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Ten reasons to consider cannabinoids in everyday clinical practice

Abstract

Medical cannabis is attracting more and more interest among both patients and healthcare professionals. Despite the long history of using this plant for medicinal purposes, the current approach to medicine, which is primarily based on facts, forces us to take a scientific approach in the selection of products and substances from the cannabinoid group. More and more scientific and clinical studies are providing evidence of their effectiveness. Clinical trials with small groups of patients as well as case reports show the benefits of medical cannabis, while larger trials often do not confirm clear improvement compared to other available treatments. Both physicians and their patients need to know in which indications clinical benefits are possible and whether the proposed therapy is safe. Only after analysing the patient's history, interviewing and examining, in a highly individualized and detailed manner (including relative and absolute contraindications) can cannabinoid therapy be considered. They are more often used as an addition to basic and standard therapy, which can improve its effectiveness. Less frequently we choose cannabinoids as drugs of the first choice used in monotherapy. The article aims to present 10 reasons why cannabinoids are worth considering for use in everyday clinical practice and to prepare practitioners to answer the questions most asked by patients.

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Key words: medical cannabis, cannabinoids, THC, CBD, pain, nausea, vomiting, anxiety, depression, epilepsy, MS, stress

Introduction

Herbal cannabis has been used for thousands of years for medical purposes [1]. Major changes have occurred in recent years concerning the legalization, production and use of medical cannabis [2]. Considering that approximately half of the states in the United States have already approved the use of medical cannabis, physicians are significantly more likely to encounter patients interested in such treatment [3]. A survey conducted among Canadian physicians shows a pressing need for education on using cannabis for therapeutic purposes [4, 5]. Moreover, almost 80% of the questioned physicians reported having

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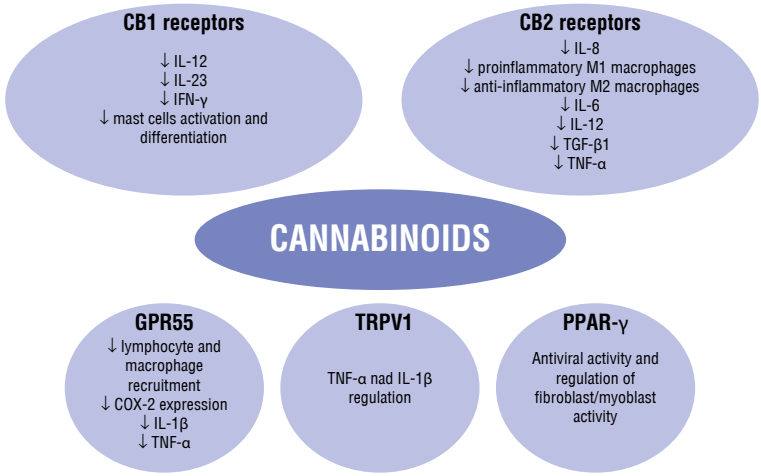

Figure 1. The receptor effects of cannabinoids [7]; CB — cannabinoid; COX-2 — cyclooxygenase-2; GPR55 — G protein-coupled receptor 55; IFN-γ — interferon γ; IL — interleukin; PPAR-γ — peroxisome proliferator-activated receptor γ; TGF-β1 — transforming growth factor β1; TNF-α — tumour necrosis factor α; TRPV1 — transient receptor potential cation channel subfamily V member 1

been asked by patients about medical cannabis and over 70% admitted they would feel more comfortable if they received better education on the subject [5]. Another survey inquired about the most common barriers and limitations of Canadian medical workers regarding the use of medical cannabis. They were mostly concerned about monitoring patients' usage of cannabinoids, prescribing proper products and doses, as well as the lack of reliable literature and support from other medical specialists [6].

The endocannabinoid system consists of endocannabinoid receptors (CB1, CB2), their endogenous ligands (anandamide, 2-arachidonoyl glycerol) and several enzymes responsible for their synthesis and degradation [7, 8]. CB1 receptors are majorly expressed in the central nervous system (CNS), while CB2 receptors are located in the immune cells, mostly in the peripheral organs [9]. Exogenous cannabinoids can be both synthetic and natural [8]. Of approximately 500 components contained in *Cannabis sativa L.*, cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) are the two predominant and most studied phytocannabinoids [7, 10, 11]. THC, a partial agonist of CB1 and CB2 receptors, is best known for the psychotropic effects associated with cannabis usage [10, 12]. CBD exhibits a very low affinity to the endocannabinoid receptors, especially CB1, which explains its lack of psychoactive properties [10, 12]. Moreover, CBD can reduce psychotropic effects and improve the tolerability of THC as it partially counteracts the CB1 receptor in the CNS [12]. The endocannabinoid receptors are not the only mode of action of cannabinoids. They also present affinity to the family of G protein-coupled receptors (GPR), transient receptor potential vanilloid channels (TRPV), peroxisome proliferator-activated receptors (PPAR), and other ion channels (5-HT3, glycine, nicotinic acetylcholine) [7, 12] (Fig. 1).

The article aims to present the potential benefits of the use of cannabinoids in a broad clinical context. Of course, each time, especially in patients with multiple diseases, all pros and cons (relative and absolute contraindications — Table 1) should be considered before starting the therapy, especially since most indications are not registered. The hemp plant itself, as well as its active ingredients — cannabinoids and terpenes, are not a panacea for all diseases and ailments that patients come to us with. They are also not recommended as first-line treatment and are often an addition to existing therapy. However, in many cases, especially when standard therapies fail or are contraindicated, the choice of natural substances may prove to be safer and more effective.

Chronic pain

Controlling severe, chronic pain with neuropathic and inflammatory components remains a modern therapeutic challenge [14]. Despite the crucial role of opioids in pain management, their prolonged use can result in severe adverse effects, physical dependence, tolerance development and the risk of overdose [15–19]. Moreover, the United States faces a major crisis due to excessive opioid use and overdose deaths [19, 20] as patients with cancer pain alone receive enormous quantities of prescribed opioids each year [21]. It is worth mentioning that around half of palliative care patients feel anxious and uncer-

Table 1. Relative and absolute contraindications to the use of cannabinoids [13]

Limitations and contraindications for cannabinoids	
Relative contraindications (limitations)	**Absolute contraindications**
— Age — elderly people (THC) — Hypotension, current use of drugs that may induce hypotension — Driving vehicles — adverse effect on psychophysical fitness, the possibility of forgetting learned activities (THC — every driver) — Performing a profession in which undisturbed psychophysical fitness is important (e.g. pilot, driver, accountant, surgeon, policeman) — The use of strong inhibitors of the cytochrome P450 isoenzyme 3A4 — Heavy tobacco smoking — Renal/hepatic failure — including patients with chronic hepatitis C — Social isolation — Children at home (access to THC)	— Age < 18 (THC) — the period of maturation and development of the CNS until the age of 26 — Pregnancy and breastfeeding (THC/CBD) — Psychopathology (THC): psychosis, bipolar disorder, psychotic disorders induced by recreational marijuana use — Lung diseases (when using inhaled forms or smoking herbs) — Heart rhythm disturbances (THC) — Ischaemic heart disease (THC) — Alcohol addiction (THC) — Addiction to drugs and/or other psychoactive substances (THC) — Proven allergies to any component of the product (history of hypersensitivity to cannabinoids)

CBD — cannabidiol; THC — tetrahydrocannabinol

tain about using opioids as they fear drug addiction, adverse effects and the stigma related to this group of medications [22].

Although currently available pharmacological and surgical methods commonly used in pain management are highly effective, often conventional therapy proves insufficient [23]. Therefore, cannabinoids emerge as a promising alternative for opioids and other analgesics in pain control [23–29].

Cannabinoids can modulate pain in a multifaceted manner, through many signalling pathways, including the endocannabinoid system [4, 30]. Combining opioids and cannabinoids leads to a cumulative analgesic effect in patients with chronic pain, inhibits the development of tolerance, as well as enables patients to reduce doses of administered opioids to amounts previously ineffective [14, 15, 19, 29–34] — even by 40–60% [19]. Interestingly, patients not only report fewer side effects compared to using opioids but also express their preference for cannabinoids [19]. Therefore, cannabis-adjunct therapy may allow physicians to reach sufficient pain control using lower opioid doses and avoid their harmful consequences [35].

There are several studies supporting the common underlying mechanisms of action, indicating possible molecular interactions of opioids and cannabinoids, such as reciprocal peptide release, direct mutual receptor impact and joint intracellular pathways involved in antinociception [28, 36]. Moreover, the development of opioid tolerance is related to the inflammatory response caused by the activation of μ-opioid receptors (MOR) on microglia and the consecutive release of proinflammatory cytokines [16]. CB2 agonists, considering their anti-inflammatory properties [7], could therefore not only help to control inflammatory pain but also reduce the adverse effects of prolonged opioid therapy [16].

A prospective cohort study enrolled 131 patients who suffered from chronic pain and were treated with opioids for over 1 year [29]. Over half of 80 patients, who completed the study, were able to reduce or withdraw opioids after adding CBD-rich hemp extract to their treatment plan. Almost 66% of patients reported pain reduction and 94% declared improved quality of life [29]. Another randomized, double-blind study recruited adult patients suffering from chronic pain with pain intensity of 6 and more on the visual analogue scale (VAS) to determine the influence of inhaled THC on their pain control [37]. The patients continued taking analgesics prescribed to them before the conducted trial. In two groups receiving 0.5 and 1.0 mg of THC per dose, respectively 63.64% and 69.57% of patients experienced a significant pain reduction, including at least a 2-point decrease on VAS in the 1.0 mg dose group compared to placebo [37].

Other reports based on clinical trials conducted to date suggest considering cannabinoids, both CBD and THC, as a potential therapeutic option and adjuvant therapy in chronic, neuropathic and cancer pain management, highlighting they are relatively safe and rarely cause severe adverse effects [27, 29, 30, 34, 37–41]. Cannabinoids show a moderate analgesic effect in patients with neuropathic pain, which is weaker than that of tricyclic antidepressants (TCA), but stronger than that of selective serotonin reuptake inhibitors (SSRI) and gabapentin [24, 25]. Interestingly, almost 90% of patients listed in the medical cannabis registries report chronic pain as the

condition qualifying for the program [19]. Moreover, given the substantial evidence, the National Academies of Science and Medicine in the USA confirmed the effectiveness of cannabis in the treatment of chronic pain in adults [42].

Chemotherapy-induced nausea and vomiting

Approximately 45 to 61% of patients suffering from cancer experience chemotherapy-induced nausea and vomiting (CINV), which are considered to be a result of highly emetogenic chemotherapy and its metabolites activating neurotransmitter receptors in the gastrointestinal system — 5-hydroxytryptamine type 3 (5-HT3) and brain — neurokinin-1 (NK-1) [3, 43]. Delayed CINV (1–5 days after starting chemotherapy) occurs more often and involves the receptors in the alimentary tract, whereas acute CINV (appears within 24 hours) is a less frequent component of the disorder and is mediated by the receptors in the brain [3]. Discovering that the blockade of 5-HT3 receptors may suppress emesis proved to be a significant breakthrough [43].

Considering that cannabinoid receptor agonists downregulate the function of the peripheral 5-HT3 receptors, therefore inhibiting serotonin release, and activate CB1 and CB2 receptors in the brainstem, where emetic reflexes are located, it can be assumed that cannabinoids may play a key role in the prevention from CINV [43, 44]. Conventional therapeutic options for alleviating nausea and vomiting include corticosteroids, 5-HT3 antagonists, NK1 antagonists, antihistamines, benzodiazepines, anticonvulsants and dopamine receptor antagonists [43]. Although cannabinoids may be similarly or less potent compared to other pharmaceuticals, in some patients they are the only line of therapy that proves effective and, moreover, they are the only antiemetics which also increase appetite [43]. In the United States, oral products based on dronabinol and nabilone (synthetic forms of THC) are already approved for the treatment of CINV in patients who did not respond to conventional antiemetics.

A double-blind, placebo-controlled study enrolled 64 patients and aimed to compare the effectiveness and tolerability of dronabinol and ondansetron (5-HT3 antagonist) in patients with delayed CINV [45]. The results indicated that dronabinol and ondansetron have similar efficacy in the treatment of CINV for the total response of nausea intensity less than 5 mm on VAS and no vomiting. The absence of nausea was reported in 71% of patients receiving dronabinol (who also had the lowest nausea intensity on VAS), 64% receiving ondansetron and 15% in the placebo group [45]. In order to assess the efficacy and tolerability of cannabinoids in the treatment of CINV in adults with cancer, the authors of the study analysed 21 randomized controlled trials that compared groups of patients receiving cannabis-based products, conventional antiemetics and placebo [46]. The proportion of patients experiencing CINV, who received cannabinoids, was similar to conventional antiemetic medicines [46]. Another systematic review compared 30 randomized studies (1366 patients) examining the efficacy of cannabinoids, such as oral nabilone, oral dronabinol and intramuscular levonantradol, as well as the effect of conventional antiemetics and placebo [47]. The evidence proved cannabinoids to be slightly more effective than conventional antiemetics for treating CINV [47]. Moreover, preclinical studies suggest that other cannabinoids, such as tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA), CBD and manipulations of the endogenous cannabinoid system, also exhibit antiemetic and anti-nausea properties [44, 48].

A meta-analysis investigating the adverse effects of cannabinoids reported that patients receiving oral dronabinol or nabilone capsules experienced a higher incidence of side effects compared to the groups taking conventional antiemetics or placebo [3]. The most common effects included disorientation, dizziness, euphoria, confusion and dysphoria [3]. Although the frequency of adverse effects argues against the use of cannabinoids as a method of the first choice [49–52], it is worth mentioning that patients still exhibit a strong preference for them [43, 46, 47]. Pooled analysis of 14 studies has shown that the majority of patients (61%) preferred cannabinoids to conventional antiemetics (26%) in the management of CINV [3].

Spasticity in multiple sclerosis

Multiple sclerosis (MS) is a degenerative neuroinflammatory disease affecting the central nervous system [53]. Patients may experience progressive deterioration related to multiple functions of the nervous system, which is often accompanied by spasticity, chronic pain, cognitive dysfunction, sleep disturbances, anxiety and depression [54]. Although there is no cure for the disease, patients are treated with disease-altering drugs, which modify the course of the disease, and symptom-altering drugs, which help to improve their quality of life by alleviating chronic symptoms [53].

Spasticity can be defined as a condition of increased muscle tone related to contractions and deprivation of muscle strength, which consecutively leads to pain and mobility limitations [55]. Dysregulation of the endocannabinoid system has been detected in the CNS of patients with MS [55]. The mechanism behind cannabinoids' properties to relieve spasticity

has not been fully discovered, but it can be explained by their capacity to reduce the presynaptic release of glutamate, leading to decreased glutaminergic transmission mediated by CB1 receptors [55].

The heterogeneous image of symptoms occurring in the course of MS made it difficult to evaluate the benefits and limitations of using cannabinoids in patients with MS [54]. Nevertheless, they seem to affect patients in a multifaceted manner, improving spasticity, reducing spasms and chronic, neuropathic pain, the quality of sleep and bladder dysfunction [54].

Analysis of data collected from 1.027 respondents suffering from MS investigated benefits related to using cannabinoids, such as CBD and THC [56]. The results proved that cannabinoid use is common among patients with MS. Most frequently the respondents listed reduction of pain (80%), as well as improvement of sleep (56%) and spasticity (49%) [56]. A cross-sectional analysis reported a similar beneficial influence of cannabinoids as almost 80% of the respondents with MS experienced spasticity relief and 54% of them admitted to ever using cannabis for symptom alleviation [57].

Systematic reviews investigating randomized controlled trials provide evidence that orally administered cannabis extract, THC and nabiximols result in reducing spasticity reported by patients suffering from MS [2]. A double-blind, placebo-controlled clinical trial enrolled 179 patients from 22 UK centres to investigate the superiority of cannabis extract over placebo [58]. The results after 4, 8 and 12 weeks proved to have significant, almost twice as high rates of relief from muscle stiffness compared to placebo. The improvement perceived by patients was supported by MS scales used in the trial [58]. Another randomized, placebo-controlled clinical trial divided 630 patients from 33 UK centres into three groups receiving oral cannabis extract, THC or placebo [59]. Although the effect on spasticity assessed with the Ashworth scale did not prove beneficial, there was evidence of muscle stiffness and pain relief reported by patients receiving cannabinoids, compared to placebo [59].

Moreover, it has been evaluated that nabiximols (Sativex®) not only can provide long-term relief from spasticity but also do not show any withdrawal symptoms after terminating their usage [60]. Sativex® has been approved in many countries, such as Canada, the UK, Spain, and New Zealand, for the treatment of symptoms associated with MS [54, 61, 62]. According to the conducted meta-analysis, cannabinoids are considered safe medications as adverse effects do not present as statistically significant [63]. Despite sometimes mixed findings, rarely confirming the substantial improvement in spasticity on objective measures, patients with MS tend to perceive cannabinoids as beneficial in symptom management [2, 55, 56, 53–66].

Epilepsy

Epilepsy is a disorder caused by multiple aetiologies, such as brain injury, genetic syndromes, stroke and infection, which can affect patients of all ages [67]. It is associated with progressing loss of brain tissue, resulting in lower quality of life and several other impairments, including sensorimotor, cognitive and psychiatric disorders [10, 67]. The deterioration of the CNS function is especially dangerous in children suffering from refractory epilepsy, which affects approximately 10–20% of patients [10]. Considering the severe adverse effects of antiepileptic drug combinations used in treatment-resistant cases of epilepsy, often used in high doses, there is a pressing need for alternative medications, which would support conventional methods [10, 67].

Although the mechanisms responsible for the anticonvulsant properties of cannabinoids remain unclear [68], the downregulation of endocannabinoid signalling associated with neuroinflammation is suggested to be a crucial factor responsible for the progression of incidence and severity of seizures [10]. Of all cannabinoids, in recent years CBD emerged as the most promising therapeutic option considering its relative safety and the lack of psychoactive effect [10, 12].

A nationwide survey in Australia reported that 13% of children and 15% of adults suffering from epilepsy use or have ever used cannabis to manage epilepsy [69]. In children, 71% of the respondents experienced symptom improvement and approximately half were able to reduce the doses of anticonvulsant drugs. In adults, adding cannabis to the treatment of epilepsy resulted in a success rate of 89.5% in terms of symptom relief. It is concerning that only 6.5% of the respondents acquired cannabis legally, after a physician's recommendation [69]. Another survey included 117 parents of children with epilepsy (infantile spasms and Lennox-Gestaut syndrome), who used CBD-enriched cannabis extracts. The results showed that 85% of the participants noticed a decrease in seizure frequency in their children and 14% reported a complete seizure termination [70]. More than a half also experienced improvements in sleep, alertness and mood [70]. A similar questionnaire study conducted in Mexico reported a reduction of seizure frequency in 81% of children with Lennox-Gestaut syndrome or unspecified refractory epilepsy, as well as complete seizure freedom in 16% when using CBD-enriched extracts [71].

Several randomized, placebo-controlled clinical trials and retrospective studies conducted on patients

with refractory epilepsy and genetic syndromes support evidence from preclinical studies and strongly indicate that CBD can reduce seizure frequency [12, 67, 68, 72–78]. The Food and Drug Administration in the USA has already approved cannabinoids for the treatment of several treatment-resistant epilepsy syndromes [68, 78]. Medical cannabis, especially CBD--based therapy, could become an important addition to conventional anticonvulsive drugs used in refractory epilepsy both in children and adults as it significantly reduces seizure frequency, improves patients' quality of life and sleep patterns and does not cause severe side effects [71, 79].

Depression and mood disorders

Chronic and difficult-to-treat depressions constitute a major issue in psychiatric care [80] as not all patients improve with available antidepressant medications alone [81].

The mood-elevating and antidepressant properties of cannabinoids have been known for a long time [82]. They are based on their ability to modulate several signalling pathways involved in the development of depression, including serotoninergic, noradrenergic, glutamatergic and endocannabinoid systems [83–85]. The homeostasis of the endocannabinoid system seems to be of key importance as the attenuation of its signalling is correlated with many psychiatric disorders, such as anxiety, depression and schizophrenia [86]. Therefore, the endocannabinoid system has been put forward as a promising new pharmaceutical target for treatment-resistant depression disorders [87]. Evidence indicates that cannabinoids indeed may prove useful in the treatment of patients with depression, who failed to respond to conventional methods and antidepressants [82, 88].

Preclinical studies demonstrate that THC, by interacting with CB1 receptors, is mainly responsible for the capacity of cannabinoids to modulate depression, mood and anxiety [83, 87, 89, 90]. The beneficial influence of cannabinoids, which was initially mentioned only in animal studies and anecdotal information reported by patients, has consecutively appeared in case studies and clinical trials [82, 85, 88, 91].

Patients suffering from various medical conditions often use cannabis, prescribed or illegal, to alleviate depression symptoms and cope emotionally [92, 93]. A total of 523 HIV-positive patients participated in a questionnaire study which aimed to investigate cannabis usage in this group of patients [94]. The results showed that 27% of all respondents used cannabis to relieve the symptoms associated with HIV. 97% reported an improvement in lack of appetite and 94% noticed pain reduction. Over half of the patients demonstrated alleviation of nausea, anxiety and depression [94]. An observational study investigated the efficacy of CBD and THC in patients suffering from symptoms related to depression, anxiety and stress [95]. The results varied depending on the dosage and the THC to CBD ratio in the administered product. The highest effectiveness in managing symptoms of depression was achieved by using a high concentration of CBD with a low concentration of THC. Additionally, the authors recommended caution in case of chronic use of cannabis, which could paradoxically reverse the initially beneficial effects of the treatment and lead to an increased risk of developing depression [95]. Interestingly, other reports indicate that dronabinol, either alone or combined with other antidepressants, led to rapid and satisfactory alleviation of depression symptoms, as well as the patient's quality of life [88].

It has to be mentioned that several studies reported the negative consequences of cannabis use, such as the increase in depressive symptoms, paranoia, irritation, dysphoria, depersonalization and demotivation [82, 96, 97]. Despite sometimes contradictory results, cannabinoids, including THC, seem to be a promising candidate in the treatment of depression resistant to conventional pharmaceuticals and should be further investigated.

Stress and anxiety

Anxiety disorders include general and social anxiety, panic, phobias and, separately classified, post-traumatic stress disorder or obsessive-compulsive disorder [98]. They all share psychological symptoms, such as concentration difficulties, excessive fear and sleep disturbances, as well as somatic ones, such as heart palpitations, tachycardia and sweating [98].

Typically the most often prescribed medications are selective serotonin reuptake inhibitors (SSRI), selective noradrenaline reuptake inhibitors (SNRI), anti-seizure drugs, serotonin 1A (5-HT1A) receptor agonists, benzodiazepines, or beta-blockers, which reduce somatic symptoms [98]. Considering that anxiety and post-trauma disorders are the most common psychiatric disorders, with therapeutic options limited by their efficacy, adverse effects or delayed therapeutic response, there is a pressing need for new, alternative methods of treatment [98]. Therefore, cannabinoids should be considered a potential drug in the treatment of anxiety disorders [9].

Endocannabinoid signalling, essential for stress adaptation, can become unbalanced and decreased if exposed to severe external stressors, leading to the development of anxiety and depression [99]. Stress, as an important source of anxiety, is related to the imbalance within the serotoninergic, glutamatergic

and GABA-ergic systems, as well as pro-oxidant events in the CNS [9, 100]. The efficacy of CBD in the treatment of anxiety disorders is mainly explained by the regulation of 5-HT1A receptors and endocannabinoid signalling [98, 100, 101]. Moreover, evidence derived from preclinical studies indicates that CB1 receptors interact with peroxisome proliferator-activated receptors (PPARs) and therefore reduce oxidative stress [9]. Activation of CB1 receptors also restores the homeostasis of GABA-ergic synapses and prevents the decrease of GABA levels [9. 100].

Numerous publications are proving the beneficial effects of using CBD in individuals suffering from anxiety [101–110]. A double-blind randomized clinical trial investigated the beneficial effect of orally administered CBD on 24 patients with social anxiety, who had to undergo a simulated public speaking test, compared to 11 healthy individuals [101]. Results revealed that CBD substantially reduced anxiety, cognitive impairment and discomfort among patients with social anxiety compared to the placebo group [101]. Results of a retrospective case series also demonstrated a sustained decrease in anxiety among 72 analysed adults [106].

Considering the acute anxiolytic effects of CBD, as well as its lack of abuse potential and safety profile, it could be used in combined treatment with the first-line SSRI, due to their long therapeutic response, and in some cases — even on its own [98, 111]. The rapid onset of action makes CBD especially suitable for patients suffering from episodic social phobia who are capable of predicting the attack [101]. Current guidelines advise caution in using THC in the treatment of patients with anxiety as taken in high doses, THC can sometimes increase fear and anxiety [82]. However, it is worth mentioning that CBD exhibits the potential to diminish the psychoactive effect of THC if co-administered [98, 100].

Sleep disorders

Sleep disturbances are a common, difficult-to-treat issue in the population, with limited therapeutic drug options, often associated with unpleasant side effects and the risk of abuse [112, 113]. The potential role of cannabinoids is suspected in the treatment of common sleep disorders, such as insomnia, sleep-disordered breathing, narcolepsy and parasomnias [112, 114], as well as sleep disturbances related to comorbidities, such as fibromyalgia, chronic pain, Parkinson's disease or MS [82, 100, 115]. However, the research is limited and still ongoing [100, 112].

Cannabinoids, such as THC and CBD, influence anxiety, mood and the sleep/wake cycle by modulating the endocannabinoid system and many other signalling pathways [116]. Evidence suggests that CB1 receptors in the CNS may lead to the activation of cholinergic neurons in the basal forebrain and pons, which are responsible for sleep induction, as well as enhance the serotonergic signalling that modulates the sleep-wake cycle [112].

A retrospective study, which included patients with posttraumatic stress disorder (PTSD), demonstrated a significant increase in time and quality of sleep, as well as a reduction of nights with nightmares within the first two weeks after starting nabilone treatment [117]. Forty-seven patients with PTSD were enrolled in a clinical trial to investigate the therapeutic impact of nabilone on the severity of nightmares [118]. The results showed that 72% of the participants experienced a satisfactory improvement, among whom almost 60% reported a total reduction of nightmares [118]. Several other clinical trials also indicate the efficacy and safety of nabilone and THC in the treatment of sleep disturbances associated with PTSD [114, 119–121]. Cannabinoids exhibit dose-dependent effects on sleep, with low doses increasing sleep time, and high doses causing sleep disorders [82]. There is evidence that CBD has the potential to improve sleep duration and quality as well [102, 106, 122, 123], however, the effect seems to be present mostly in anxiety-related disorders and requires further investigation [106].

Although most preclinical and clinical studies provide insufficient evidence to recommend routine use of cannabis in the treatment of sleep disorders due to scarce literature and too high bias, the preliminary reports provide promising results and substantial indications to conduct future randomized control trials [100, 116].

Withdrawal symptoms in opioid use disorder

Reports dating back to 1889 called attention to the extraordinary properties of cannabis in the treatment of substance abuse disorder and withdrawal symptom control during addiction therapy [124]. In the face of high rates of unsuccessful outcomes of conventional opiate dependence therapies and the opioid epidemic in general, cannabinoids emerged as a new non-opioid therapeutic option [125, 126]. The findings are especially meaningful as at the same time cannabinoids can lead to a reduction of administered opioid doses in patients suffering from chronic pain [19], which may become useful in everyday clinical practice.

The interactions between the endocannabinoid and opioidergic systems in reward and withdrawal are mainly based on the overlapping co-localization

of the CB1 and MOR receptors, distributed in the same areas of the brain, as well as their behavioural pharmacology [19, 127]. Evidence indicates that the relationship between CB1 and MOR receptors leads to significant reciprocal effects on the reward properties of cannabinoids and opioids [19].

In opioid abuse disorder patients tend to suffer from multiple physical and emotional withdrawal symptoms [125], such as craving and anxiety, which strongly contribute to relapse [126]. Numerous preclinical studies have proved the capacity of cannabinoids, such as THC and CBD, to reduce opioid withdrawal symptoms [19, 128]. A double-blind randomized placebo-controlled trial proved the CBD's potential to substantially mitigate cue-induced craving and anxiety in individuals suffering from heroin use disorder [126]. Another study enrolled participants, who co-used opioids and cannabis, as well as experienced withdrawal symptoms during the previous 30 days [128]. The results showed that 63% of 200 respondents, who completed the study, reported using cannabis to reduce opioid withdrawal. 72% of them noticed the alleviation of the symptoms most often in the form of reduced anxiety (76.2%), tremors (54.1%), improved sleep (48.4%), decreased muscle aches (45.1%), restlessness (45.1%), nausea (38.5%) and craving (37.7%). Additionally, withdrawal severity scores were nearly 50% higher when cannabis was not used [128]. The results of a double-blind, placebo-controlled clinical trial, which recruited opioid-dependent patients undergoing treatment with XR-naltrexone proved the positive influence of dronabinol on withdrawal symptoms, such as insomnia and anxiety, during the acute phase of withdrawal [129]. Patients using cannabis were also more likely to sustain the treatment [129].

At least four states in the USA have approved medical cannabis as a treatment option for opioid use disorder [128]. Although the emerging evidence indicates that medical cannabis can become an efficient method of substituting opioids and alleviating withdrawal symptoms, further clinical trials on the subject are still necessary [128]. It should be remembered that chronic exposure to cannabis can lead to physical dependence and withdrawal symptoms similar to those in nicotine withdrawal, although the severity of the adverse effects is prominently more benign than opioid withdrawal and does not lead to death [19].

Anti-inflammatory and antioxidant action

Ingested, absorbed, or inhaled THC and CBD, along with other cannabis compounds, counteract oxidative stress and exhibit anti-inflammatory properties [130, 131]. Multiple reports indicate that cannabinoids suppress inflammatory responses by modulating immune cell metabolism [132], downregulating proinflammatory cytokine and chemokine production and upregulating T-regulatory cells [133].

The therapeutic effect is based on the modulation of activity and migration of the immune cells (macrophages, monocytes, neutrophils, lymphocytes, dendritic cells, NK cells, fibroblasts and endothelial cells), downregulation of pro-inflammatory cytokines [interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-12, IL-17, IL-18, interferon γ (IFN-γ), tumour necrosis factor α (TNF-α), monocyte chemoattractant protein 1 (MCP-1)], as well as increased production of anti-inflammatory cytokines [IL-4, IL-10, IL-11 and transforming growth factor β [134]. The multimodal effects of phytocannabinoids and the endocannabinoid system are presented in table 2. It is worth mentioning that using more cannabis compounds together, especially terpenes, can potentiate the beneficial effects compared to the administration of just one, which is known as the entourage effect [12, 135].

A systematic search conducted by using PubMed, Web of Science, EMBASE and Scopus aimed to gather and examine eligible preclinical studies, which evaluated the anti-inflammatory effects of phytocannabinoids [136]. The results demonstrated that CBD, CBG and CBD/THC combination consistently reduced proinflammatory cytokines, such as TNF-α, IL-1β, IL-6 and INF-γ 136]. Other preclinical and clinical studies suggest that cannabinoids can attenuate symptoms of many chronic inflammatory and autoimmune disorders, such as MS, rheumatoid arthritis, colitis, Parkinson's disease, hepatitis, and other [7, 133, 134, 137–142], as well as neuropathic and inflammatory pain [143–145]. Considering that the SARS-CoV-2 infection is associated with a cytokine storm and overproduction of IL-6, IL-8 and TNF-α, cannabinoids have been preliminarily tested for alleviating the symptoms of the disease and reducing the ongoing inflammation [99].

The anti-inflammatory properties of the plant and its individual components open brand new perspectives for their usage. From typically inflammatory diseases, with the activation of pro-inflammatory mechanisms, to their use even in prophylaxis [146]. The anti-inflammatory properties may be used as a valuable addition to the treatment of numerous diseases, however, further clinical trials are warranted [147].

General well-being

It is hypothesized that all humans have a basic endocannabinoid "profile" that reflects endocanna-

Table 2. The main anti-inflammatory modes of action of cannabinoids [7]

Type of cannabinoid/receptor	Mode of action	Effect
Cannabinoids (natural and synthetic)	Modulation of the release of pro-inflammatory mediators (IL-1β, TNF-α, and COX-2) and leukocyte recruitment mediated by GPR55	Involvement in the development of neuropathic and inflammatory pain
CBD — phytocannabinoid of *Cannabis sativa L.*	Affinity to PPAR-γ, 5-HT1A, adenosine A2A, and TRP	Antioxidant, immunomodulatory and anti-inflammatory effects, mitigation of uncontrolled cytokine production, antiviral activity, regulation of fibroblast/myoblast activation, amelioration of lung function
THC — phytocannabinoid of *Cannabis sativa L.*	Inhibition of the release of IFN-γ, TNF-α, IL-17A, and IL-22	Inhibition of the release of pro-inflammatory chemokines and cytokines by T lymphocytes
Cannabigerol — phytocannabinoid of *Cannabis sativa L.*	Reduction of the inflammatory molecules — TNF-α, IL-1β, IL-6, PGE2 MIP-1α in microglial cells	Anti-inflammatory and antioxidative properties; neuroprotective potential to reduce the severity of neurologic illnesses
CB1 receptor agonists	Limitation of the activation and differentiation of mast cells, inhibition of the release of pro-inflammatory cytokines IL-12, IL-23, and INF-γ by T lymphocytes	Anti-inflammatory effect possibly beneficial in treating chronic inflammatory skin disorders
CB2 receptor agonists	Stimulation of the receptors expressed in B lymphocytes, NK cells, monocytes, neutrophils, and leucocytes CD8 and CD4; significant decrease in pro-inflammatory M1 macrophages, increase in anti-inflammatory M2 macrophages; Inhibition of the release of cytokines IL-6, IL-12, CD86, iNOS; decrease in MCP-1, SDF-1, IL-6, IL-1β, TNF-α, TGF-β1, VEGF	Mitigation of the inflammatory response; immunomodulatory effects; Reduced infiltration of neutrophils and macrophages

5-HT1A — serotonin 1A receptor; CB — cannabinoid; CBD — cannabidiol; COX-2 — cyclooxygenase-2; GPR55 — G protein-coupled receptor 55; IFN-γ — interferon γ; IL — interleukin; iNOS — inducible nitric oxide synthase; MCP-1 — monocyte chemoattractant protein-1; MIP-1α — macrophage inflammatory protein 1α; PGE2 — prostaglandin E2; PPAR-γ — peroxisome proliferator-activated receptor γ; SDF-1 — stromal cell-derived factor 1; TGF-β1 — transforming growth factor β1; TNF-α — tumour necrosis factor α; TRP — transient receptor potential; THC — tetrahydrocannabidiol; VEGF — vascular endothelial growth factor

binoid levels (e.g. anandamide), their production, metabolism, and the relative amount and state of cannabinoid receptors [148]. Under certain conditions, congenital or acquired, the endocannabinoid "profile" becomes insufficient and generates pathophysiological syndromes. Therefore, it is necessary to consider whether there is a possible deficiency of endocannabinoids (primary or secondary) causing system failure and whether the deficiencies in this area translate into our daily functioning, especially in times when chronic stress, excess stimuli, as well as the feeling of burnout and fatigue are defining characteristics of our time.

Medicine still struggles with many common, but subjective symptoms or pain syndromes that are difficult to objectively assess and effectively treat. The most important of these are migraine, fibromyalgia, and irritable bowel syndrome. These disorders, which may overlap in the affected populations, often carry the stigma of psychosomatic etiquette and failure of subsequent therapies. In these conditions, the symptoms include hyperalgesia and central sensitization, which may suggest a common origin, namely clinical endocannabinoid deficiency (CECD) [148]. The hypothesis proposed in 2001 was based on the overlapping of genetic aspects, comorbidities, and patterns of symptomatology mediated by the endocannabinoid system. The significant fact is that the administration of exocannabinoids often provided benefits in the treatment and symptom control. Currently, people affected by migraine have documented statistically significant differences in the levels of anandamide in the cerebrospinal fluid, and advanced imaging studies have shown CECD in PTSD. Additional studies provided a firmer basis for this theory, and clinical data provided evidence of pain reduction, improved sleep, and other benefits of the cannabinoid treatment [148].

Stress has become an inseparable part of the current model of life, and the incessant chronic tension associated with functioning in the modern world can have a devastating effect on our nervous system and the ability to generate energy. A growing body of evidence points to an important role of the endocan-

Table 3. Summarized effects of CBD and THC [7, 157]

Effect	CBD	THC
Analgesic (relieves pain)	X	X
Anti-emetic (reduces nausea and vomiting)		X
Anti-spasmodic (suppresses muscle spasms)	X	X
Anti-epileptic (reduces seizures and convulsions)	X	
Antidepressant and mood-regulating (alleviates symptoms of depression)	X	X
Anxiolytic (relieves anxiety)	X	
Anti-insomnia (aids sleep)		X
Anti-inflammatory (reduces inflammation)	X	X
Immunosuppressive (modulates the immune system)	X	X
Stimulates appetite (helps to gain weight)		X

CBD — cannabidiol; THC — tetrahydrocannabinol

nabinoid system in the regulation of cognition, mood, stress and sleep [149–151]. We experience chronic mental dangers that our nervous system is no longer able to manage. This leads to a dysregulation of the stress-responsible system, as well as the endocannabinoid system [152]. Disruption of the endocannabinoid signalling results in a neurobehavioral response that mimics the classic stress response. This is manifested by activation of the hypothalamic-pituitary-adrenal axis, increased anxiety, excessive alertness, agitation, inhibition of eating behaviour, decreased response to rewarding stimuli, and impaired cognitive flexibility [153, 154]. It can cause changes in the brain and body, due to which we will feel exhausted, chronically tired, irritable, and there will be problems with concentration and remembering. Hemp, and CBD in particular, can be very useful tools to help with regaining lost balance [82].

Administration of a CB1 receptor antagonist causes several negative consequences, resulting in a multi-level deterioration in the functioning of the organism. In addition to the expected decrease in appetite, mood and sleep disorders have also been reported in its users. Patients became more irritable and agitated, and the incidence of depression and even suicide increased [155, 156].

Nowadays we live longer, but we also experience a different pace of life and levels of stress. Medicine has so far managed to significantly extend people's lives, but more needs to be done to improve its quality.

Conclusions

The presented 10 reasons why cannabinoids should be considered in everyday practice are just a shortened list of potential indications (Table 3). The prospects and clinical benefits of cannabinoids are much broader. Their use in the combination with the natural substances of the plant (the entourage effect) gives additional benefits, maximizing their therapeutic effects. So far, no standardized doses of cannabinoids have been established for selected ailments and syndromes. As in the case of other drugs, we are looking for the lowest effective dose, considering individual titration according to the "start low, go slow" principle. Optimizing the treatment with attention to detail will have potential benefits for patients with possible, but predictable side effects (especially with THC-rich strains). In medical practice, it is sufficient to maintain appropriate attention both when deciding to include cannabis in the treatment and its possible modification during the therapy. Although our knowledge and practice in this area continue to grow, more research is needed to provide conclusive evidence that would give cannabinoids a well-deserved place among "drugs made from nature".

Declaration of conflict of interests

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