiazepines are useful for anxiolysis and psychomotor agitation. For psychotic symptoms or psychomotor agitation and aggression, antipsychotics can be used (inconclusive data on the choice of antipsychotic, but clozapine and olanzapine are the most frequently used drugs). In severe cases, cardiovascular, cerebrovascular, neurological, psychiatric and renal disorders may be associated (comorbidities must also be treated)^(4,5).

There are no approved medications for synthetic cannabinoid withdrawal or addiction, but studies show relatively good results with baclofen and naltrexone⁽⁴⁾.

Discussion

Cannabis and its derivatives are extremely popular products due to their psychoactive effects, being sold both in stores and on the internet⁽³⁾. Most drugs are

found on the dark web and deep web which requires an "open-source" web browser capable of data encryption for protection and anonymity. Currently, however, there are sites even on the surface web where you can purchase cannabinoid compounds, both natural ("light cannabis") and semi-synthetic (HHC, HHC-O, TCHP and combinations of compounds) accessible to the general public⁽²¹⁾.

Taking into account the availability and consumption trends in Romania, the identification and monitoring of semi-synthetic and synthetic compounds represents a legal, pharmacological and toxicological challenge. Sustained efforts to investigate HHC and related semisynthetic and synthetic compounds are needed to better describe these molecules and to be able to train medical personnel to address the disorders caused by these new substances. The health risks are still unknown, and severe adverse effects, accidents and fatal overdoses can occur⁽¹⁴⁾. ■

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