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Pharmacotherapy and pharmacotoxycology of synthetic cannabinoid receptor agonists

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Abstract Cannabinoid use is increasing at an alarming rate. The easy way to procure them, the perception of their legality contributes to the increased use and popularity of synthetic cannabinoids (SC). Although laws and regulations of these substances have been implemented in many countries, the production of new types of synthetic cannabinoids it happens quickly. The primary psychoactive ingredient in cannabis is Δ 9-tetrahydrocannabinoid (THC), which partially binds to cannabinoid receptors, while SC are potent and full agonists of these receptors. Increased medical interest in these substances has led to the development of various drugs based on SC: dronabinol, Marinol®, a synthetic analogue of THC, approved for the treatment of nausea and vomiting in cancer and HIV patients. This paper is a review of the bibliography and an overview of SC, their pharmacotoxicology and therapeutic use.
Key words : pharmacotherapy, pharmacotoxycology, Δ9-Tetrahydrocannabinol (THC), new psychoactive substances (NPS), CB_1, synthetic cannabinoid (SC).

1. Introduction

The therapeutic ingredients of the *Cannabis* plant are concentrated mainly in the female flowers of the plant, the so-called "resin". Medicinal properties are related to content of cannabinoids, terpenophenolic compounds. To date, nearly one hundred and fifty different cannabinoids have been identified. Among them we can identify the two major components in the *Cannabis* plant: the main psychoactive compound, THC and the non-psychoactive compound, cannabidiol (CBD) [1]. Hemp has gained substantial attention in recent years due to the fact that an increasing number of countries legalize cannabis for medicinal and recreational use. Cannabis has a very complex matrix, contains many secondary cannabinoids and terpenes, is a generic term attributed to various forms of drugs obtained from the species *Cannabis sativa (var. indica)* [2], [3], [4].

Taking into account the current legislation, there are slight differences in the amounts of THC allowed in hemp preparations, ranging from 0.05 to 0.6%. As a result, if the plant contains THC shows a high illicit use and interest, consequently, its cultivation is prohibited by national laws [5]. Among the illicit preparations of *Cannabis*, we can mention the

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following: marijuana (a mixture of leaves, flowers and seeds of the hemp plant), hashish (obtained from unfertilized buds) and also oils that can be easily prepared [6].

Romania, among many other countries, has been experiencing a worrying increase in substance abuse use over the past 10 years. Known as "ethnobotanical", new psychoactive substances (NPS), by their scientific name, are becoming increasingly popular, endangering a large part of the population. Described by researchers and specialists as extremely powerful and harmful drugs, NPS are known by the population as "legal highs" [7] and have become readily available in recent years, endangering the population. Some of these compounds target cannabinoid receptors and are called synthetic cannabinoids (SC) [8, 9, 10] and they can be purchased via the Internet.

Due to the addictive character and especially because many young people fell ill or even died, Law nr. 194/2011 which prohibited Possession and Use of NPS [11]. However, the text of the Act is yet to be amended which is why NPS has returned to the spotlight and more research is needed to better understand the possible effects of NPS, the mechanism of action of SC [12]. Several studies have investigated the mechanism of action for SC. According to them, stimulants such as cannabinoids interact with monoamine transporters and especially induce sympathomimetic adverse effects [13, 14]. Because of their similarity to amphetamines and their action on multiple adrenergic and serotonergic receptors, the use of SC is mainly associated with sympathomimetic toxicity manifested as agitation, tachycardia, hypertension [8, 15, 16] and less often with lower levels of consciousness, hallucinations, hyponatremia, chest pain, palpitations and nausea. Also, SC can cause damage to skeletal muscle [17]. Similar to Δ9-tetrahydrocannabinol (THC), the main psychoactive constituent in cannabis, SC act on cannabinoid receptors, CB_1 and CB_2, and cause cannabimimetic effects [8, 9, 18-20].

The endocannabinoid system is involved in various physiological functions, including cognition, behavior, memory, motor control, pain sensation, appetite, cardiovascular parameters, gastrointestinal motility, and immunoregulation. The psychoactive effects of SC are associated with a less desirable profile and more severe adverse effects compared to cannabis. The most severe common adverse effects of SC include agitation, drowsiness, dizziness, confusion, hallucinations, high blood pressure, tachycardia, chest pain, nausea, and vomiting [8, 18-20].

2. **Synthetic cannabinoids**

Synthetic cannabinoids were originally designed for research into the endogenous cannabinoid system (ECS). Synthetic cannabinoids are referred to as substances with structural features that allow binding to one of the known cannabinoid receptors, namely CB_1 and CB_2 in human cells. Synthetic cannabinoids, as defined above, could encompass a wide variety of structurally different compounds, with the possibility of further structural changes, namely analogues and derivatives, which could also have affinity for one of the cannabinoid receptors [8, 9, 20].

Past studies have demonstrated the use of cannabis to increase appetite, and this trend was called into question when the CB_1 receptor was shown to play a role in appetite control and body weight regulation. While the obese population faces the problem of weight loss, another segment of the population, such as cancer or HIV patients, faces anorexia. Administration of dronabinol (synthetic THC, known as Marinol® and approved for the treatment of nausea and vomiting in oncology and HIV patients) is associated with a steady improvement in appetite. It has been found to be safe and effective for combating anorexia in HIV patients, being

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associated with increased appetite, improved mood and combating emesis. In clinical trials, weight was held constant in patients receiving dronabinol, while patients receiving placebo lost weight. Two synthetic CB_1 agonists are currently on sale, Marinol® (dronabinol, synthetic Δ9–THC) and Cesamet® (nabilone, synthetic analogue of Δ9–THC). Dronabinol is used as an appetite stimulant in patients with AIDS syndrome and for nausea and vomiting associated with oncological treatments [8, 9, 20-22].

Synthetic cannabinoids are a class of "designer drugs" that bind to the same receptors to which endocannabinoids (eCBs) attach. Synthetic cannabinoids are derivatives of Δ9-THC produced under laboratory conditions that have been approved by the Food and Drug Administration (FDA) for various uses [8, 20-22].

Synthetic cannabinoids have a greater affinity for CB_1 receptors than natural cannabinoids and produce stronger effects. Unlike natural cannabis, they do not contain CBD, and some are also active against serotonin (5-HT) receptors. The binding of SC to cannabinoid receptors can lead to agonist effects (partially), inversely agonists or antagonists. Synthetic cannabinoids of interest in the forensic scientific context are mainly compounds that show sufficient affinity for the CB_1 receptor and show agonistic or partially agonist activity, and the effects are usually mediated by agonist stimulation of this type of receptor. Activation of CB_1 receptors decrease cyclic adenosin monophosphate (cAMP) activity, and disclose cannabimimetic responses [8, 9, 20].

Synthetic cannabinoid agonists interact with voltage-gated ion channels and consequently inhibit K, Na+, and P/Q type Ca^{2+} channels [7]. While all synthetic cannabinoids are associated with greater harm than natural cannabis, new generations of SC are associated with increased levels of harm compared to previous generations. In their pure state, synthetic cannabinoids are either solids or in the form of oils. Synthetic cannabinoids are usually sprayed on to inert plant materials [8, 20, 21, 23]. However, they can theoretically be sprayed on to any material, and there are reports of SC sprayed onto paper or textiles, particularly to avoid detection. Other forms have also been reported, including:

- similar products to cannabis resin;
- powder, injectable forms and liquids for electronic cigarettes;
- in mixtures containing stimulants, hallucinogens and sedatives/hypnotics, and in "ecstasy" tablets;

Products containing SC are often very varied, both in chemical content and concentration.

3. Effects of consuming synthetic cannabinoid receptor agonists

The desired effects and motivation for consumption include: a strong sedative effect and the possibility of consumption without detection due to the absence of toxicological tests in clinical centres.

In some European countries, SC are mainly used by vulnerable groups, including homeless people and people in places of detention. The duration of effect of various SC compounds can range from 1-2 hours for some compounds to 6-8 hours for others. Synthetic cannabinoids produce subjective effects unique and different from those of cannabis. Studies have reported hangover effects as well as other negative effects not attributed to natural cannabis [8, 20, 24, 25].

4.1 Acute intoxication following consumption of synthetic cannabinoid receptor agonists

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Synthetic cannabinoid pharmatoxicology is characterized by cannabis-like effects including psychosis and sympathomimetic effects, convulsions, hypertension, tachycardia, diaphoresis, hyperthermia, agitation, and combativeness. Some SC may be associated with serotonin syndrome. Research has reported that these SC would cause a number of other toxic effects, including acute kidney damage, and newer generations are associated with severe toxicity and deaths [10, 12, 13, 24, 25].

4.2. Acute psychological, cognitive and neurological adverse effects following consumption of synthetic cannabinoid receptor agonists

Symptoms of the acute phase (within the first 24 hours): symptoms of this phase include agitation or irritability, short-lived impairment of memory, restlessness, anxiety, confusion, changes in perception, and psychosis.

- Uncontrollable laughter, agitation, anger, sadness, flat affect, anxiety, panic attacks, persecution mania, auditory and visual hallucinations, changes in perception, depression and suicidal thoughts.
- Short-term and cognitive memory impairments, blocked thoughts, confusion, sleepiness and sedation;
- Numbness, tingling, dizziness, pallor, nystagmus, tinnitus, diaphoresis, tremor, convulsions, amnesia, decreased consciousness, syncope, catatonic states and coma. Temporary loss of vision and speech has also been reported [10, 12, 13, 24, 25].

The use of SC has been associated with psychosis, possibly with a higher risk of psychosis, than with natural cannabis. Psychosis related to SC has been associated with more significant agitation than would be expected from natural cannabis. There are reports of transient acute psychosis associated with taking SC, as well as reports that some people may experience psychosis that persists for weeks after acute intoxication [10, 12, 13].

4.3. Acute physiological effects of consumption of synthetic cannabinoid receptor agonists

Acute physiological harm associated with the consumption of SC include:

• Neuro-muscular and musculoskeletal effects: hypertonia, myoclonus, muscle convulsions, myalgia, rhabdomyolysis;

• Cardiovascular side effects: most prevalent side effects of SC include tachycardia, hypertension or hypotension. Patients can present with palpitations, chest pain or arrhytmia. In rare cases, synthetic cannabinoids have been suspected to induce myocardial infarction or even death. However coronary artery spasms can be presumably associated with other ingredients of SC–hypokalemia, myocardial ischemia, cerebrovascular accidents;

• Cardiotoxic effects: studies have reported that they are two or three times more likely to be associated with sympathomimetic effects, such as tachycardia and hypertension, than natural cannabis;

• Gastrointestinal side efects:

Synthetic cannabinoids can induce vomiting, and nausea, and increase appetite. However their users have indicated that SC increased appetite less frequently than cannabis [2, 8, 10, 12, 13, 19].

effects – nausea, vomiting;

• Renal effects: acute kidney injury;

• Other effects –pulmonary effects, cold extremities, dry mouth, dyspnea, mydriasis, vomiting.

4. *Neurological, cognitive and psychological effects of consumption of synthetic cannabinoid receptor agonists*.

Neurological side efects: among side effects reported for SC, tremor, ataxia, nystagmus, fasciculations, hypertonicity, hyperextension. The most common cognitive effect of SC is impairment of attention, concentration, memory, and operational skills, anxiety, agitation, aggression, disorganized thinking, thought blockage, persecution thoughts, delirium, auditory and visual hallucinations, suicidal thoughts, acute psychosis, reduced levels of consciousness; coma, numbness, tingling, fainting, dizziness, pallor, tinnitus, diaphoresis, drowsiness, syncope, apathy and convulsions; short-term memory and cognitive impairments, confusion, sedation and sleepiness, incoherent speech and amnesia [10, 12, 13].

These effects are generally seen during intoxication period, however they can extend beyond this period [24, 25]. Epileptic seizures can be observed due SC use [25]. These effects are generally seen during intoxication period, however they can extend beyond this period [24-25]. Chronic harmful effects associated with long-term and frequent use of SC receptor agonists**.**

Harmful and addictive use, tolerance and withdrawal:

• Synthetic cannabinoids seem likely to cause addiction;

• Tolerance develops faster for synthetic cannabinoids than for natural cannabis, with a much more severe and prolonged withdrawal syndrome.

Their effects on laboratory parameters: hyperglycemia, hypokalemia, increased creatinine, creatinine phosphokinase levels, acidosis.

Harmful and addictive use can lead to tolerance and withdrawal. Little is known about the long-term and harmful effects of consuming SC. Available research suggests that prolonged and frequent consumption of SC is associated with psychosis, cognitive impairment, various forms of carcinoma, and lung disease, although further research is needed to confirm these initial findings [10, 12, 13, 24, 25].

5. Treatment

A specific antidote for SC does not exist. Limited data suggest that antipsychotics (haloperidol, olanzapine, and quetiapine) or benzodiazepines (lorazepam) can be effective as supportive treatment. Theoretically, CB_1 receptor antagonists can reverse CB_1 agonistic effects of SC, however commercially marketed CB_1 receptor antagonists are not available. Vital signs of the patients should be monitored, fluid replacement should be made to prevent dehydration, and rhabdomyolysis. Diphenhydramine can be used to relieve muscular rigidity [23-25].

6. About legal status

Legislation on SC does not cover all forms and types of these substances. Buying them online or from unregulated sources can be associated with numerous risks, even if their packaging says "legal", there is no guarantee that the substance contained is truly legal or harmless.

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