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PHARMACOTHERAPEUTIC MEASURES IN PATIENTS WITH PSYCHOTIC DECOMPENSATION DUE TO ABUSE OF THE PSYCHOACTIVE SUBSTANCE CANNABIS SATIVA AND ITS DERIVATIVES

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Abstract

This paper explores pharmacotherapeutic strategies for patients experiencing psychotic decompensation due to abuse of Cannabis sativa and its derivatives. Cannabis abuse can induce serious mental disturbances, including psychosis, necessitating urgent and effective treatment. The paper thoroughly discusses the use of antipsychotics, mood stabilizers, benzodiazepines, and additional medications for comorbid conditions such as depression and epilepsy. Additionally, it emphasizes the importance of psychotherapy and counseling as adjunct therapeutic approaches crucial for long-term patient rehabilitation. Monitoring patients and adjusting therapy according to their responses are crucial for achieving optimal outcomes. This paper highlights the need for a personalized approach in treating cannabis-induced psychosis, aiming to stabilize symptoms, prevent relapses, manage comorbid conditions effectively, and minimize potential risks of pharmacotherapy.

Key words: *Cannabis sativa, psychotic decompensation, pharmacotherapy, antipsychotics, mood stabilizers, comorbid conditions.*

Introduction

Indian hemp (marijuana, Cannabis sativa) is a plant known to man since ancient times, and one of the first descriptions of the ritual use of this plant among the Scythians was given by the ancient historian Herodotus (484-425 BC). The plant originates from the Asian continent and was first used in human and animal nutrition, and then in industry to make 20,000 different industrial products. It is little known that textiles, paper, oil, paints, glues, ropes, etc. are made from hemp. In fact, the very meaning of the plant's name indicates its usefulness: Cannabis-hemp and sativa-useful.

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Unfortunately, Cannabis sativa contains 400 chemical constituents, including more than 60 cannabinoids, powerful psychoactive substances. Cannabinoids are aryl-substituted meroterpenes and are found in nature only in plants of the genus Cannabis sativa [1].

The most powerful cannabinoid derivative is delta-9-tetrahydrocannabinol (D9-THC), which is why the use of this psychoactive substance, usually by smoking the dried leaves of this plant, is the most abused psychoactive substance in the world. Data from the Office for Narcotic Psychoactive Substances of the United Nations (United Nations Office on Drugs and Crime) state that about 160 million people aged 15 to 64, or about 4% of the population, at least once consumed cannabis or its derivatives during the year. Between 30-34% of US residents have tried marijuana. The frequency of cannabis abuse has been increasing in recent decades, from 3-5% 50 years ago to 10-15% at the beginning of the XXI century. The most commonly abused form is made from dried hemp parts and can contain any combination of leaves, roots, seeds and buds. Marijuana is also known by its street, slang, names: trava, vutra, ganja, gras, vulja, grinta, jiđa, žiža, marica, mara, pot and the like. The substance that is abused can be of different strengths, depending on the type of plant and the climate in which it was grown, but also on the specific combinations of parts of the plant. A typical D9-THC concentration is around 2-5%. Derivatives of this plant can contain up to 20% D9-THC, and they are: hashish, which is obtained by extracting the resin from the dried plant; The resin contains an average of 5-12% D9-THC, while some forms have as much as 20%; hashish oil is obtained by alcoholic extraction of cannabinoids from hemp. Hash oil is a thick, waxy liquid and can contain up to 70% D9-THC; Dronabiol obtained by synthetic process D9-THC. Dronabiol is used in patients suffering from cancer and AIDS to control nausea or vomiting due to cytostatic therapy, as well as to stimulate appetite and improve the quality of life of patients [2, 3].

Mechanism of psychoactive effect

Cannabis is well resorbed in the lungs (21-50%), while orally administered it has low bioavailability due to the first pass phenomenon. Resorbed, it binds to plasma proteins and accumulates in fatty tissue. It quickly and well crosses the blood-brain barrier and binds to endocannabinoid receptors, predominantly cannabinoid receptor type 1 (CB1) in the mesolimbic system. D9-THC bound to CB1 receptors modulates responses to external stimuli that lead to emotional and/or intellectual stimulation, also called the reward phenomenon. On the other hand, long-term use causes a significantly weaker reaction due to downstream regulation and desensitization of the CB1 receptor, and a sudden cessation of D9-THC abuse causes an abstinence syndrome [4].

Effects of cannabis in humans

Cannabis affects almost all organ systems in the body. It combines the effects of alcohol, sedatives, opioids and hallucinogens. It has anxiolytic, sedative, analgesic and psychedelic effects, stimulates the appetite and has many systemic effects. In addiction, acute toxicity is very rare: no deaths due to acute cannabis intoxication have been reported.

Clinical use of cannabis and its components

The use of cannabis extract as medicine has been recorded as far back as ancient India and China before Christ. The therapeutic use of cannabis in Western medicine began in the first half of the 19th century. Today, this situation has changed considerably. The main active psychotropic ingredient of cannabis, D9-tetrahydrocannabinol (D9-THC) was isolated, identified and synthesized as early as 1960. Almost three decades later, cannabinoid receptors in the brain were described, and endogenous cannabinoids were also isolated. As a result of these discoveries, interest in cannabis research has grown significantly.

Although D9-THC is generally accepted as the main factor responsible for the effects of cannabis, several reports have shown that other components of the plant influence its pharmacological activity. One of these components is cannabidiol (CBD), which can represent up to 40% of cannabis extracts, and is devoid of the typical psychological effects of cannabis in humans. Several studies, however, have described antagonism of the effects of D9-THC when both compounds are administered simultaneously in animals and humans. CBD (1 mg/kg) in combination with D9-THC (0.5 mg/kg) significantly reduced anxiety and psychotomimetic symptoms induced by the previous drug in healthy volunteers. When administered alone, CBD will produce its effects, including hypnotic, anticonvulsant, neuroprotective, and hormonal (increased corticosteroid and cortisol) effects. These effects lead to the hypothesis that CBD could have anxiolytic and/or antipsychotic effects [5-13].

Cannabis and psychosis

Cannabis is often abused by people with mental disorders, although it itself can lead to numerous, very diverse disorders. Described in practice: psychotic and manic reactions, dysthymia, hypomania, various forms of depression, then generalized anxiety disorder, panic reactions, as well as a wide range of phobic reactions. The frequency of these disorders is higher in psychiatric patients compared to the general population and it is treated as psychotic decompensation under the influence of psychoactive substances (31% vs. 0.7-1.3% in the general population). According to the latest DSM-5 classification (Diagnostic and Statistical Manual of Mental Disorders), cannabis abuse is classified as a mental disorder that requires serious therapy, and sometimes longer hospitalization.

Biological basis for the development of a psychotic episode

Cannabis, although the most used psychoactive substance in the world, is used by millions of people, however, only a small proportion of users develop a psychotic disorder. This leads to the conclusion that certain genetic factors must play a role in changing individual sensitivity to the psychotic-induced potential of cannabis, which implies the interaction of genes, i.e. hereditary basis and environment [14].

Differential diagnosis of endogenous psychosis and psychotic episodes caused by cannabis abuse

The differential diagnosis between a substance-induced psychotic episode and a primary psychotic episode arising from the use of psychoactive substances is relevant in planning appropriate treatment. What draws attention is that the early onset and long-term use of cannabis in predisposed persons can lead to the appearance of a psychotic illness, which is clinically indistinguishable from schizophrenia, and only the outcome differs, i.e. in those who stop taking cannabis after a psychotic episode, there is a complete recovery, with adequate psycho-socio-pharmacotherapeutic treatment. In those who continue to use cannabis, there is a chronic worsening, when cannabis plays a key role in the development of schizophrenia.

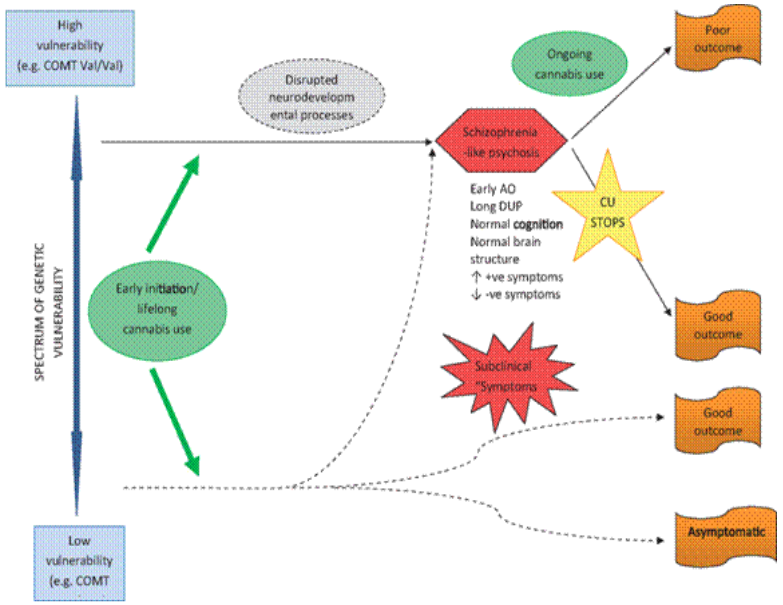

Figure 1. Pathways from cannabis to psychosis (long-term cannabis users)

Pharmacotherapy of psychotic episodes caused by cannabis abuse

The pharmacotherapeutic protocol in the treatment of these patients is not universally prescribed, and hospital protocols that are adapted to the patient are most often used. Access depends on many factors, the most frequently mentioned of which are: gender, age, length of cannabis use, concentration of D9-THC, lifestyle, BMI, other diseases and more. It can be said that the pharmacotherapeutic approach is individual and varies from patient to patient. However, most authors single out two main goals of pharmacotherapy: therapy of abstinence syndrome and therapy of psychotic decompensation. The treatment of withdrawal syndrome in these patients is complex and requires the use of several pharmacotherapeutic groups of drugs, along with simultaneous cognitive-behavioral psychotherapy. The following drugs are in use: CB1 receptor antagonist rimonabant (40 mg/day), opioid receptor antagonist naltrexone (50-200 mg/day), entacapone, COMT inhibitor (dosing is individual - up to 2000 mg/day), atomoxetine (selective uptake inhibitor noradrenaline), buspirone (anxiolytic), lithium (mood stabilizer) and others. Psychotic decompensation is treated with the use of typical antipsychotics, e.g. haloperidol, but also atypical ones, such as olanzapine, risperidone, clozapine, aripriprazole. In addition to the mentioned antipsychotics, drugs from other groups are also used: antiepileptics, lithium, anxiolytics, antidepressants and other drugs [2-4, 15-17].

Therapy of psychotic episodes and cannabinoid dependence using aripiprazole

In the therapy of acute psychotic decompensation after the use of cannabis, aripiprazole proved to be particularly effective, most likely due to its combined effect, i.e. partial agonism with dopamine D2 and serotonin 5-HT1a receptors and antagonism with serotonin 5-HT2a receptors. The recommended doses of the drug are 15 mg/day in the first days of hospitalization, and are later adjusted. Aripiprazole is the first partial agonist of dopaminergic D2 receptors with a clear antipsychotic effect. Many patients with schizophrenia develop a co-occurring substance abuse disorder. Cannabis use can worsen the psychotic symptoms of schizophrenia. It was noted that in patients who included aripiprazole in the therapeutic protocol, the consumption of cannabis decreased, which suggests that it was aripiprazole that contributed to the occurrence of this decrease. Various mechanisms may play a role, such as partial agonism of dopamine D2 receptors by aripiprazole. Second, dopamine stimulation in the nucleus accumbens has been proposed to cause addictive behavior and aripiprazole's partial agonistic dopamine effect in this region may reduce this behavior. In addition, aripiprazole has a number of serotonin activities unrelated to potential dopamine modulation of the response to D9-THC. Other mechanisms may be involved and this rapid cessation of cannabis use after initiation of aripiprazole indicates the need to systematically check these mechanisms as well as the need to design controlled trials [18].

Conclusion

Cannabis is one of the most abused psychoactive compounds in the world. According to the latest DSM-5 classification (Diagnostic and Statistical Manual of Mental Disorders), cannabis abuse is considered a mental disorder that requires multidisciplinary therapy, and sometimes requires hospitalization of the patient. The relationship between cannabis use and psychosis is very complex. Assessment and treatment planning are important in the early stages of psychotic decompensation, because this is the time when the clinical picture is not clear enough and correct diagnosis, as well as adequate therapy, is extremely important for the final outcome.
Most often, hospital protocols are used that are adapted to each patient separately, i.e. an individual approach is applied, and due to numerous factors, e.g. length of cannabis use, D9-THC concentration, lifestyle, BMI, comorbidities and more.
The consequences of continuous consumption of cannabis for many years are not entirely clear, which is the subject of further research.
The work is part of the research of the specialist academic work of the author Dr. Anita Milanović on the topic: Pharmacotherapeutic measures in patients with psychotic decompensation due to abuse of the psychoactive substance Cannabis sativa and its derivatives.

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