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Is there anything beyond addiction psychotherapy in patients with cannabis use disorder? A rationale for prescribing medical marihuana as a harm reduction strategy.

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Abstract: Marihuana has been known to people for hundreds of years. Today, marihuana is either legal or decriminalized in many countries, particularly in Europe and the Americas, which may encourage use of the drug. Cannabis and its derivatives are used in medicine on the recommendation of doctors, including for the treatment of multiple sclerosis or drug-resistant epilepsy. There is a group of people who turn to marihuana on the street without regard to contraindications and side effects, and these are the recreational users who struggle with problematic use or addiction. Buying marihuana outside of the medical market means that the user may not realize the negative health effects of their use, and there are serious risks associated with the negative effects of the natural substances found in marihuana or the numerous and common marihuana contaminants, such as mercury and pesticides, among others. This review justifies the prescription of pharmaceutical-grade medical marihuana as part of health harm reduction for a group of cannabis use disorder patients who are unlikely to stop using marihuana from untested or illicit sources, while also discussing ethical and economic issues.

marihuana; cannabis; harm reduction; prescription; medical marihuana

1. INTRODUCTION

Marihuana, also known as cannabis has been known to people for hundreds of years, according to the available sources of information, it was first used for medicinal purposes around 400 AD [1]. The next reports of the medicinal use of marihuana date from around 900 AD, when a plant cultivated in Western and Central Asia was adapted to the rituals of Ayurvedic medicine [2]. The 1830 description of the Irish physician O'Shaughnessy, who had observed the healing effects of marihuana during a stay in India, was the beginning of the popularization of cannabinoids in Europe and the broader study of these substances. This researcher suggested the efficacy of cannabinoids in the treatment of epilepsy and described their muscle relaxing and pain relieving properties [3]. Many of the medicinal properties of cannabinoids have been described based on empirical observations made over hundreds of years when these substances were used for medicinal purposes in ancient cultures (including China, India, Egypt, and Greece) [3]. Cannabinoid treatment was widespread during the years 1850-1940, when approximately 600 medications were documented worldwide that contained marihuana in their composition [4]. The beginning of the era of marihuana prohibition is considered to be the intro-

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duction of the Marihuana Tax Act in the United States in 1937, which taxed the sale of cannabinoids for both recreational and medical purposes. In the following decades, laws were then enacted that criminalized the possession of marihuana and eventually prohibited its use – these acts not only restricted the use of marihuana by individuals, but also contributed to limiting the ability to study the properties of cannabinols for scientific purposes [5].

Currently, marihuana is legal or decriminalized in many countries, especially in Europe and America, so its users do not face legal repression. Combined with the presence of marihuana in mass culture, this situation has the potential to encourage use of the drug. Currently, it is legal to purchase or grow marihuana for personal use in several U.S. states and in several European countries. This type of policy contrasts with the position of the United Nations (UN), whose Commission on Narcotic Drugs (CND) in December 2020 removed marihuana from Annex IV of the 1961 Single Convention on Narcotic Drugs, where it was listed along with heroin, among others, as a drug with no potential therapeutic benefit. The CND emphasizes that nonmedical use of marihuana can still be harmful from a public health perspective [6]. Nonetheless, marihuana use is increasing worldwide, especially in countries that choose to legalize or decriminalize it. According to the annual World Drug Report 2022, released by the UN on June 27, the legalization of marihuana has accelerated the upward trend in reported daily use of the drug. The same document states that by 2020, approximately 284 million people, or 5.6 percent of the world's population, used drugs of any kind, 209 million of whom used marihuana [7]. Marihuana can have negative effects on health, but it should not be forgotten that there are also medical preparations of pharmaceutical quality prescribed by a doctor (dried preparations, concentrated active ingredients) for central sensitivity syndromes (fibromyalgia, chronic fatigue syndrome, migraine, irritable bowel syndrome), multiple sclerosis, neuropathic pain, refractory nausea, epilepsy, and cancer, along with scientifically recommended prescribing methods, side effects, and specific contraindications that include pregnancy, lactation, psychosis, and angina [8]. However, there is a group of people who, unconcerned about contraindications and side effects, will reach for marihuana, and these are recreational users who struggle with problematic use or addiction to cannabis. Buying marihuana outside of the medical market means that the user may not notice the negative health effects of its use, and no medical practitioner will have the opportunity to see them. The risk of such a situation could be greatly reduced if, as part of harm reduction, medical practitioners controlled the consumption of marihuana by people struggling with problematic use or addiction and who are not motivated to stop using it. This manuscript discusses this idea by reviewing the mechanism of action of marihuana, harm reduction, and subjecting the information gathered to debate. The article also aims to support the need for additional research and guidelines for practitioners on the impact of legalized marihuana use, both medically and recreationally, especially concerning mental health. Despite the increasing trend of legalization in many countries, there is a lack of studies examining how this trend affects marihuana use in society and the potential for harm reduction methods, particularly for individuals dealing with addiction or problematic use [9].

2. HOW CANNABIS AFFECTS THE BODY

It is crucial to distinguish between marihuana and cannabinoids, as they represent distinct components of the cannabis plant with diverse pharmacological effects. Marihuana, commonly known as a recreational drug, encompasses the entire cannabis plant and contains a myriad of compounds, including cannabinoids, terpenes, and flavonoids. On the other hand, cannabinoids refer specifically to the active compounds found within marihuana, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which exert various physiological effects by interacting with the endocannabinoid system. While marijuana possesses a complex chemical profile, cannabinoids are isolated entities responsible for the plant's psychoactive and therapeutic properties. This differentiation is fundamental for elucidating the intricate pharmacological mechanisms and potential therapeutic applications of cannabinoids while avoiding

the broader implications associated with marihuana use. The pharmacokinetics of cannabinols depends on the method of administration. The best known and most frequently described substance in marihuana is THC, partly because of its psychoactive properties and the possibility of using it in various therapies [10]. The half-life is approximately 1.4-10.9 hours when the substance is ingested as an oral aerosol, 2-5 days after long-term oral ingestion, 31 hours after smoking, and 24 hours after intravenous administration of the drug. The bioavailability of THC after smoking is about 31%, and the current studies do not refer to this parameter for other ways of taking this drug [11]. THC is a direct partial agonist that binds to the G-protein-coupled metabotropic receptors CB1 (mainly on the surface of the central and peripheral nervous system, but also in adipose tissue, muscle, heart, lungs, liver, kidneys, testes, and ovaries) and CB2 (mainly in keratocytes, hematopoietic cells, and on the surface of cells of the immune system) [12,13]. The physiological effects of THC are not fully understood, although the effects of this substance on the body are probably related to the opioid, GABAergic, dopaminergic, cholinergic, serotonergic, noradrenergic, prostaglandin, and glucocorticoid systems [14]. The metabolism of THC is mainly carried out in the liver via the cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP3. Due to its lipophilic properties, THC is distributed to well-vascularized lipophilic tissues after absorption in the blood, i.e., adipose tissue, liver, lung, kidney, spleen, adrenal cortex, thyroid gland, or pineal gland [9,15]. 20% of cannabis is excreted in urine, with several metabolites identified (the most important being 11-nor-9-carboxy- 9-tetrahydrocannabinol), most of which increase water solubility by conjugation with glucuronic acid, while 65% of metabolites (the most important being 11-hydroxy-9-tetrahydrocannabinol) are excreted in faeces [13]. A 2014 study showed that THC has a relatively low potential to interact with drugs [16]. Alterations in the endocannabinoid system have also been found to be associated with the development of diseases such as cancer, neurodegenerative disorders, and cardiovascular disease, so pharmacological modulation of this system is now becoming a valuable research topic [17]. Another well known cannabinoid is CBD, which has high affinity on a series of receptors, including Type 1 cannabinoid receptor (CB1), Type 2 cannabinoid receptor (CB2), GPR55, transient receptor potential vanilloid (TRPV) and peroxisome proliferator-activated receptor gamma (PPARγ). By modulating the activities of these receptors, CBD exhibits multiple therapeutic effects, including neuroprotective, antiepileptic, anxiolytic, antipsychotic, anti-inflammatory, analgesic and anticancer properties. CBD could also be applied to treat or prevent COVID-19 and its complications [18]. Because CBD appears to also be partial agonist of 5HT1a serotonin receptors, it is believed that it could be helpful in depression treatment [19]. Cytochrome P450 enzymes, specifically CYP3A4 and CYP2C9 in the liver, hydroxylate CBD to produce 7-OH-CBD and 7-COOH-CBD. CBD is predominantly excreted through feces, with a lesser amount excreted in urine. The plasma half-life of CBD ranges from 18 to 32 hours [20].

Occasional use of marihuana does not cause serious health damage, but its regular abuse over a long period of time can have many negative consequences, such as mental and physical health problems, but also social difficulties – lower educational level among users, higher risk of causing traffic accidents, unemployment, and relegation to a lower social class [21]. Short-term side effects of marihuana use include impairment of short-term memory, disturbances in psychomotor coordination, and, at higher doses, psychotic disorders [22]. Long-term marihuana use can lead not only to the development of dependence, but also to damage to brain development, cognitive dysfunction, decreased life satisfaction, an increased risk of developing chronic psychotic disorders, and triggering symptoms of chronic pneumonia [23]. Studies have also shown that long-term use of large amounts of cannabis can lead to worsening symptoms of depression and anxiety disorders [24]. According to recent research reports, marihuana may also negatively affect the cardiovascular system by causing inflammation in the arteries and affecting vascular contractions and platelet aggregation [25]. Despite the widespread belief that prior marihuana smoking may contribute to increased susceptibility to schizophrenia, data remain mixed in this regard, as one randomized trial showed that the onset of schizophrenic dis-

order did not correlate with age at onset of cannabis use, so it would be appropriate to distinguish between psychotic disorders triggered by marihuana use and schizophrenia [26].

3. REDUCING THE HARMFUL EFFECTS OF MARIHUANA USE

Harm reduction is the set of activities aimed at reducing the risks associated with specific activities [27]. Harm reduction includes both education and direct actions, such as providing clean needles and syringes to intravenous psychoactive substance users. Harm reduction does not aim to eliminate specific behaviors in an individual, but rather to minimize as much as possible the complications for those who are not motivated or willing to give up the behaviors in question. An example of harm reduction used by physicians is the prescription of preexposure prophylaxis (emtricitabine and tenofovir) to groups at risk for HIV infection, such as people who have sex with multiple unprotected partners [28]. The idea of prescribing pharmacy drugs to replace street-purchased substances is not new; buprenorphine and methadone are commonly used as replacement therapy for people who struggle with opioid addiction [29].

The idea of a physician prescribing marihuana to people who have no incentive to stop using it is related not only to monitoring the patient in question and keeping track of their condition, but also to the potential risks associated with the composition of street marihuana. Pharmaceutical companies grow marijuana following strict rules set by state agencies. This ensures a standardized and safe product. However, drug dealers don't follow these rules. Nonmedical marijuana can have harmful contaminants like microorganisms (Aspergillus spec, Penicillium spec, Fusarium oxysporum, Escherichia coli, Salmonella, Clostridium), heavy metals (cadmium, lead, mercury), insecticides and fungicides (bifenazate, abamectin, imazalil, myclobutanil), and other substances. These contaminants can cause infections, complications, disrupt various processes in the body (e.g. disruption of synaptic processes or abnormal hormone production), and even lead to cancerogenesis. [30]. There are also repeated warnings against street marihuana with fentanyl or methamphetamine added, and accidental ingestion of a substance other than the intended one should be considered an immediate threat to health and life [31-33]. These risks do not exist in controlled cultivation of pharmaceutical grade. In addition, contamination can have different health effects depending on how the product is obtained; popular among consumers is not only smoking but also eating so-called "edibles," i.e., foods containing marihuana, often cookies, chocolate, or jelly candy.

Harm reduction, as the name implies, does not aim to eliminate a particular behavior in a person, but to reduce the risk associated with it.

4. DISCUSSION

It seems advisable to learn from the experience of countries that have chosen to pursue a particular type of drug policy over a long period of time without significant changes. One such country is the Czech Republic. Since January 1, 2010, possession of small amounts of most drugs, including marihuana, amphetamines, MDMA, LSD or cocaine, and heroin, has been decriminalized, with tangible results: Over the past decade, when new psychoactive substances (NPS) were a significant problem in neighboring Poland, Czechs were far less likely to seek addiction treatment for NPS than Poles (16% in the Czech Republic and 25% in Poland) [34]. In September 2022, the Czech National Coordinator for Combating Drugs, Jindřich Vobořil, called on European Union countries to decriminalize and regulate marihuana at the European level, suggesting that the only effective way to combat the negative effects of marihuana use could be the introduction of a marihuana market controlled from above [35]. The role of physicians in drafting appropriate regulations should not be overlooked, because it is they who must help people who have developed health problems as a result of using the drug. It is equally important not to forget that harm reduction is more important than ever in an era of widespread legalization.

The process of legalizing marijuana is not new, as it began in 1970 when the first medical professionals gained access to use marijuana to treat their patients. However, even though more than

50 years have passed since then, the idea still raises concerns from a public health perspective. Proponents state that legalization could have important and positive impacts on sectors such as the economy, criminal justice spending, traffic safety, and health, considering that marijuana could play a crucial role in combating the opioid crisis that North America is currently struggling with [36-37]. On the other hand, when analyzing data from the National Survey on Drug Use and Health 2002-2014, an American national survey aimed at identifying current trends in psychoactive substance use, it can be clearly seen from data from states that have legalized marijuana use that legalization increases the number of people who choose to use, and this trend is particularly evident in the 12 to 17 year old and 18 to 25 year old groups [33]. Some reviews have noted that initiation of marijuana use at a young age leads to numerous deficits, including impaired general well-being and cognitive abilities and negative health outcomes, including psychiatric problems, that sometimes might be comparable with the ones from various synthetic cathinones [38-40]. This needs to be considered when discussing further legislation and public health guidelines, as youth protection is critical to the preservation of society.

Like stated in the introduction, one should know it is worth emphasizing that the term "medical marihuana" in the literature usually refers to dried marihuana, which is no different from "street" marihuana except that it comes from controlled cultivation. Cannabinoids, on the other hand, are substances and concentrates extracted from the plant, most of which already have specific registration indications. It is worth knowing this difference, because the marihuana plant contains about 400 different substances, 60 of which are cannabinoids, while some that are used to treat multiple sclerosis, contain only tetrahydrocannabinol and cannabidiol [41-42]. Differences in administration are also significant. Thus, some formulas are available in the form of an oral spray, while the generally recommended method of consumption of dried marihuana is vaporization, thanks to which the active ingredients can be heated to the boiling point, significantly reducing harmful tars [43].

Clinical trials are advisable before introducing a new therapy. It is doubtful to design an effective safety trial for replacing prescription marihuana with street marihuana, because marihuana use can have consequences like any other psychoactive substance use, and it does not matter whether the substance was purchased from a dealer or prescribed by a physician. Probably the only measurable indicator for evaluating the effectiveness of treatment would be a multiyear, multicenter follow-up of patients using marihuana under medical supervision and a comparison of this group with street marihuana users. The safety of long-term use of marihuana under medical supervision has been demonstrated for chronic pain and other conditions, providing a valuable guide for further development of this idea [44].

As mentioned earlier, harm reduction is not limited to direct interventions, but also to educational activities. Important in the implementation of this type of therapy by a physician is the assessment of whether the patterns of marihuana use have the characteristics of harmful use, and possible psychoeducation with a view to taking appropriate therapeutic or preventive measures. At the same time, the presentation of validated scientific data on the health aspects of marihuana use is particularly important at a time when the use of marihuana is increasingly socially acceptable and widespread in mass culture.

It is also important to consider the ethical issues of the concept of harm reduction for people struggling from addiction or problematic use through a physician's prescription of marihuana. It is doubtful that the physician is not reduced to the role of a dealer. Two arguments against such a proposition seem relevant here: 1. The physician's role in the proposed harm reduction model is not only to prescribe high-quality marihuana from the dispensary, but also to monitor use, provide regular checkups, observe physical and mental health, and provide health education. 2 A common method of harm reduction for opioid-dependent patients is to prescribe buprenorphine under medical supervision, as the benefits outweigh the risks associated with both the side effects of buprenorphine and the possibility of overdose or mistaken ingestion of a substance other than that intended [45]. Prescribing marihuana by physicians should be reserved only for patients with

cannabis use disorder who are not motivated or willing to quit marihuana use.

The development of recommendations or guidelines for the treatment under consideration necessitates careful consideration of various factors. Given the intricate nature of addiction, an imperative requirement is the adoption of an interdisciplinary approach. Collaboration amongst practitioners spanning family medicine, psychiatry, addiction specialists, and mental health professionals is strongly advocated to holistically address the physiological and psychological dimensions inherent in addiction. The diagnosis of marijuana dependence mandates adherence to established criteria, notably the DSM-5 criteria for substance use disorders. Crucial to this process is an assessment of the addiction's severity and its ramifications on the individual's daily life. A comprehensive evaluation by healthcare professionals is imperative and should encompass a detailed medical history, a thorough mental health assessment, and a meticulous review of the patient's substance use patterns. Employing standardized screening tools, such as the Drug Use Disorders Identification Test (DUDIT), facilitates an accurate diagnosis. A pivotal aspect involves gauging the patient's readiness for change, wherein motivational interviewing techniques serve as invaluable tools for evaluating their preparedness to address marijuana use. Patients expressing reluctance to discontinue usage merit further evaluation to elucidate the underlying reasons for their resistance, encompassing psychological, social, or environmental factors. Integration of addiction psychotherapy stands as an indispensable component of a comprehensive treatment regimen. Evidence-based approaches, such as Cognitive Behavioral Therapy (CBT), addiction management, and motivational therapy, are pivotal in this regard. The focus of addiction psychotherapy should extend to the identification and addressing of the root causes of addiction, fostering motivation for change, and formulating strategies to cope with cravings and triggers. Should a judicious evaluation determine medical marijuana as a suitable harm reduction strategy, its prescription by healthcare providers should be executed with stringent control measures. Vigilant monitoring of dosage, frequency, and mode of administration is imperative to minimize potential risks. Regular follow-up visits are paramount for progress monitoring, treatment plan adjustments, and addressing emerging issues. The frequency of follow-up visits, tailored to individual needs, should be more frequent initially, gradually transitioning to a less intensive schedule as stability is attained. Patients must receive comprehensive education elucidating the risks and benefits of medical marijuana use, potential side effects, and its interactions with concurrent medications. Informed consent, obtained through active patient involvement in treatment decisions, is paramount to ethical practice.It is worth noting that pharmaceutical-grade medical marihuana from pharmacies is taxed, unlike black market marihuana. The economic benefit is not only in taxing marihuana from the dispensary, but also in removing some of the funds from the circulation of criminal groups, which in turn can have a positive impact on social security in general. In addition, regular medical examinations of individuals who may be using marihuana can minimize costs associated with late detection of health problems and unnecessary hospitalizations.

5. CONCLUSIONS

Physicians should consider prescribing pharmaceutical-grade medical marihuana topeople struggling with problematic use or addiction to cannabis who are unwilling to people stop using street-bought marihuana. Expert working groups should be formed to develop precise guidelines for this process. As marihuana use increases worldwide, comprehensive research and analysis on the widespread use of marihuana should be a priority of public health agencies throughout the world.

List of abbreviations
CND – Commission on Narcotic Drugs
UN – United Nations
THC – Tetrahydrocannabinol
WHO – World Health Organization

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