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GLOBAL EXPERIENCE WITH MEDICAL CANNABIS USE: INDICATIONS AND SAFETY PROFILE (literature review)

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Ключові слова: *Δ9-тетрагідроканабінол, канабідіол, медична марихуана, канабіс, канабіноїди, Cannabis sativa L., ендоканабіноїдна система*

Abstract. Global experience with medical cannabis use: indications and safety profile (literature review). Kaidash S.P., Sliesarchuk V.Yu., Sokolova K.V., Potapova T.M. *Over the past decades, medical cannabis has received official recognition in more than 40 countries around the world, including Germany, Canada, Italy, and Israel. Medical cannabis is considered a potentially effective remedy for incurable conditions accompanied by pain, spasms, or nausea. Despite its relative safety compared to opioids, the issue of side effects remains relevant. The aim of the study was to systematize information on the main pharmacological properties of medical cannabis and its bioactive components, available dosage forms and medically approved cannabis-based drugs, as well as analyze the evidence base for assessing the effectiveness of medical cannabis in various pathological conditions, taking into account potential risks and safety of use in clinical practice. To achieve the aim of the study, a search for scientific publications was carried out using the queries: medical marijuana, cannabis, cannabinoids, names of medical cannabis drugs, names of cannabinoids in the PubMed, Scopus and Google Scholar databases (2005-2025). 8254 results were obtained for the query. The exclusion criteria were: publications that did not meet the purpose of the review; language of publications (except Ukrainian, English); annotations that did not contain complete information about the results of the studies; publications with closed access. 44 publications were selected for analysis. The article analyzed clinical conditions in which the use of cannabis may be potentially beneficial (mental disorders (post-traumatic stress disorder, anxiety, depression), pain, drug addiction, diseases of the central nervous system and gastrointestinal tract). The safety of medical cannabis is highlighted: risks of addiction, neuro- and cardiotoxicity, psychotic reactions, side effects and features of using by vulnerable groups. Despite the growth of therapeutic use, the evidence base for clinical benefit remains incomplete, and undesirable effects limit its use. The choice of form and route of administration should be adapted to the individual needs of the patient. Thus, the analysis of the literature confirms the significant potential of medical cannabis in the treatment of various diseases, but the safety of its use requires further research.*

Реферат. Світовий досвід використання медичного канабісу: призначення та профіль безпеки (огляд літератури). Кайдаш С.П., Слєсарчук В.Ю., Соколова К.В., Потапова Т.М. *Упродовж останніх десятиліть медичний канабіс отримав офіційне визнання в понад 40 країнах світу, зокрема в Німеччині, Канаді, Італії, Ізраїлі. В Україні державне регулювання обігу рослин роду коноплі (Cannabis) відбувається з 2023 року. Медичний канабіс розглядається як потенційно ефективний засіб при невиліковних станах, що супроводжуються болем, спазмами чи нудотою. Попри відносну безпеку порівняно з опіоїдами, питання побічних ефектів залишається актуальним. Метою дослідження була систематизація інформації про основні фармакологічні властивості медичного канабісу та його біоактивних компонентів, наявні лікарські форми та медично схвалені препарати на основі канабісу, а також аналіз доказової бази щодо оцінки ефективності медичного канабісу при різних патологічних станах з урахуванням потенційних ризиків та безпеки застосування в клінічній практиці. Для досягнення мети дослідження здійснили пошук наукових публікацій за запитами «medicalmarijuana», «cannabis», «cannabinoids», назви препаратів медичного канабісу, назви канабіноїдів у базах PubMed, Scopus та GoogleScholar (2005-2025). За запитом отримано 8254 результати. Критеріями виключення були: публікації, що не відповідали меті огляду; мова публікацій (крім української, англійської); анотації, які не містили повноцінної інформації про результати досліджень; публікації із закритим доступом. Для аналізу були відібрані 44 публікації. У статті було проаналізовано клінічні стани, при яких може бути потенційно корисним застосування канабісу (психічні розлади (посттравматичний стресовий розлад, тривога, депресія), біль, наркотична залежність, захворювання центральної нервової системи та шлунково-кишкового*

тракту). Висвітлено питання безпеки медичного канабісу: ризики залежності, нейро- та кардіотоксичність, психотичні реакції, побічні ефекти та особливості застосування у вразливих групах. Незважаючи на зростання терапевтичного використання, доказова база щодо клінічної користі залишається неповною, а небажані ефекти обмежують його застосування. Вибір форми та способу введення слід адаптувати до індивідуальних потреб пацієнта. Таким чином, аналіз літературних даних підтверджує значний потенціал медичного канабісу в лікуванні різних захворювань, проте безпека його застосування потребує подальших досліджень.

In modern medicine, there is growing interest in the use of medical cannabis as an alternative or complementary treatment for various diseases, including chronic pain, mental disorders, epilepsy, cancer, multiple sclerosis, drug addiction, and other pathologies. In recent decades, more and more states in the US and other countries have legalized the use of cannabis (at least some components of Cannabis sativa) for medical purposes to treat various somatic pathologies, mental disorders, and palliative care. Licensing of cannabis-based medicines, including cannabis herbs for people with chronic (neuropathic) pain, has already taken place in Canada, Germany, and Israel and is planned in some other countries [1, 2]. Lebanon became the first Arab country to legalize cannabis for medical and industrial use in 2020. Other Middle Eastern and Arab countries continue to completely ban the use of cannabis and products derived from hemp [3]. In Ukraine, state regulation of the circulation of plants of the genus Cannabis was introduced by Law of Ukraine No. 3528-IX of 21 December 2023 (On Amendments to Certain Laws of Ukraine Regarding State Regulation of the Circulation of Plants of the Genus Cannabis for Use in Educational, educational, scientific, and scientific and technical activities, and the production of narcotic drugs, psychotropic substances, and medicines with the aim of expanding patients' access to necessary treatment).

Despite a significant amount of scientific research, questions about the effectiveness, safety, and appropriateness of cannabis use remain a subject of debate.

The aim of the study was to systematize the available information on the main pharmacological properties of medical cannabis and its bioactive components, available dosage forms, and medically approved cannabis-based drugs, as well as to analyze the evidence base for assessing the effectiveness of medical cannabis in various pathological conditions, taking into account the potential risks and safety of its use in clinical practice. Research on medical cannabis is particularly relevant in the context of reforming treatment approaches and searching for new therapeutic opportunities in clinical practice.

MATERIALS AND METHODS OF RESEARCH

We searched for scientific publications using the following keywords: *medical marijuana, cannabis, cannabinoids* in the PubMed and Scopus scientific databases, and searched for the names of medical cannabis preparations and cannabinoids in the Google Scholar database. In the PubMed database, we additionally used the "publication language" filter, where, in addition to works in English, we separately analyzed publications in Ukrainian. The electronic search was performed in PubMed and Google Scholar in the time interval 2005-2025.

When processing information in the PubMed (Medline) database, the inclusion criteria were study design, which included books and documents, clinical studies, meta-analysis, randomized controlled trials, reviews, systematic reviews, etc. The keyword search was conducted among abstracts and full texts with open access. The exclusion criteria were publications that did not correspond to the purpose of this review, the language of publication (other than English and Ukrainian), and abstracts that did not contain complete information on the results of studies with restricted access. A preliminary selection of publications indexed in PubMed and Google Scholar yielded 8,254 publications. Further analysis and identification of publications by their titles allowed us to select 44 publications whose titles and abstracts were relevant to our study.

The study took into account measures to ensure human health safety, respect for human rights, human dignity, and moral and ethical standards in accordance with the principles of bioethics set forth in the Helsinki Declaration "Ethical Principles for Medical Research Involving Human Subjects." Since the article is a review and did not involve the use of personal data and patient examination results, nor did it involve any interventions, no bioethical conclusion or written consent was obtained.

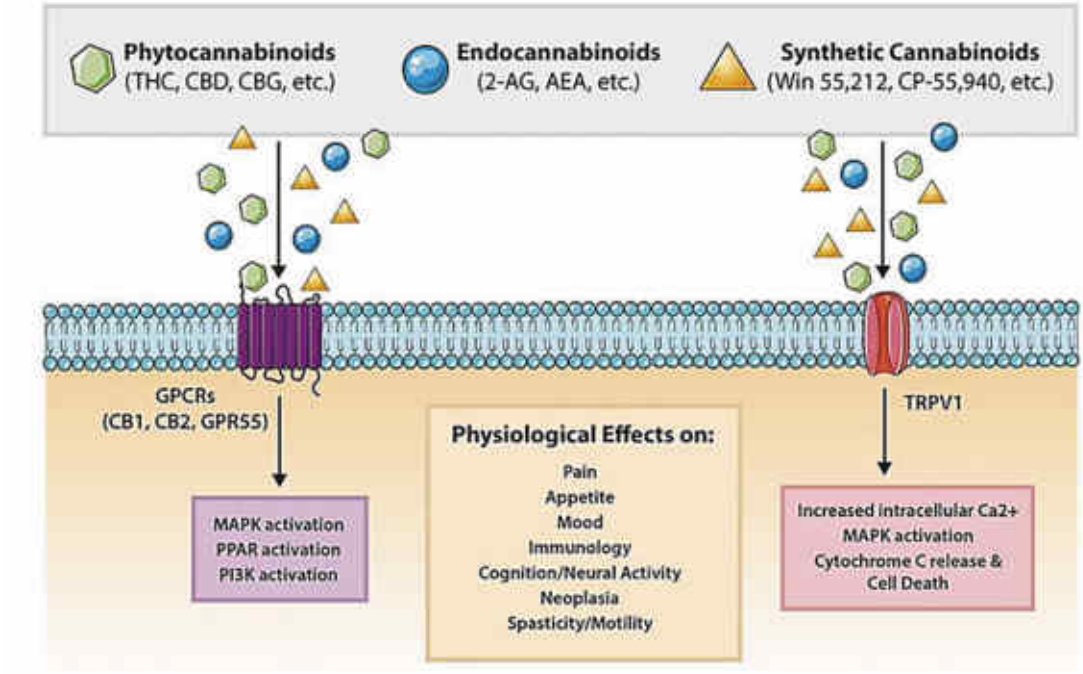
RESULTS AND DISCUSSION

Following the discovery of the endocannabinoid system (ECS) and its role in the human body, interest in cannabis and its extracts (phytocannabinoids) has been renewed [1]. Recently, there has been growing interest in the therapeutic use of cannabis and phytocannabinoids, which have potential medicinal properties, being the subject of numerous studies and discussions in the scientific and medical community.

Main bioactive components (cannabinoids, terpenoids, alkaloids, flavonoids). Cannabis and its derivatives include all products obtained from plants of the Cannabis genus. Plant products of cannabis include: marijuana (the tops of the plant with flowers, with a high content of Δ9-tetrahydrocannabinol), hemp (with a low THC content), hashish (pressed cannabis resin),

cannabis oils (cannabidiol), wax (concentrated cannabis extract), and food products (e.g., muffins, cookies, candies, tinctures). The cannabis plant contains many chemically active substances, such as cannabinoids, flavonoids, terpenoids, and alkaloids. There is no standardized form of cannabis, and each plant contains varying amounts of these substances. All phytocannabinoids are formed from cannabigerolic acid (CBGA), with the highest concentrations of CBGA found predominantly in female cannabis inflorescences [1]. Among more than 150 phytocannabinoids, two are the most widely studied: Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has psychoactive effects, causing relaxation, euphoria, and heightened sensory perception (it is for these effects that it is consumed for "recreational" purposes), stimulates appetite and digestion, and has antiemetic and analgesic properties. CBD is a non-psychoactive phytocannabinoid that exhibits anti-inflammatory, anticonvulsant, neuroprotective (antioxidant), and antispasmodic properties, as well as stimulating appetite and mitigating the psychoactive effects of THC. Cannabinol (CBN) is formed during the decomposition of THC and has a weak psychoactive effect. Synthetic cannabinoids are laboratory-synthesized substances that can interact with cannabinoid receptors and mimic the action of THC (e.g., nabiximols) or the action of other cannabinoids [4]. The term "medicinal cannabinoids" refers only to cannabinoids extracted from plants or synthesized, which have undergone standardization and controlled clinical trials to assess their safety and efficacy and have been licensed for use as medicinal products [5].

The mechanism of action of cannabinoids on the human body. The main active components of cannabis – phytocannabinoids (THC and CBD), as well as other active cannabinoids – affect various organs and systems of the body (central and peripheral nervous systems, endocrine and immune systems) through the modulation and activation of endogenous lipid signaling pathways, i.e., the so-called endocannabinoid system (ECS). The ECS consists of receptors, their ligands (endocannabinoids), and enzymes that regulate the biosynthesis and inactivation of endocannabinoids (regulatory enzymes). The most important are cannabinoid receptors 1 and 2 (CB1 and CB2), as well as GPR55 and GPR119 receptors. CB1 receptors are mainly located in the central nervous system (mostly in the frontal cortex, basal ganglia, and cerebellum), in the peripheral nervous system, and are also present in adipose tissue, the gastrointestinal tract, adrenal glands, thyroid gland, liver, reproductive organs, chondrocytes, osteocytes, fibroblasts, and immune cells. CB2 receptors are mainly expressed in immune cells and can also be found in chondrocytes, osteocytes, and fibroblasts, as well as in nervous tissue (dorsal ganglia and microglial cells). Seven different endogenous ligands that act in the endocannabinoid system have now been identified. Two of the endocannabinoid ligands (anandamide (AEA) and 2-arachidonoylglycerol (2-AG)) are formed from arachidonic acid phospholipids under the action of specific synthesizing enzymes. The ECS can be activated by endocannabinoids, phytocannabinoids, and synthetic cannabinoids [7]. Cannabinoid signaling pathways and effects are shown in Figure.



Cannabinoid signaling pathways and effects

Regardless of the type of cannabinoid ligand (phytocannabinoid, endocannabinoid, or synthetic), these compounds primarily interact with GPCR proteins, such as CB1, CB2, GPR55, or TRP (TRPV1) receptors, to induce a cellular response. The activated pathways vary depending on receptor activation and have physiological effects on pain, appetite, mood, immunology, and many other effects in the body [1].

The endocannabinoid system (ECS) primarily maintains homeostasis of the internal environment (temperature, immune system), as well as energy metabolism in the human body. In addition to regulating physiological processes, the ECS directly affects the psychoemotional sphere (mood, emotions, anxiety, depression, eating behavior, appetite) and nervous functions (neurogenesis, neuroprotection, cognitive processes, pain perception, fertility, pregnancy, as well as pre- and postnatal development). The ECS is also involved in the pathophysiology of certain diseases, such as cancer, cardiovascular disease, and neurodegenerative diseases [8].

It should be noted that many cannabinoids (including THC) exert their physiological and pharmacological effects through agonism of CB1 and CB2 receptors in the endocannabinoid system (ECS) (Fig.). Incidentally, it is precisely because of the partial agonism of CB1 receptors that THC exhibits its psychoactive and analgesic effects. However, some cannabinoids, such as CBD, have low affinity for cannabinoid receptors (CBD is a partial antagonist of CB1 and a weak inverse agonist of CB2) and act outside the ECS [1], i.e., they bind to other non-cannabinoid receptors.

Medically approved cannabinoid preparations. The modern pharmaceutical approach to application may begin with the use of the Cannabis plant for medical purposes, and then move on to the development of extracts with controlled quality, a complete assessment of their analytical profiles, and research to evaluate the delivery of the correct dose to achieve the optimal therapeutic effect.

The two most studied and proven cannabinoids in terms of efficacy and safety are THC and CBD; based on them, four cannabinoid pharmaceuticals have been registered and approved for medical use by the Federal Drug Administration (FDA) and the European Medicines Agency (EMA), including:

1) dronabinol, nabilone, CBD – pure cannabinoid compounds;

2) nabiximols – a partially purified extract of medicinal cannabis (Table 1).

The potential applications of other cannabinoids and their delivery methods are currently being investigated (Table 2) [2].

Table 1

Cannabinoid drugs currently available on the market

Cannabinoid Medications	Ingredients	Dosage form	Indications	Side effects
Dronabinol (Marinol®, Syndros®) approval FDA, EMA (1985)	**synthetic TNS (has 10-20% bioavailability and short action)**	**capsules and oral solution**	**anorexia in patients with AIDS; nausea and vomiting during chemotherapy (CINV)**	**heart palpitations, asthenia, abdominal pain, amnesia, very rarely – depersonalization [9]**
Nabilone (Cesamet®) approval FDA (1985, 2016), EMA	**synthetic, structurally similar to TNS (has 95% bioavailability and long-lasting action)**	**oral capsules 1 mg**	**chemotherapy-induced nausea and vomiting (CINV)**	**orthostatic hypotension, dry mouth, drowsiness, dizziness, euphoria, shortness of breath, headache, very rarely – psychosis [10, 11]**
CBD (Epidiolex®) approval FDA (2018), EMA (2019)	**98% pure plant-based CBD**	**oil oral**	**complex convulsive disorders (Lennox-Gastaut syndrome or Dravet syndrome) in children aged 2 years and older**	**hepatocellular toxicity, decreased appetite, diarrhea, drowsiness, fatigue [12]**
Nabiximols (Sativex®) approval EMA (2010)	***C. sativa* plant extract, containing THC and CBD in a 1:1 ratio**	**oromucosal spray**	**spasticity associated with multiple sclerosis**	**dizziness, fatigue, blurred vision, constipation, decreased or increased appetite, depression, very rarely – palpitations, changes in blood pressure, and hallucinations [13]**

Table 2

Investigated medicinal forms of cannabinoids and innovative delivery systems

Route of administration	Composition	Dosage form	Indications	Application	Stage of development
Oral	CBD	solid	Crohn's disease, GVHD*		Clinical trials
Oral	THC	SEDDS**		improved solubility, stability	Preclinical
Oral	THC-glycosides	pro-medicines	drug-resistant inflammatory bowel disease	inflammation	Clinical trials
Oromucosal	nabiximols (THC CBD 1:1)	spray	cancer	pain	Clinical trials
Oromucosal	CBD	powder			Research into formulation
Oromucosal	THC CBD 1:1	chewing gum	several potential diseases	pain, spasticity, dementia, etc.	Preclinical
Intranasal	CBD	liquid compositions		bioavailability studies	Preclinical
Intranasal	CBD	solid/liquid			Research into formulation
Intranasal	CBD	powder metered dose inhaler		bioavailability studies	Clinical trials
Transdermal	phytocannabinoids		induced dermatitis	inflammation	Preclinical
Transdermal	CBD	gel	arthritis	inflammation	Preclinical
Transdermal	CBD	etosomes	edema	inflammation	Preclinical
Transdermal	CBD	gel	epilepsy, osteoarthritis, fragile X syndrome		Clinical trials
Transdermal	CBD	oil, spray, cream	bullous epidermolysis	pain, blistering	Clinical treatment
Transdermal	CBD	patch			Research into formulation
Transdermal	CBD + hyaluronic acid	gel		pain, wound treatment	Research into formulation
Transdermal	CBD+ argan oil		rheumatic diseases	inflammation	Research into formulation
Transdermal	CBD + boswellic acid			inflammation	Research into formulation
Ocular	analogue THC	prodrugs	glaucoma	lowering intraocular pressure	Research into formulation

Notes: GVHD* – graft-versus-host disease; SEDDS** – self-emulsifying drug delivery systems.

The search for important targets for the development of new drugs, in particular, enzymes that destroy endocannabinoids such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) remains to be a promising area for scientists [14].

Routes of administration and dosage forms of medical cannabis (including those under investigation) and cannabis-based medical products.

Parenteral route: intravenous injections, inhalation (smoking, powder dosed inhaler), transdermal (transdermal patches, gel, cream). Enteral route: oral (capsules, oil, edible products with cannabinoids), sublingual/transbuccal (lozenges, oil), oromucosal (oromucosal spray for the oral mucosa, chewing gum), intranasally (liquid formulations), rectally.

Cannabinoids are highly lipophilic molecules with very low water solubility, prone to degradation, especially in solution, under the influence of light and temperature, as well as due to auto-oxidation. Thus, the formulation can play a decisive role in increasing the solubility and physicochemical stability of the drug. Given the low oral bioavailability of cannabinoids, promising routes of administration include transdermal, intranasal, and mucosal absorption. The high lipophilicity of cannabinoids provides an opportunity for the implementation of advanced nanoscale drug delivery systems that can be administered in a variety of ways. For example, self-emulsifying drug delivery systems (SEDDS) may be essential for improving the solubility, stability, and bioavailability of THC and other cannabinoids. SEDDS, which are isotropic mixtures of oils, surfactants, solvents, and co-soluble substances/surfactants, can be used in the design of compositions to improve the oral absorption of highly lipophilic drug compounds. Various forms of administration and delivery have been tested for therapeutic use. Cannabis products are typically either inhaled by smoking/vaporization or taken orally. Oromucosal, topical transdermal, and rectal routes of administration are secondary but interesting. The pharmacokinetics and pharmacodynamics of cannabinoids vary depending on the route of administration, with absorption showing the greatest variability in the main pharmacokinetic steps. Absorption is influenced by both the intrinsic lipophilicity of the product and inherent differences in organ tissues (i.e., alveolar, dermal, or gastric). Various factors, such as recent food intake (for oral administration), depth of inhalation, duration of breath holding, and vaporizer temperature (for inhalation) affect the absorption of cannabinoids, which can range from 20-30% for oral administration to 10-60% for inhalation [2].

Medical conditions with potentially beneficial use of cannabis and evidence base for treatment efficacy.

According to an analysis of literature data from contemporary scientific studies, cannabis may be useful as an alternative treatment or as symptomatic control for certain pathological conditions and diseases. The results of a number of controlled clinical studies show that certain cannabinoids can modulate the symptoms of some diseases but do not affect the course of the disease itself [15]. Such cannabinoids are usually used in combination with other drugs and, as a rule, as an alternative treatment. Cannabinoids are not used as a first-line therapy for the treatment of any disease [16].

Mental disorders (post-traumatic stress disorder (PTSD), anxiety, depression, sleep).

There is compelling preclinical evidence confirming the great potential of CBD as an anxiolytic and anti-compulsive agent; it eliminates the psychotic and anxiogenic effects of THC and activates CB1 and serotonin 5-HT receptors [16, 17]. Cannabis use can improve global PTSD symptoms, as confirmed by a double-blind study involving Canadian military personnel for whom standard treatment was ineffective, and nighttime doses of nabiximols had a significant and beneficial effect on the frequency of PTSD-related nightmares [18]. Cannabinoids have also been found to be effective in reducing anxiety, but not depression, associated with PTSD.

The role of the endocannabinoid system (ECS) in modulating mood has been proven, and thus cannabinoids with a high CBD content may have therapeutic benefits for reducing anxiety [19]. In a double-blind, randomized controlled trial, 24 patients with public speaking anxiety took 600 mg of CBD 1.5 hours before speaking and showed a significant reduction in anxiety compared to healthy control subjects [20]. Clinical trials are currently underway with CBD as a potential treatment for anxiety. Nabiximols has also been shown to reduce anxiety, whereas cannabis with high THC content is more likely to cause anxiety symptoms in patients.

There is no convincing evidence of the benefits of CBD for sleep (this can be explained by the variability in the content and quality of medical cannabis); on the contrary, one-time use of THC increases sleep duration, while regular use of THC can lead to sleep disturbances (possibly due to tolerance), and withdrawal from THC is associated with an increase in vivid dreams and sleep disturbances [21].

Cannabinoids in the treatment of opioid addiction and as an alternative to opioids.

The analgesic effect of cannabinoids and the absence of the euphoric effect of CBD have potential therapeutic applications for the treatment of opioid addiction, including as an adjunct to traditional medication-assisted treatment (methadone, buprenorphine, and naltrexone). For example, CBD has been found to reduce withdrawal symptoms after taking opiates [22]. It should also be noted that THC (dronabinol) is ineffective as an analgesic on its own, but new data may indicate synergism between THC and opioids [23]. According to the analysis, there is no evidence that cannabis can have an opioid-sparing effect [24]. Unfortunately, however, the problem of replacing one drug of abuse with another remains, although cannabinoids have a higher safety profile and a lower likelihood of dependence and death than opioids [25].

Chronic pain.

Medical cannabis has the greatest potential in the treatment of chronic pain. A recent meta-analysis of

eleven randomized controlled trials found a significant reduction in pain in patients with peripheral neuropathy compared to patients with central neuropathic pain. In addition to pain reduction, most patients also experienced improvements in quality of life, sleep, anxiety, and sensory sensitivity. These studies used dronabinol (2.5-10 mg/day), nabiximols (1-4 mg/day), and nabiximols (average THC and CBD content comparable to 22.4 mg: 20.8 mg/day), Nabilone was found to be the most effective, nabiximols the least effective, and dronabinol (THC) alone ineffective for the treatment of neuropathic pain, but it may have synergistic effects with opioids [23]. In cancer patients, in a double-blind study, nabiximols was found to be ineffective in relieving pain caused by radiation therapy. However, in general, a number of studies indicate the benefits of synthetic nabiximols and, conversely, insignificant results in nabiximols [1, 26]. Unfortunately, although these studies confirm the therapeutic potential of medical cannabis, the results for synthetic nabiximols cannot be extrapolated to phytocannabinoid mixtures. It would also be useful to conduct studies comparing the analgesic effects of cannabinoids and other analgesics (e.g., NSAIDs).

Cannabis for treating CNS disorders: spasticity and pain caused by multiple sclerosis.

Nabiximols (Sativex®) has been approved in several countries for treating spasticity and relieving pain (more effective than a placebo) associated with multiple sclerosis [26]. There is research suggesting that nabiximols (Sativex®) is even more effective in reducing spasticity in multiple sclerosis than first-line antispasticity treatment [27, 28].

Epilepsy.

In recent years, there has been scientific interest in cannabinoid-based drugs for the treatment of epilepsy, particularly its resistant forms [29]. Phytocannabinoids such as CBD, cannabigerol (CBG), cannabidavarin (CBDV), and THC have demonstrated anticonvulsant properties and may be promising for the development of safer alternatives (or even supplements) to traditional antiepileptic drugs. The most pronounced anticonvulsant properties have been found in THC and CBD, with CBD being of particular interest because it does not cause psychotropic effects. CBD has demonstrated efficacy as an adjunctive treatment for Lennox-Gastaut syndrome and Dravet syndrome, as it has reduced the frequency of epileptic seizures in many studies [30]. Currently, CBD (Epidiolex®) is the first and only plant-based CBD pharmaceutical drug approved by the US Food and Drug Administration (FDA) for the treatment of Lennox-Gastaut syndrome and Dravet syndrome in children aged 2 years and older. However, further research is needed to determine the optimal dosage in order to reduce the number of epileptic seizures and minimize the side effects of CBD. Clinical studies are also needed to determine the effectiveness of CBD for the treatment of other forms of epilepsy in children and adults.

Neurological/neurodegenerative diseases (amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease).

Scientific data show that cannabinoids play an important role in modulating inflammation (neuroinflammation) and also provide and enhance neuroprotection. In addition, cannabinoids such as CBD have demonstrated analgesic, anxiolytic, and immunosuppressive properties, making them attractive for the treatment of certain neurological disorders [26]. However, the research data are not conclusive. Although surveys show that patients experience subjective improvement and therefore prefer to use medical cannabis over prescription drugs.

Tourette syndrome.

To date, according to the results of two small controlled studies using dronabinol in Tourette syndrome, the number of tics decreased and the side effects of dronabinol were insignificant. However, this evidence needs to be confirmed, so a larger multicenter clinical study is also underway to evaluate the effectiveness of nabiximols in the treatment of Tourette syndrome[26, 31].

The effect of cannabis on the gastrointestinal tract.

THC and CBD are proven appetite stimulants, a property that is particularly useful in cases of eating disorders (anorexia of various origins). It has been found that dronabinol increases body mass index in patients with cachexia associated with cancer or acquired immunodeficiency syndrome. On the other hand, stimulation of the ECS increases insulin resistance, causes dyslipidemia, fatty liver, reduces satiety centers in the brain, and hyperphagia. Incidentally, hyperphagia is caused by THC, while CBD suppresses it. Interestingly, chronic use of cannabis reduces the incidence of obesity and fatty liver disease. The mechanisms behind this phenomenon are being studied, and the results may be useful in the practicel application of obesity treatment [7]. The cannabinoids THC and CBD also have antiemetic and antinausea properties. It was for this purpose that synthetic THC preparations such as dronabinol and nabilone were developed to treat nausea and vomiting, as well as chemotherapy-related anorexia in cancer and HIV/AIDS patients [8]. The latest oncology guidelines recommend dronabinol as a “rescue therapy” for chemotherapy-induced nausea and vomiting. There are also a small number of studies on the antiemetic effects of cannabinoids in pregnant

women and real medical prescriptions of cannabis to pregnant women (in the US, Colorado), but it should be noted that cannabis use by pregnant women is unjustified because the risks outweigh the benefits [7].

Regarding the use of cannabis with high THC content in inflammatory bowel diseases (Crohn's disease, nonspecific ulcerative colitis), it should be noted that it is mainly used for symptomatic relief of pain and dyspepsia [32]. Research data on the effect on the pathogenesis and prognosis of the disease are contradictory and require further testing. Currently, a number of studies are being conducted on nabiximols in inflammatory bowel diseases [33].

Data confirming the ability of cannabinoids to alleviate the symptoms of certain diseases does not justify the "medical prescription" of cannabis by smoking. Smoking cannabis that has not undergone processing is not a safe and reliable way to obtain standard doses of cannabinoids.

Safety of medical cannabis use

Potential dependence. More severe dependence on cannabis is observed with a high THC content as compared to cannabis with a low THC content [34], and patients with a history of psychiatric or drug dependence are more prone to dependence.

Neurotoxicity and effects on cognitive function. The neurotoxicity of cannabis, in the form of a sedative effect (drowsiness, decreased attention and reaction time), is associated with the stimulation of the inhibitory neurotransmitter GABA by THC and, thus, a decrease in brain excitability. Exocannabinoids also in constant, prolonged use, have a negative effect on the neuroplastic processes of the brain and in adolescence (up to 16 years of age), they halt cortical maturation, which affects cognitive processes, impairs cognitive function, memory formation, attention, decision-making, and reduces IQ scores by approximately 2-6%. It should be noted that this negative effect of cannabis is partially irreversible, even after discontinuing the use of cannabis products [35].

Psychotic reactions. Psychotic symptoms are observed in 20-50% of cannabis users (probably due to THC or other cannabinoids with euphoric effects). Manifestations may take the form of positive (fragmented thinking, suspiciousness, grandiose delusions, etc.) and negative (psychomotor retardation, dullness, emotional detachment) symptoms. Usually, these symptoms are temporary and disappear after cannabinoid intoxication, but in some individuals, the symptoms persist. That is, acute persistent psychosis occurs, caused by cannabis with a high THC content, with manifestations of hallucinations, amnesia, disorientation, paranoia, and depersonalization [36]. Psychotic reactions are also possible in the form of confusion, disorientation, euphoria, behavioral and sensory disturbances, hallucinations, and panic attacks. Prolonged use of cannabis with a high THC content from adolescence can lead to depression and suicidal tendencies, increased risk of psychotic symptoms and schizophrenia [37]. The risk of developing schizophrenia is four times higher in people with marijuana addiction than in people without addiction [38]. It should also be noted that THC is lipophilic and that psychotic reactions are dose-dependent (significant cognitive and psychomotor impairments occurred at blood THC concentrations >5 ng/ml)[39].

However, there is speculation that, "... although some evidence suggests that cannabis is associated with negative effects on mental health, this evidence is generally weak, as studies are of low quality, have a limited number of participants, are short in duration, have a wide range of cannabinoid preparations and doses, and often have a high level of bias" [2]. It is also interesting that CBD has antipsychotic properties and may reduce the psychotic activity of THC, so further research is needed to confirm these findings.

Cardiotoxicity of cannabis. THC preparations cause tachycardia, but simultaneous administration of CBD reduces it [40]. There are also reports of the likelihood of acute coronary syndrome and stroke in young cannabis users.

Dyspeptic symptoms. Cannabis use often causes dry mouth and increased appetite (especially for sweet foods). Some patients (more often young people and adolescents who use marijuana frequently and for a long time, i.e., every day for at least a year) may experience excessive cannabinoid vomiting syndrome (ECVS) [7]. ECVS is also possible in people who use cannabis for the first time.

Special considerations for vulnerable groups (pregnant women, children). Lipophilic THC crosses the placenta and is excreted in breast milk, potentially causing neurotoxicity in the developing brain [41, 42, 43]. Regular cannabis use in childhood and adolescence causes more severe and persistent negative effects than in adults.

Interaction with other drugs. The exocannabinoids THC and CBD affect the cytochrome P450 system; CBD is a potent inhibitor of CYP2C19 enzymes; cannabis induces CYP1A2. This creates the possibility of pharmacokinetic interactions between THC and CBD and other drugs through the inhibition or induction of liver enzymes. Concomitant use of THC and CBD with sedatives and hypnotics causes an increase in effect due to pharmacodynamic interaction [44].

Despite the increase in the therapeutic use of cannabis and its ligands, evidence of their clinical benefits remains incomplete [14, 42]. The pro-neurogenic

and other effects of CBD, THC, and other cannabinoids on humans need to be more clearly elucidated. In addition, some undesirable effects currently limit its medical use [41, 43]. It is also necessary to be cautious when extrapolating data between different methods and forms of cannabis administration; their selection should be tailored to the individual needs of the patient [41].

CONCLUSIONS

1. Analysis of the literature confirms that medical cannabis has significant potential in the treatment of various diseases, but safe use of it requires further research.
2. It is important to assess the balance of benefits and risks for each patient and to develop appropriate regulatory mechanisms to control its use.
3. Studying global experience and the evidence base regarding the efficacy and safety of medical cannabis is important for the formation of sound public policy in this area.

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