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BEYOND THE HIGH: CBD AND THC IN THE ERA OF DESIGNER DRUGS

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Abstract: THC and CBD are spread worldwide and well known for their beneficial and psychoactive effects. Due to the usage restrictions, the drug market is constantly creating new psychoactive substances to avoid legal implications. The newest synthetic cannabinoid on market in Romania is HHC (hexahydrocannabinol). In this paper the known facts and effects of the natural cannabinoids compared to synthetic cannabinoids such as HHC will be reviewed.

Material and methods. Literature review and synthesis of multiple articles related to usage and effects of natural cannabinoids compared to those of designer drugs, assessing the possible risks and effects. Sites such as google scholar, pub med and Clarivate were used to gather the necessary information, as well as the Romanian Criminal Code.

Results. NPS constantly suffer modifications in order to avoid the legal implications, the most problematic being the unknown possible effects due to insufficient research and the impossibility of detection by usual drug tests;

Conclusions. The medical and psychoactive short and long-term effects of CBD and THC are well known. The constant change in chemical formulas of the NPS (new psychoactive substances) are making research and testing for these compounds difficult. HHC is sold mostly as e-cigarettes with high concentration (94-99HHC%) compared to the max 30-40%THC the natural cannabis has(raisin->40%THC). European countries laws do tend to have a legislative void when it comes to NPS due to the lack of routine tests to detect these new substances, thus as they appear for a shorter/or longer period of time they are sold legally.

Keywords: NPS,HHC,THC,CBD.

INTRODUCTION

Tetrahydrocannabinol (THC) and CBD (Cannabidiol) represent the most well-known cannabinoids that are found in the cannabis plant. These compounds have distinct effect and properties.

THC (Tetrahydrocannabinol) is the main psychoactive component of the cannabis plant- responsible for the "high" state of consciousness upon marijuana consumption. It also has medical uses such as alleviating pain, nausea and vomiting in patients undergoing chemotherapy, also stimulating the appetite in different pathologies, such as AIDS, sleep aid in insomnia, muscle relaxant. THC is mainly considered a high-risk substance thus it is illegal in many countries worldwide, even though some have legalized it for medical/recreational use (Holland, Canada, some USA states- below 0.3 %THC) [1, 2].

CBD (Cannabidiol) represents the non-psychoactive component of the cannabis plant. The psychoactive effect of the THC can be lowered/ countered by consumption of CBD. From a medical point of view, CBD has many proven benefits – anti-inflammatory, anticonvulsant, anxiolytic, antipsychotic, pain relief and neuroprotective effects. It has been used in the therapy of epilepsy, anxiety, inflammation and chronic pains. Hemp derived CBD (with a THC level <0.3%) is legal at a federal level in USA, and many other countries around Europe [3-5].

Both compounds interact with the endocannabinoid system of the body, by different paths. THC has a high affinity and binds directly to the CB1 receptor, causing psychoactive effects while CBD follows a more complex path, using modulation of the

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receptor without binding to it directly; it is believed this contributes to the lack of psychoactive properties of CBD.

Both CBD and THC can also lead to side effects- short term ones being psychoactive effects, impaired motor coordination, anxiety and paranoia, red eyes and dry mouth, increased appetite (munchies) and long-term effects – cognitive impairment was found in long term cannabis use in adolescence [6].

The manufacturing of designer drugs goes back to the 1920, firstly met in USA, after banning morphine, cheap synthetic replacements appeared on the market [7].

Synthetic cannabinoids are compounds that are chemically engineered to mimic the effects of THC, by acting on the cannabinoid receptors; they were developed initially in research purposes for the endocannabinoid system study but ended up being sold as designer drugs/legal highs- often sold as liquids for vapes/e-cigarettes or smoking blends. They are usually sold as ilicit substances at lower prices than the natural cannabis, but present risks of unpredictable effects occurrence including agitation, hallucinations, tachycardia, hypertension, chest pain, seizures and other effects that can be different and more severe from those of THC. Designer drugs as researched by Liana Fattore and Walter Fratta, by evaluation of some reported cases of synthetic cannabinoid usage concludes that the "legal highs" currently available on the market are inducing "severe peripheral and central effects, including drug dependence and psychosis" [8].

Hexahydrocannabinol (HHC) is the hydrogenated form of THC. It is reported to have less potent psychoactive effects than THC, depending on the individual response and the dose administered, but unfortunately, the available literature does not asses such advanced testing and research on this subject [9].

MATERIAL AND METHODS

Literature review and synthesis of multiple articles related to the structure, usage and effects of natural cannabinoids and those of new designer drugs, assessing the possible risks and effects. Sites such as google scholar, pub med and Clarivate were used to gather the necessary information, also the Romanian criminal code was analyzed in what concerns the antidrug laws and limitations.

DISCUSSION

From The National Report regarding the drugs situation in Romania 2022, there is a significant increase in medical emergencies due to the consumption of NPS, the most common being synthetic cannabinoids, which supports the hypothesis of increased risks of severe adverse effects compared to THC and CBD. Also, an analysis of national reports over the years 2004-2021 shows a significant increase in drug consumption - the emergence of rapid drug tests that can also identify cases of DUI (driving under influence) must be taken into account [10].

From the 2022 list of prohibited substances released by RNADA (National Anti-Doping Agency of Romania), following the latest changes, it appears that: cannabis, THC and its derivatives and "Synthetic cannabinoids that mimic the effects of THC" are prohibited [11].

While synthetic cannabinoids have been valuable for scientific research to understand more about the endocannabinoid system, the illicit use of these substances poses significant and severe risks due to their unpredictable effects, lack of regulation, and potential for harm [12,13].

The issue of HHC appearing positive on drug tests has been also assessed by Lisa Höfert *et al.*, concluding that regarding the saliva tests the police uses on DIU suspicions "the consumption of exclusively HHC, especially of small amounts, without consumption of THC may not be detected", but the LCMS and GCMS can be crucial in the detection of the new synthetic drugs. We have to take into consideration the similar structure of THC and HHC could lead to false positive results on some drug tests, since the HHC might be contaminated. The amount of time HHC can last in blood is currently unknown but considering the similarities to THC we can assess that it could be up to a few weeks/months as we can conclude from the researches made by Harvey D *et al.* and Marilyn A Huestis *et al.* [14-18].

Tanaka Rie & Ruri Kikura-Hanajiri have studied the types of HHC present in e-cigarettes by LCMS and GCMS assessing the various different molecular structures of HHC in different products [19].

THC and CBD's effects, benefits, and risks are well-documented, becoming regulated substances under many jurisdictions compared to synthetic cannabinoids, that are considered to be more dangerous, firstly because of unpredictable effects, diversity of chemical morphology and the lack of regulation. Considering Victor R. L. J.

Bloemendal *et al.* research, the synthetic cannabinoids are valuable for research and for the development of more potent medication in certain diseases, also to elucidate the mechanisms of the endocannabinoid system, thus the recreational and illicit use of this yet not well-known substances should be avoided in order to decrease the risk of side effects [20,21].

Depending on the individual, the effects of cannabis can vary depending on the consumption method, and using other compounds like CBD, which can modulate THC effects, protecting against some of the psychoactive effects [22].

One of the major risks in consuming synthetic drugs, such as HHC is that even though the potency of HHC is below that of THC we should take into consideration the concentration it has in each e-cigarette or product. Cannabis usually has the following THC concentrations depending on the products used:

Low THC strains: These can have a THC content of 0-5%. This category includes hemp, which is legally accepted in many countries if it has less than 0.3% THC.

Mid-range THC: These are more common in strains used for medical purposes and often have a THC content of 5-15%.

High THC Strains: Many strains used recreationally are grown to have high levels of THC, they can reach >30% THC levels.

Extracts and Concentrates: Oils, shatter, waxes and other concentrates can have extraordinarily high levels of THC, ranging from 40% to over 90% THC.

While the HHC products do come in ranges from 20 to 99% HHC, most vapes and e-cigarettes sold are mainly with >90%HHC, which can intensify the psychoactive effects and increase the rate of side effects appearance [23,24].

In conclusion, THC and CBD have been used worldwide for centuries and their medical and psychoactive benefits and effects are well known, some countries even legalizing medical marijuana as support medication in various neurological/psychiatric/ chronic pain/ palliative care cases.

The constant change in chemical formulas of the NPS are making research and testing for these compounds very complicated for the toxicologists, so the identification and implementation of stable laws regarding these substances and creation of routine tests is delayed, as well as the knowledge of the action and side effects of these substances is not known, the change in chemical formulas increasing the risk of other effects to appear.

The way HHC is sold – as vape pens with high concentration of HHC (94-99%) compared to the max 30-40%THC the natural cannabis has(raisin->40%THC), the high dosage being able to give very intense symptoms also increase in the occurrence of side effects.

The Romanian and most European countries laws do tend to have a legislative void when it comes to NPS due to the fact that there is no routine test that can detect these new substances, thus as they appear for a shorter/or longer period of time they are sold legally – as HHC is in Romania at the current moment.

The Romanian government is applying various methods of tightening the antidrug laws by massive testing and searches but have little to no effect on the new psychoactive substances.

Due to the similarities between the structure of HHC and THC, it is possible for HHC consumers to appear positive to THC at the normal drug tests, since the sensitivity of the quick saliva tests might mistake HHC for THC, in the same time there is a possibility the tests turn out negative. Further research could reveal more about the efficiency of the drug tests concerning NPS.

Long term effects of HHC are unknown due to the lack of research on the matter and due to the constant change in the chemical structure of NPS in general. The usage of synthetic cannabinoids could lead to better therapeutic methods in the future, as well as a deeper understanding of the endocannabinoid mechanisms if future research is invested in these subjects. For now recreational use of designer drugs poses a great risk regarding unknown immediate and late side effects.

Conflict of interest

The authors declare that they have no conflict of interest.

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