

# Review of Contemporary Knowledge of the Treatment Effects of Cannabis and Related Products and Its Outlook

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## Abstract

**Aim:** To briefly review recent knowledge about the evidence-based use of medical cannabis and its derivatives. **Tools:** A selective review of clinical trials and relevant literature reviews and meta-analyses focusing primarily on the medical use of cannabis and phytocannabinoids. **Results:** A substantial part of the clinical research into the treatment effects of cannabis still suffers from several methodological and technical issues. Despite the relatively long history of medical research on cannabis and on substances isolated from the cannabis plant, only a relatively small number of sound clinical trials have been published. The gaps in clinical knowledge are caused, *inter alia*, by the administrative scheduling of cannabis and its major compounds into the United Nations Schedule/s of the most dangerous and least medically useful regulated drugs; this obsolete scheduling of cannabis and cannabinoids still remains effective, even though it is 55 years since the 1961 Single Convention on Drugs came into effect. The research on the treatment effects of the whole plant is further complicated by the fact that it contains at least 1,252 different chemical compounds. Many of them interact with each other and only within this interaction do they affect the human organism. Such a situation is difficult to analyze fully even with all the steadily-growing computing power available for recent research. Despite all the limitations, it is safe to summarize that medical cannabis and products made from it are safe drugs of choice for very common symptoms of highly prevalent diseases: (i) mid-severe and severe chronic pain, (ii) spasticity related to neurodegenerative and post-traumatic disorder, and (iii) the treatment of nausea and vomiting – be it a symptom of the disease itself or of its aggressive (chemo- and/or radiotherapeutic) treatment. Evidence of somewhat lower quality exists supporting the effectiveness of medical cannabis for the treatment of (iv) Parkinson's disease, (v) inflammations in general, including the idiopathic inflammatory bowel diseases and Crohn's disease, (vi) post-traumatic stress disorder (PTSD), and (vii) Tourette syndrome. Despite the wide publicity, only very limited scientific evidence exists on the effectiveness of cannabis and cannabinoids (CBD in particular) for the treatment of extremely frequent seizures occurring in refractory epilepsies among very young children (e.g., Dravet syndrome). There are high hopes that the known anti-tumor activity of cannabis and its direct effects on immunity and other homeostasis mechanisms will be successfully used for causal (curative) treatment of a wide array of diseases in the foreseeable future. However, there is not enough clinical evidence available to allow the introduction of cannabis-based medications for causal treatment; the cases of reportedly successful treatment are mostly published by patients and their healers, and are not verifiable by scientific methods. **Conclusion:** When assessed in accordance with the principles of Evidence-Based Medicine (EBM), cannabis and its derivatives are safe and effective treatment agents for highly prevalent symptoms: pain, spasticity, vomiting, and nausea. While further research on isolated endo-, phyto-, and synthetic cannabinoids can widely use the standard research methods, successful studies of the effects of the whole plant (and its "entourage effect") would most probably require novel scientific methodologies and designs reflecting a somehow different scientific paradigm.

## Key words

cannabis, medical use; cannabinoids; Evidence-Based Medicine; review; outlook

## Recommended citations:

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## Introduction

According to key Czech papers on the historical use of the treatment effects of cannabis [1-3], signs exist that the Chinese used cannabis for medical treatment as early as in the 28th century BCE, but actual written records only go back to the 9th century BCE. This is apparently a reference to the Chinese pharmacopoeia Shen-nung Pen Ts'ao Ching, which was founded on much older recipes handed down orally; it mainly mentions the alleviation of pain caused by rheumatism [4]. Kabelík states that by no later than the 7th century BCE, cannabis was used medically in the area of what is now southern Russia. According to Paulus Aegineta (625-690 CE), the broth from hemp seeds "dries and chases away winds, dampens sexus (and hashish just the opposite). Hemp seeds cooked and drunk while hot alleviate and disperse a dry hacking cough. It increases the fertility of hens, where they lay eggs in winter" [citováno in 2].

The Indians knew cannabis and hashish at least since the 4th century BCE. They did not use them for treatment at that time, but rather only for their psychotropic effects. In the Ayurvedic culture, the first medical use of cannabis was documented at the turn of the 13th century CE in both human and veterinary medicine. From that time on, the role of cannabis (and opium) continued to flourish in Indian folk and traditional medicine. In a text dating from 1965, a worker at the Indian Health Ministry mentioned Ayurvedic prescriptions for cannabis-based products for falling asleep (*nidraprada*), enhancing the libido (*kamada*), improvement of appetite, metabolism, and digestion (*vanhivi – vardhin*), against nausea and for getting rid of gas (*pachani*), for mental stimulation (*kaphajit*), and others [5]. The same source mentions that a substantially older inspiring force of Ayurvedic medicine, Arab healing science in India, which became known locally as the *Unani Tibbi*, had all the uses mentioned above for the cannabis plant, and used it additionally for stopping diarrhea, against bed-wetting, for alleviating pain, against conjunctivitis, against migraine headaches, and for releasing cramps and muscle tension.

According to Kabelík [2], the use of cannabis in folk medicine in the mid-20th century included the treatment of neuralgia, migraine headaches, rheumatism, melancholy, hysteria, stomach pain, and loss of appetite – all of this using a cannabis butter and/or alcohol-based extract from the upper leaves and female (rarely male) inflorescences. A water-based solution or infusion was then used for constipation and pulmonary tuberculosis and even for getting children to sleep; in Argentina it was used for stimulating urination and perspiration and in Brazil the leaves were smoked for sedation and getting to sleep, as well as against asthma. In the Czech lands, the leaves were used as a bandage against

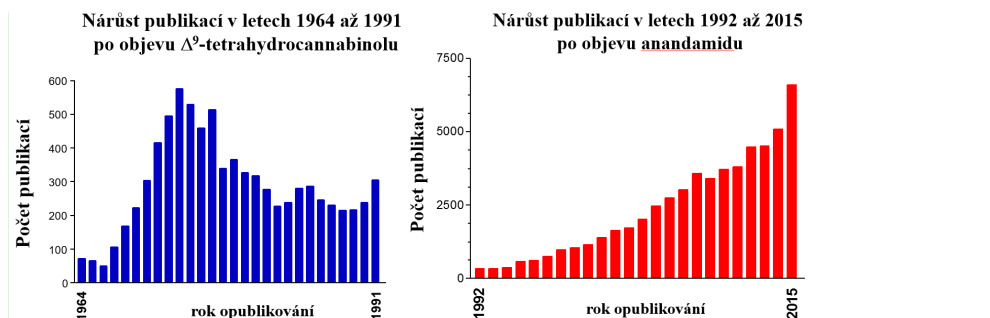
inflammation, and used in combination with vinegar and juniper in bandages to treat headaches. According to Zimmerman, [4] before its prohibition in Europe cannabis was regularly used by women for relief from menstrual pain (even apparently by the United Kingdom's Queen Victoria). Cannabis was also used in North America until the mid-20th century for the treatment of, or relief from, a series of illnesses. Kabelík recalls the use there of crushed marijuana leaves as a healing and antibiotic agent for erysipelas and boils. He also mentions its antibiotic use in Southern Rhodesia against malaria and haemoglobinuria, sepsis, anthrax, and dysentery, that the Xhosa tribe used it to treat inflammation of hooves, the Fingo tribe used the leaves to treat snakebite, and that the women of the Suto tribe smoked marijuana to quell the pain of childbirth [2].

It is essential to emphasize the utterly vital Czech contribution, not only to summarizing the history of cannabis in medicine, but especially to modern research into cannabis and its derivatives. At the start of the 1950s, led by the professor of microbiology and epidemiology Jan Kabelík (1881-1979) and his colleagues from the Faculty of Medicine at Palacký University in Olomouc (FM PU) – mainly his colleagues from the Institute of Hygiene and Epidemiology Zdeněk Krejčí (1923-1992) and pharmacological chemist František Šantavý (1915-1983) – a systematic research project developed out of Kabelík's initiated research into around 2,000 plants for antibiotic properties that dealt with potential medical methods of cannabis use. On December 10, 1954, five years of effort culminated in a scientific conference at FM PU and a monograph was published as a result of it in *Acta Universitatis Olomouensis* [6]; the impact of this revolutionary achievement was, because of the solidly built Iron Curtain, only local, so the first systematic effort to return cannabis to the place it had held even in modern medicine had to wait for the world to rediscover it 40 years later. A similar fate was shared by two utterly groundbreaking discoveries by the team from Olomouc: (i) the discovery and isolation of the first cannabinoid acids were performed by Šantavý and Krejčí back in 1955 [7], but instead of them, this was attributed to German authors [8], who "discovered" the acid only later in 1958 (without even identifying its structure), and (ii) the identification by Šantavý of the absolute configuration of cannabidiol (CBD) and delta-9-tetrahydrocannabinol (the most important psychoactive substance in cannabis; generally abbreviated to THC) including the determination of the position of their double bond in the monoterpene cycle, which he had already performed by 1963 and published at the start of the following year [9] – i.e., a year before Mechoulam and Gaoni isolated THC [10] and four years before the same authors determined the absolute configuration of delta-9-tetrahydrocannabinol [11] – identical with the absolute configuration discovered by Šantavý in 1963.

The publishing of the discovery, or rather, the resolving of the structure of THC caused a rapid growth in the number of publications dealing with cannabis and its derivatives: in 1963 in this field there were less than 100 publications per year, and after that the volume grew to several hundred papers. The discovery of cannabinoid receptors in 1988 and especially the discovery of human endogenous substances binding to these receptors in 1992 [12] clarified why cannabis is a successful medicine for such wide-ranging syndromes and why case reports and very numerous studies on the successful causal treatment of a wide range of illnesses may be based on truth – they showed what the actual aim of cannabinoids and endocannabinoids in our body is, and how deeply this system is engaged in the control of homeostasis from the system level (e.g., changes in mood, feelings of hunger, fluctuation of blood pressure) down to the cellular and subcellular level (here it is mainly important to emphasize the role of cannabinoids in controlling apoptosis – cell death). In reaction to the discovery by Devan,

Hanuš, and their team, the number of scientific papers literally exploded – it grew exponentially to several thousand papers each year (see Graph 1). The global explosion of medical and other research into cannabis and its derivatives was and is accompanied by an explosion of the use of cannabis for treatment – despite the ban on its use in a number of countries, but gradually also in the legislative environment, which systematically enables legal medical treatment by cannabis and allows for the provision and growing of medical cannabis by a special law.

By the adoption of Act No. 50/2013 Coll., the Czech Republic joined other medical cannabis countries, currently including, inter alia, a majority (27) of the states of the USA, Israel, Canada, Macedonia, Italy, Germany, Holland, Croatia, and certain other EU countries, but also, e.g., India, South Africa, and Australia. Despite this, medical cannabis is not yet being used in the Czech Republic to the extent that its positive effects for patients deserve, although the extremely low risk of adverse effects in terms of modern pharmacotherapy is sufficiently documented. That is yet another reason why the authors decided to provide this review for the journal that you are currently holding in your hands.



Graph 1: Growth in publications after the discovery of the structure of THC (1964) and after the discovery of the endogenous cannabinoid – anandamide (1992).

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Czech	English
Nárůst publikací v letech 1964 až 1991 po objevu $\Delta^9$ -tetrahydrocannabinolu	Growth in publications from 1964 to 1991 after the discovery of $\Delta^9$ -tetrahydrocannabinol
Nárůst publikací v letech 1992 až 2015 po objevu anandamidu	Growth in publications from 1992 to 2015 after the discovery of anandamide
Počet publikací	Number of publications
Rok opublikování	Year of publication

## Methods

We searched the MedLine (PubMed), Scopus, Web of Knowledge, and Google Scholar databases. The terms we searched included *cannabis*, *marijuana*, *cannabinoid/s*, *THC (tetrahydrocannabinol)*, *CBD (cannabidiol)*, *Sativex*, *Nabilone*, *Marinol*, *dronabinol*, *nabiximol/s*, and *Cannador*. We excluded studies

that dealt with recreational, harmful, damaging, and dependent use of cannabis, and concentrated on those whose topics involved the potential treatment effects of cannabis and its derivatives. In the selection presented here we concentrated primarily on the latest clinical trials, though in some cases we found it necessary to dig deeper into history with regard to references in the articles we discovered. The result is a selective review of the effectiveness of cannabis, with an emphasis on those illnesses or symptoms with the strongest cumulative evidence of the effectiveness of cannabis for their treatment/alleviation, and on current review papers that use sound classification schemes for their results.

## Results

### Current reviews of the effectiveness of medical cannabis and its derivatives for treatment

Lately, as this topic has become an ever more frequent subject of technical and political discussions, the number of authoritative reviews and meta-analyses of the therapeutic effectiveness of medical cannabis and its derivatives has mushroomed. What is considered a classic and still valid example is the monograph of the National Academy of Sciences of the USA from 1999 [13, 14]. In the Czech Republic, so far apparently the most comprehensive material is an extensive chapter in the comprehensive monograph "Hemp and cannabis-type drugs: addictological compendium" [15].

When this article was being elaborated, the latest comprehensive summary in the area of the use of cannabis and its derivatives for treatment was the comprehensive critical review of 20,000 published studies compiled at the initiative of the UK Parliament [16]. This summary concluded that today there exists

- *good* evidence supporting the effectiveness of one or more products from cannabis or "natural" cannabis for handling (i) chronic pain, including neuropathic pain, (ii) spasticity, (iii) nausea and vomiting, especially in consequence of chemotherapy, and (iv) handling states of anxiety;
- *moderate* evidence for their effectiveness for (v) sleep disorders, (vi) stimulating appetite, especially in the context of chemotherapy, (vii) fibromyalgia, (viii) post-traumatic stress disorder, and (ix) certain signs of Parkinson's disease;
- *some limited* evidence for which it is necessary to produce further studies, for (x) handling agitation as a part of dementia, (xi) epilepsy, especially young children's epilepsies resistant to other pharmacotherapy, (xii) urinary bladder dysfunction, (xiii) glaucoma, and (xiv) Tourette syndrome;
- the effectiveness of cannabis and its derivatives was designated as theoretically supported, but so far without convincing evidence from human studies (*there is a theoretical basis, but so far no convincing evidence of efficacy*), for (xv) dystonia, (xvi) Huntington's disease, (xvii) headaches, (xviii) the neuroprotective effect upon traumatic damage to the brain, (xix) depression, (xx) obsessive-compulsive disorder, (xxi) gastrointestinal diseases, (xxiii) antipsychotic effects of CBD, and (xxiv) cancer/the control of tumors.

The taxonomy used in this review [16] comes from the classification of the American Academy of Neurologists (AAN),<sup>1</sup> which distinguishes four degrees of quality of scientific studies [17]. The authors indicate as "convincing" the classification of evidence of the effectiveness of cannabis for the given diagnosis or sign if the studies are supported by at least two studies in class I, supported by a theoretical basis and further studies in classes II/III/IV; the authors indicate as "satisfactory" evidence supported by at least one study in class I and/or at least two studies in class II, supported by a theoretical basis and further studies in classes II/III; then they indicate as "limited" such evidence as is not based on any study in class I and only on one study in class II and is supported by a theoretical basis and further studies in classes II/III; the authors do not consider the lowest level of evidence as adequate for any recommendation.

In June 2015, the medical use of cannabis and its derivatives was examined in detail by one of the most widely respected medical science journals: the *Journal of the American Medical Association (JAMA)*. In sum, by reacting to the expansion of official medical treatment using cannabis into over half of the states in the USA, it states:

"The medical literature on medical cannabis was reviewed from 1948 to March 2015 via MEDLINE with an emphasis on 28 randomized clinical trials of cannabinoids as pharmacotherapy for indications other than those for which there are two US Food and Drug Administration approved cannabinoids (dronabinol and nabilone), which include nausea and vomiting associated with chemotherapy and appetite stimulation in wasting syndrome. We found that use of cannabis (marijuana) for chronic pain, neuropathic pain and spasticity due to multiple sclerosis is supported by high-quality evidence. Six randomized clinical trials with a total of 325 patients examined chronic pain, 6 trials with 396 patients examined neuropathic pain, and 12 trials on a total of 1,600 patients examined multiple sclerosis." [18]

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<sup>1</sup> AANC – the American Academy of Neurologists Classification – recognizes four quality classes of clinical trials (Koppel et al. 2014, in which

- those belonging in class I are randomized controlled clinical trials (experiments) with masked or objective assessment of outputs (dependent variables), which take place in a representative population; the relevant initial characteristics of the probands are explicitly stated and should be generally identical in all groups of studies, or the differences should be adequately statistically adjusted; also required are: (a) double-blind classification of probands into groups; (b) *a priori* definition of an unambiguous success criterion of the experiment; (c) unambiguous definition of criteria for classification into a study and elimination from it; (d) unambiguous indication of subjects who did not complete the study (and at least 80% of those who did complete it), and (e) further criteria are required for studies of equivalence or non-inferiority of treatments;
- those belonging in class II are randomized clinical experiments in representative populations with masked or objective assessment of outputs (dependent variables) which do not meet one of the criteria a-e of class I, as well as prospective structurally balanced cohort studies with masked or objective assessment of outputs in the representative population which satisfy the criteria b-e of class I;
- those belonging in class III are all other controlled clinical experiments, including those using as a control group a well-defined population of patients with a natural course of an illness (*natural history controls*) or using a design in which the control group involves patients themselves, if the experiments are performed in a representative population;
- those belonging in class IV are all studies failing to meet the criteria of the previous classes.



More detailed results and a review of the method used for a metaanalysis in that same issue of JAMA are introduced in a robust report by Whiting et al [19]. It researched 79 clinical trials with a total of 6,462 participants; only four were judged to be at a (low) risk of bias. It was proven in the vast majority of (meta-)analyzed clinical trials of the use of medical cannabis that there was substantial improvement of the symptoms that were being researched compared with a placebo, but the association did not achieve the required level of statistical significance (standard 95%) in all the studies. This metaanalysis too finds

- *moderate-quality* scientific evidence for the effectiveness of cannabis in the treatment of chronic pain and spasticity, whereas
- the metaanalysis found *low-quality evidence* for effective treatment using cannabis for nausea and vomiting in consequence of chemotherapy, for treatment of loss of body weight resulting from HIV infection, and for sleep disorders and Tourette syndrome

A summarized article from 2013 in the *Pharmacotherapy* journal [20] deals exclusively with medical cannabis and phytocannabinoids. It concentrates on the current controlled randomized clinical trials of the effects of medical cannabis in the treatment of pain and muscular spasms and its clinical implications and the direction of further research, and arrives at an absolutely positive conclusion on the therapeutic effectiveness of cannabis.

The prestigious German medical journal *Ärzteblatt International*, in an article from 2013 [21], summarizes the results of more than a hundred controlled clinical trials using medical cannabis and its derivatives. It concludes,

"Today there exists clear (scientific) evidence about the fact that cannabinoids are effective for a series of medical conditions."

The German review summarizes the state of knowledge especially for the treatment of spasticity, nausea, and vomiting in consequence of chemotherapy, weight loss/loss of appetite, and chronic pain. It also mentions small and successful randomized controlled clinical trials for bladder dysfunction for patients with multiple sclerosis, tics in Tourette syndrome, and levodopa-induced tremor of Parkinson's disease.

The same peer-reviewed journal (impact factor 3.76) published research on available clinical trials in 2012, which reached the same conclusions and quotes the official position of the Drug Commission of the German Medical Association, elaborated at the request of the Committee for Health of the German Parliament (the Bundestag), which supports the use of cannabis-based products for patients suffering from spasticity, pains, nausea, vomiting, or loss of appetite, amongst whom treatment using other drugs has not met with success [21].

In 2011, a review published in the *Magazine of the American Academy of Family Physicians (USA)* [22] 'provides in the table on pages 456-7 "Clinical Studies of Cannabis and Its Derivatives with SORT Level of Recommendation" a generally recognized methodology aimed at assessing a particular medicine or procedure, as assessed according to the principles of patient-oriented EBM<sup>2</sup> [23].

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<sup>2</sup> The assessment of patient-oriented evidence measure assesses the results of treatment, which concerns patients: morbidity, mortality, improvement of symptoms, improvement of the quality of life, and reducing treatment costs. The assessment of

The table on clinical trials of the effects of medical cannabis and its derivatives is summarized in the text as follows:

"The effectiveness of smoked or vaporized marijuana was [positively] assessed for Gilles de la Tourette syndrome, glaucoma and pain, with the highest level of proof of clinical benefit for neuropathic pain in consequence of HIV infection. Orally administered products derived from cannabis have the best clinical level of proof of relief from spasticity caused by multiple sclerosis. The oromucosal form of the cannabis extract is effective for peripheral and central neuropathic pain, especially for pain caused by multiple sclerosis" [22, str. 455].

## Detailed analysis of selected pathological conditions and the effects of cannabis and its derivatives with strong evidence supporting effectiveness

### Chronic pain

Chronic pain is an exceptionally widespread pathological symptom; it is estimated that (in relation to the definition), it is suffered at some time in their life by 8-46% of the world population [24]; most common estimates indicate 30%. This makes it one of the top priority aims of current pharmacotherapy. Most analgesics, however, have significant side effects – especially opioids, which are used most frequently for handling moderately severe to severe pain; they exhibit a significant risk of overdosing, and even lethal overdosing, as well as a very strong potential for addiction (e.g., in the USA the number of lethal overdoses on pharmaceutical opioids has long exceeded the number of such overdoses from illegal opioids, including heroin [25]); this naturally leads to a search for safer therapeutic alternatives.

The endocannabinoid system is one of the key regulators of pain, acting on all levels of its track. Neural signaling by the CB1 and CB2 receptors plays a key role in normal perception of pain and a significant quantity of preclinical trials and animal models exist confirming that modulation of the endocannabinoid system can reduce pain [26-31].

There have, moreover, been a rather substantial number of clinical trials testing synthetically produced analogs of delta-9-THC – nabilone and Marinol® – for the treatment of various types of pain, in which the control group was made up of TAU patients – *treatment as usual* – and the experimental group or groups were treated with synthetic THC alone and/or they were given it in combination with a common drug; according to the aforementioned current summary [16], the effect on pain in the experimental group was comparable to, or better than, that in the control group, and with fewer adverse side effects.

Even more clinical trials were performed for so-called nabiximols – i.e., mixtures of pure monomolecular THC and monomolecular CBD, extracted from specially cultivated plants; this is no surprise in the light of the fact that the mass-produced drug Sativex® is prepared by just the supercritical CO<sub>2</sub> extraction of those two substances from two patented cultivars of cannabis; both cannabinoids in the ratio 1:1 are then administered in sesame oil sublingually. The primary and

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disease-oriented evidence assesses the intermediary, physiological, or surrogate markers, which need not necessarily reflect an objective and subjective improvement in the patient's condition (e.g., blood pressure, blood circulation, physiological functions, or pathological findings).

generally recognized indication of this drug is for spastic pain resulting from multiple sclerosis (for which it is also approved in the Czech Republic (CR), where extensive clinical verification of the drug also took place within the framework of multicentric clinical trials, subcontracted by the manufacturer) [see, e.g., 32]; Sativex®, however, is not available in the CR, and patients are reliant on extensive individual imports not covered by health insurance; the clinical trials nevertheless proved its effectiveness even for other types of pain – rheumatoid arthritis [33], allodynia [34], and cancer pain [35], as well as for pain refractory to treatment with opioids [36].

A key study in relation to the treatment of pain using cannabis was recently published by Canadian authors: the clinical trial designed as a prospective cohort study dealt not with further research on the effectiveness of cannabis for the treatment of pain, which is considered sufficiently proven, but rather with the safety of this treatment, involving a total of 215 patients with chronic non-carcinogenic pain in the experimental group (using cannabis) and 216 patients in a control group (using a different analgesic appropriate for the given type of pain). The measuring involved serious adverse side effects and less serious adverse side effects, and along with them secondary safety outputs – pulmonary and neurocognitive functions, standard hematological and biochemical indicators, and renal, liver, and endocrinologic values. Also considered were the desired side effects for symptoms including pain, mood, and overall quality of life. The study found no difference between the groups in terms of the risk of serious adverse side effects; the experimental group had a slightly higher (IRR=1.73) risk of less serious adverse side effects. The study concludes that the safety profile of the monitored use of medical cannabis for the treatment of chronic pain<sup>3</sup> is entirely satisfactory.

Another current clinical study – a randomized, double-blind and placebo-controlled clinical trial in cross design for 16 patients – tested the effectiveness of four types of aerosolized cannabis (THC 0%, 1%, 4%, and 7%) for the treatment of painful diabetic neuropathy of these probands [37]. The study proved the dependence of the success in treating spontaneous and the pain evoked per dose or per concentration of THC in cannabis; the highest concentration showed significant worsening of the results of the probands in two of the three neuropsychological tests that were used.

A systematic review of randomized clinical trials (RCTs) of the effectiveness of cannabis and its derivatives for treating chronic non-carcinogenic pain was published in 2011 in the *British Journal of Clinical Pharmacology*; this review, adhering strictly to the PRISMA (EBM) criteria for systematic reviews of randomized clinical trials, found that the quality of all the studies included was exceptionally high. The products tested included smoking medical cannabis (four randomized controlled clinical trials with a placebo), oromucosal extract from cannabis (seven RCTs), nabilone (four RCTs), dronabinol (two RCTs), and a new analog of THC labeled as CT-3 (two RCTs). All four randomized controlled clinical trials with a placebo that tested the effectiveness of smoked cannabis in alleviating neuropathic pain (of these two studies dealt with neuropathic pain caused by HIV) proved the effectiveness of the administration of such cannabis without significant side effects [38].

Another current and widely conceived summarized article on the prospects and current use of medical cannabis and cannabinoids in medicine in treating pain and spasms [20] identifies six randomized controlled clinical trials researching the effects of medical cannabis used by means of smoking in a

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<sup>3</sup> The average dose in the experimental group was 2.5 grams of cannabis with a standardized THC content of 12.5%.

summarized table; all the RCTs assessed proved the high therapeutic effectiveness of medical cannabis administered by this means.

An extensive review of the state of knowledge on the use of cannabis for pain treatment was published in 2009 by the *Pain Med* journal, with the unambiguous conclusion of proof of the effectiveness of medical cannabis and its derivatives for the treatment of chronic pain of varying etiology, including neuropathic and carcinogenic etiology [39], and regarding negative results in terms of acute pain treatment. Several other summarized articles arrive at the same conclusion [see, e.g., 40].

A brief review of the current state of knowledge on the treatment effectiveness of cannabis and its derivatives for the treatment of pain and other symptoms for HIV and malignant diseases was published in the *Journal of Palliative Medicine*; it describes their effectiveness and mentions (psychotropic) side effects and the variably wide therapeutic window which cannabinoids have in this regard [41]. A summarized article on the treatment of pain for multiple sclerosis emphasizes the therapeutic value of cannabis and cannabinoids, especially for patients resistant to other (older) treatments [42].

In an extensive controlled clinical trial of the effectiveness of medical cannabis for patients with type 1 or type 2 diabetes mellitus, an Israeli study prepared for publication finds significant relief of neuropathic pain in the experimental group in comparison with the control group (TAU), and describes a significant decrease in therapeutic doses of insulin in the experimental group (personal message in correspondence with Dr. Yehuda Baruch, T. Záborský).

In relation to the discussion of the potential acute or chronic threat to the cognitive skills of patients treated with medical cannabis, it is necessary in conclusion to point out the relatively recently published double-blind RCT proving the exceptional effectiveness and safety of the treatment of neuropathic pain by relatively low doses of medical cannabis, administered by means of a vaporizer [43].

Two years ago, in a long-awaited editorial of a special section of the scientific journal *General Hospital Psychiatry*, Professor Bostwick of the Mayo Clinic, after carefully assessing research articles and the latest research in the area, concludes: "[To our oftentimes very complex questions] we have no easy answers, and in their absence, medical cannabis should be available as another tool at the physician's disposal for careful and considerate building of [individual] analgesic programs for patients" [44].

#### Vomiting and nausea

The positive effects of cannabis – especially when smoked but also used in other ways – to alleviate nausea and vomiting have been known for centuries [45]. Clearly the most effective antiemetics are selective antagonists of serotonin receptors, but in many countries they are not used as the drug of first choice for the given indication because of their adverse side effects and for several other clinically important reasons. Meanwhile, the importance of medical cannabis and cannabinoids in the treatment of these often life-threatening states is constantly strengthening [46], *inter alia* because a mechanism has been proven, mainly by CBD and THC (and CBG and certain other phytocannabinoids contained in cannabis) acting on CB2 receptors suppressing nausea.

A review of clinical trials published in 2001 and performed in six states of the USA found 70-100% relief from nausea and vomiting amongst patients taking chemotherapeutic treatment for various types of

cancer who smoked medical cannabis (N=748) and 76-88% relief of those who took THC orally in capsules (N=345) [47].

The review of clinical trials in the area of chronic pain treatment [46] mentioned above recommends considering the treatment of vomiting and nausea by means of cannabis-based products, especially in palliative treatment of elderly patients.

Published last year and also already cited, the authoritative *Cochrane Systemic Review* compared 23 randomized controlled clinical trials that compared cannabis and/or products derived from cannabis with control groups which received either a placebo or the usual antiemetic treatment. The authors conclude that cannabis and cannabinoids are more effective than a placebo and comparably as effective as conventional antiemetic products (typically prochlorperazine and metoclopramide). Patients using cannabinoids nevertheless mentioned unwanted sedation, intoxication, and the feeling of a dry mouth more frequently. The summary concludes that cannabis/cannabinoids may be a useful therapeutic choice amongst ill persons where other antiemetics fail [48].

A research report from 2015 on studies of the antiemetic and vomiting episode-alleviating effects of cannabis and cannabinoids in treating malignant diseases also deals, inter alia, with the lower reduction of bone matter during radiotherapy with cannabinoid use, its protective effect against chemotherapeutic nephrotoxicity and cardiotoxicity and relief of pain, moodiness, and insomnia, and also mentions its cancer-fighting effect [49].

And lastly, we refer to 2015 detailed review by Whiting et al. [19] in the prestigious journal *JAMA*, which explicitly states that cannabis and its derivatives act against vomiting and nausea at least as well as conventional antiemetics or somewhat more effectively.

#### Spastic conditions and related symptoms in neurology

Spasms in neurological disease are linked with sleep disorders and pain, and are one of the causes of increased patient morbidity [50]. Just behind pain, they are the next most researched area of the potential use of cannabis and its derivatives in human medicine [16].

In this area, robust examination is being conducted of the effects of the mass-produced drug (HVLP) Sativex® on multiple sclerosis ("MS"); there is an entire series of publications, but it is not the aim of this paper to assess the effectiveness of Sativex® for MS – inter alia, also in the light of its factual unavailability in the CR (see above). Let us therefore mention at least the latest published studies and reviews by Flachencker [51-53], the follow-up study confirming the long-term safety of Sativex® by Ferre [54], and the study by Zettl [55], which, on a large sample of 1,600 patients and covering 1,500 patient years, confirms only a less serious degree of side effects – fatigue and a feeling of loss of balance [16].

Also studied was a standardized extract from the entire cannabis plant administered sublingually, but also an orally administered extract from medical cannabis – primarily for MS [20]. The effectiveness of the extract is considered proven by several RCTs [recently, 32, 56], and in countries where it is available, it is normally recommended as a drug of second choice for the given indication.

The American Academy of Neurology (USA) published its recommendation for the use of complementary and alternative methods for treating multiple sclerosis in March 2014. The

effectiveness of the oral use of cannabis extract for short-term relief of symptoms affiliated with spasticity was assessed at the level "A" (the highest level, with utterly convincing scientific evidence); the same assessment was gained by the *ineffectiveness* of ginkgo biloba for the improvement of cognitive functions amongst patients with MS [57].

In April 2014, *Neurology* published systematic research aimed at the effectiveness and safety of medical cannabis for selected neurological diseases, which is a basis for relevant directives of the Classification of Evidence of the American Academy of Neurology (AAN)1 [17]. Thirty-four studies met the criteria for classification into the research, of which eight were classified as "Class I." For classification purposes, the classification scheme of the AAN for reports on the therapeutic effect was applied. According to these criteria:

- for spasticity in multiple sclerosis, an oral cannabis extract is effective, and nabiximols and THC are probably effective for reducing subjective symptoms; it is possible that the oral extract and THC are effective in reducing subjective and objective symptoms over a period of at least one year;
- for central pain and painful spasms (including spastic pain, excluding neuropathic pain), an oral extract from cannabis is effective, and THC and nabiximols are probably effective;
- in terms of bladder dysfunction, nabiximols are probably effective for reducing the daily frequency of urination, while THC and an oral extract from cannabis are probably ineffective;
- for reducing tremors, THC and an oral extract from cannabis are probably ineffective and nabiximols are possibly ineffective;
- in terms of other neurological diseases, an oral extract from cannabis is probably ineffective for the treatment of levodopa-induced dyskinesia in Parkinson's Disease; oral cannabinoids have no significant effectiveness for the treatment of non-choreic symptoms of Huntington's disease, Tourette syndrome, cervical dystonia (spasmodic torticollis), and epilepsy.

Certain studies also verified the effect of orally administered medical cannabis for spastic conditions incidental to multiple sclerosis. In a double-blinded RCT, the patients from the experimental and control groups did not report statistically significant differences in relief from spasms according to the (problematic) Modified Ashworth Scale ("MAS"); a significant decrease in the number of spasms and in the spasticity score, as well as improvement of mobility, were all proven [20].

A complex explanation of the effect of medical cannabis and illegal "street" marijuana on symptoms associated with multiple sclerosis (as well as amyotrophic lateral sclerosis) is given by a recent review of literature published in the *Handbook of Experimental Pharmacology* [58]. The research also discusses the therapeutic potential of phytocannabinoids from cannabis as a means for slowing down the progression of both illnesses, as well as providing relief from their symptoms.

Pertwee, in his review from 2002 [59], mentions eight RCTs of smoked medical cannabis, oral THC and nabilone. All of these studies found a statistically significant decrease in spasticity, pain, tremor, and nocturia.

A Canadian randomized single-blind trial from 2012 investigated the effects of smoking cannabis on a sample of 37 patients with multiple sclerosis, whose symptoms were resistant to other forms of therapy. The results of the sophisticatedly designed trial proved a significant improvement on all scales

of pain and their spastic score; a limitation, however, is the small number of participants and a discussion was even led regarding blinding.

#### *Spastic conditions after spinal cord injury*

There is as yet just one specific study of spastic symptoms after a spinal cord injury [60]: a double-blinded controlled clinical trial with a crossover design on 11 subjects ascertained a substantial reduction in the MAS score for the most affected muscle and a significant decrease in the total score.

In agreement with Barnes and Barnes (2016), we conclude that convincing evidence exists supporting the effectiveness of the treatment of subjectively perceived spastic symptoms in a series of diseases – among these especially multiple sclerosis – with the help of nabiximols and oral (total) extracts from cannabis; convincing evidence also exists for the safety of their administration. Also considered sufficient are cases of evidence of the effectiveness of these products for reducing the spasticity score. According to the same source, it is not possible to give a proper reliable recommendation of the effectiveness of other types of products made from cannabis.

### Detailed analysis of selected pathological conditions and effects of cannabis and its derivatives with weaker clinical evidence and a strong theoretical basis favoring effectiveness

#### Parkinson's disease

This disease, whose symptoms especially include a decrease in the number of dopaminergic neurons in the basal ganglia ("BG"), is, because of its high prevalence (especially among older patients) and the simultaneous existence of endocannabinoid receptors in the BG system, often cited as a potential aim of therapy with cannabis [61, 62]. It is also known that oftentimes patients themselves experiment with cannabis for treatment – e.g., in an anonymous questionnaire from the Movement Disorders Center of the Clinic of Neurology of the 1st Medical Faculty and General Teaching Hospital, Charles University in Prague, up to 25% of the patients who responded mentioned experimenting with cannabis, and nearly half of them claimed there had been a subjective improvement of their condition [63].

However, there exist relatively few clinical trials on this topic and they exhibited mixed results.

A well-known study from 2004 did not prove any statistically significant improvement in consequence of using an oral extract from cannabis for levodopa-induced dyskinesia in 17 Parkinson's disease patients [64]; on the contrary, a new study 10 years later involving 22 patients [65] identified significant improvement on the *Unified Parkinson's Disease Rating Scale* 30 minutes after smoking cannabis, and it also found statistically significant improvement among specific motor symptoms of the type – tremors, rigidity, bradykinesia, and others, and, moreover, without serious side effects.

Chagas et al. experimented for Parkinson's disease with pure CBD; their most thoroughly elaborated study on 22 patients did not find by objective measuring any statistically significant differences between the placebo group and the groups with the doses of 75 mg and 350 mg daily; differences, however, were found in their perceived quality of life [66].

Though there exists a theoretical basis supporting the effectiveness of cannabis and/or substances derived from it for alleviating symptoms of Parkinson's disease, there still exist few quality clinical

trials with a sufficient number of patients which reliably verify such effectiveness. According to Barnes and Barnes (2016), it is possible to consider as merely limited the clinical evidence supporting the effectiveness of cannabis and its derivatives for treating Parkinson's disease and/or its symptoms. Trials with pure CBD need not be completely relevant as the entourage effect (see *Discussion*) is not reflected in their designs.

### Sleep disorders

The use of cannabis as a medicine for insomnia and other sleep disorders was already described in antiquity, and a series of cannabis users reports a positive effect in this direction – both recreational users and those who use cannabis as a (self-) treatment [67, 68]. The role of the endocannabinoid system in regulating sleep is relatively well described [69] and the use of cannabis for relief from sleep disorders has been described in the oldest available written materials [2]. Nevertheless, only few modern clinical trials exist dealing with the effects of using cannabis and its derivatives for sleep. The study by Ware et al. [70] dealt with the effects of nabilone<sup>4</sup> on the quality of sleep for fibromyalgia and found it was superior to amitriptyline. Other studies that are regularly cited in reviews of the effects of cannabis and various types of cannabinoids on sleep also cite this effect as a secondary finding – it typically concerns primarily studies on pain, multiple sclerosis, rheumatoid arthritis, the aforementioned fibromyalgia, or PTSD.

It is somehow surprising, as sleepiness and fatigue are generally well-known symptoms of "recreational" use of cannabis substances [71], the participation of the endocannabinoid system in the sleep process is considered proven [69], and the effects of cannabis and its derivatives on sleep disorders have been known since antiquity [2].

However, according to the principles of EBM, it is necessary for now to consider the evidence of the effectiveness of cannabis products for sleep disorders as only "satisfactory" [16], and for its routine introduction to the pallet of treatment agents, further studies will be needed.

### Fibromyalgia

This is a relatively very frequent disease affecting, according to various sources, around 5-8% of the population, and affects women eight times more frequently than men. Its most explicit symptoms are chronic pain affecting every part of the body and increased painful response to pressure stimuli. The cause of fibromyalgia is not known, but it is clearly an autoimmune disease [16]; it is also considered unambiguous that neurotransmitters are involved, including endocannabinoids. A recent systematic review of the relationship of the endo/cannabinoid system and autoimmune diseases [72] illustrates the significant potential of cannabinoids as an immunosuppressive and antifibrotic – and therefore also are generally potential for the treatment of fibromyalgia (and rheumatic diseases).

There are relatively few studies dealing primarily with the therapeutic effect of cannabis and its derivatives on fibromyalgia; they rank among observational or analytical studies and suffer from relatively small group sizes: despite this, however, they all refer to decreased pain and stiffness, improved relaxation, and a subjectively perceived improvement in quality of life both for isolated THC [73] and for an extract from the entire cannabis plant [74].

Two studies analyzed the effect of the synthetic cannabinoid nabilone on the quality of sleep [75] and pain relief [76] for fibromyalgia; both concluded their findings in favor of nabilone over the usual



therapy.

Barnes and Barnes (2016) conclude in their review that sufficient clinical evidence exists for the handling of pain and sleep disorders using nabilone and the entire cannabis plant for fibromyalgia. For routine implementation, however – just as for other diagnoses described in this subchapter – further studies are needed, with a stronger design and applied to larger samples.

It is therefore possible to recommend the implementation of this therapy only in those cases in which a different treatment does not bring relief.

### Idiopathic bowel inflammation: Crohn's disease and ulcerative colitis

With regard to the known anti-inflammatory effect of a series of phytocannabinoids (and terpenes) and since the activation of CB1 receptors influences several functions of the gastrointestinal tract (GIT) (occurring in its neurons, and in sensory endings of the vagal nerve and spinal neurons) and CB2 receptors appear in immune system cells, inflammatory bowel diseases (“IBDs”) have become a logical focus of the current interest of researchers.

The first study on the use of medical cannabis by persons suffering with Crohn's disease was published in 2011. According to this retrospective observational study, 21 out of a total of 30 research subjects reported substantial improvement in their condition and significantly decreased use of other drugs [77]. The authors continued by founding a study with a stronger design – a prospective blind placebo trial on 21 patients for whom Crohn's disease did not react to any available treatment; in the experimental group, complete remission of the disease occurred for five out of 11 subjects (in the control group for one subject), and for 10 out of 11 subjects, the condition substantially improved (for four in the control group) [78].

Lal et al. [79] performed a questionnaire-based study on 100 patients with ulcerative colitis and 191 patients with Crohn's disease: 51% of the patients stated that they had used cannabis at some time in their lives, and another 12% stated current use – this was especially concentrated in a group with chronic abdominal pain, and a low quality of life index, and/or who had just had surgery. All the patients with a history of use or current use of cannabis claimed a subjectively perceived improvement of their symptoms.

The last clinical study we found from the GIT area was published in 2012 by Tel Aviv physicians: in their pilot prospective study of 13 individuals with IBDs not reacting to standard treatment, they ascertained after three months of application of inhaled cannabis a statistically significant increase in body weight, improvement in perception of their own health condition, and ability to work and social performance, along with a decrease in pain and depression. For all the patients with Crohn's disease, a significant decrease was registered in CRP and other inflammation markers [80].

For the group of diseases characterized by (idiopathic) inflammation of the gastrointestinal tract, theoretical justification therefore exists for the effectiveness of cannabis and its derivatives. The as yet small quantity of studies with small numbers of participants and other methodological limitations – though promisingly indicating both symptomatic and curative effects of cannabis and its derivatives – does not suffice for other than trial administration of cannabis in this diagnostic area.

## Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is, along with moderately severe to severe pain, the most frequent cause of the indication of medical cannabis in Israel (personal correspondence with Ilya Reznik; Tomas Zabransky, 2016), the country with the highest per capita use of medical cannabis. It is also a frequent indication for treatment by cannabis and its derivatives in 27 states of the USA where the medical use of medical cannabis is legal (personal correspondence with Michael Krawitz; Tomas Zabransky, 2016). Persons suffering from PTSD often seek out cannabis for self-treatment and consider it successful [81, 82]. According to the current state of knowledge, PTSD is apparently caused by hyperactivity of the amygdala, and cannabis evidently reduces the impact of the traumatic memories by some kind of "calming" of the amygdala, thus leading to an improvement in sleep and a decrease in the frequency of experiencing "flashbacks" and the resulting anxiety [83, 84]. Influencing the endocannabinoid system is therefore the logical aim of treating both maladaptive cognitive and emotional problems after traumatic experiences – especially for those patients where the medicines of first choice (selective serotonin reuptake inhibitors) do not bring improvement [85, 86].

In 2014, a double-blinded placebo controlled clinical trial was published utilizing functional magnetic resonance to research the effect of cannabinoids (orally administered nabilone was used<sup>4</sup>) to suppress the recalling of traumatizing memories. The results showed, *inter alia*, that those areas of the brain engaged in the suppression of fear were significantly more active among subjects to whom this synthetic THC was administered [87]. A Canadian double-blinded placebo controlled clinical trial of military veterans suffering from PTSD also used nabilone; the results proved a significantly lower occurrence of nightmares among the experimental group and overall improvement of their health condition.

In 2012, Israeli psychiatrist Ilya Reznik published a naturalistic observational study describing the monitoring of the effectiveness and safety of medical cannabis during treatment of 80 of his patients suffering from PTSD. The results showed good tolerance, an improvement in objective measurements of quality of life and a decrease in traumatic scores, especially among patients with comorbidities [88].

Back in 2011, a large research project took place in the USA among 5,672 adults with the aim of describing the relationship between PTSD and the use of cannabis; according to expectations, it ascertained a statistically significantly higher use of cannabis among persons with PTSD, and a strong correlation between the seriousness of the symptoms of PTSD and the quantity of cannabis consumed. This could support the literature that considers the consumption of cannabis for PTSD as self-medication – however, because of the cross-sectional nature of the survey, it is not possible to draw any conclusions from this study about the causality or its direction (i.e., whether hypothetically cannabis could not be a cause of more severe forms of PTSD, and not self-medication of persons suffering from these forms of the illness).

There exists a relatively large quantity of studies on PTSD and cannabinoids, similar in quality to the Reznik's one – in their review, Barnes and Barnes (2016) quote further retrospective studies using nabilone and the entire cannabis plant and case reports where cannabis was used successfully for alleviation of the symptoms of PTSD.

Thus, enough evidence exists supporting the effectiveness of nabilone for the treatment of PTSD

symptoms, and quality-limited (by design and/or sample size) evidence of the effectiveness of the whole cannabis plant. In this regard, the situation may be changed by studies that have been prepared by Dr. Sisley in Colorado [89] and further study centers in the USA and Israel – according to the available information, the medical form derived from the entire cannabis plant would be used in her study.

### Tourette syndrome

This very socially challenging disease has a significantly higher prevalence – around 1% – than had been previously estimated [90]; despite this, treatment results have been highly unsatisfactory. A series of case reports exist of successful relief from symptoms (frequency of tics and involuntary expressions of speech) with the help of cannabis over a relatively long historical timeline [4]. Surprisingly, only two controlled clinical trials exist, which, however, did not deal with the effectiveness of the plant or complex extract from it, but only of isolated THC, and both were performed under the leadership of the same author [91-93]. Both were successful – the study from 2002 proved in a sample of 12 persons suffering from Tourette tics the effectiveness of a single dose of THC for reducing tics and obsessive-compulsive behavior; later, a single-blinded and placebo controlled trial on 24 patients confirmed the results of the previous study; up to 10 mg of THC daily was administered to the experimental group. The study also proved only negligible acute side effects of the selected dosage, and zero impact on cognitive abilities [94]. Despite this, it is possible to consider this clinical evidence of relatively good-quality clinical trials as only limited, with the need for further replications of trials, and on larger samples if possible. The authors of this review also hypothesize that studies using (products from) the cannabis plant instead of isolated THC could lead to even more favorable results than when using only one cannabinoid (see *Discussion*).

### Epilepsy

This widespread disease affects around 1% of the population. It is stated that an effective treatment exists for around 80% of epileptic manifestations by a single anticonvulsant, which fully controls the disease. A minority of epileptics suffers from refractory epilepsy, but even the condition of most of this minority is well controlled by a combination of two or three anticonvulsants. Despite this, there exists a significant minority of epileptics among whom the available pharmacotherapy fails; this especially applies to wide-ranging forms of serious childhood epilepsy with high frequency of seizures such as Dravet syndrome or Lennox-Gastaut syndrome. A fundamental complication of mainstream treatment of forms of epilepsy is the serious side effects of the anticonvulsants: this most frequently involves blurred vision, nausea, drowsiness, and dizziness, while more rarely more serious somatic damage and allergic reactions appear.

The anticonvulsant effects of phytocannabinoids have been known for many years [4, 95, 96] and have been convincingly demonstrated in preclinical and animal models [97]. It seems that while in certain cases, THC is anticonvulsant and in certain others proconvulsant, CBD has uniformly anticonvulsant effects, and the same is expected for Cannabidiol.

GW Pharmaceuticals has developed a liquid HVL containing CBD extracted from plant material under the commercial name Epidiolex, and it is performing clinical testing for the aforementioned high-frequency refractory childhood epilepsies; the only result published as yet states a median decrease in the frequency of seizures by 36.5% [98].

The study, based on reports by the parents of children who used products from cannabis containing CBD for their refractory epilepsy, found a significant decrease in the frequency of seizures in 85% of cases, and for 14% even their complete disappearance [99]. The Israeli retrospective study described the effect of the use of medical cannabis with an increased content of CBD (THC-CBD ratio of 1:20), administered orally in olive oil: 89% of the children reported a reduction in their seizures; 18% reported a 75-100% disappearance; behavioral improvements, reduced agitation, and improvements in communicativeness and motor skills, along with improvements in sleep, were also described.

Unfortunately, all these studies are insufficient in proving a causal link, suffering mainly from a significant systematic selection error inherent in the designs of the studies. Therefore, we are waiting for the results from more robust studies that may enable the projection of unambiguous theoretical bases, convincing results of animal studies, and promising results of already published studies into clinical practice, thereby alleviating the suffering of thousands of children and their families.

### Cancer

The antineoplastic activity of cannabinoids has been known for a relatively long time [100] and a massive volume of publications describing this effect *in vitro* exists [e.g., 101, 102-114].

Mainly in recent decades, one cannot help but notice a sharply rising wave of interest in the treatment of all sorts of tumors through cannabis, which relates in particular to so-called "Phoenix Tears": cannabis concentrates prepared by organic solvents, normally with a very high concentration of THC and trace quantities of other substances contained in the cannabis plant; two non-physician healers have contributed most to its development and still do – its Canadian (re-) discoverer Rick Simpson and the Czech Jindřich Bayer; currently, however, it concerns a massive global phenomenon reaching all developed and developing countries, and spreading mainly by means of social networks and specialized websites. Though, according to their proponents, "Phoenix Tears" are a treatment for just about all illnesses, thus embodying some kind of panacea (see [www.hempcures.work](http://www.hempcures.work)), the Simpson's extract is mainly drawing the attention of tumor diseases due to increasing prevalence of cancer in the developed world. At various places on the Internet, numerous publicly available case studies exist from various countries and social layers, which could (and should) direct research, especially towards use of the entire plant and products derived from it, because that is just how it is used in these case reports (see *Discussion*). These case studies of widely varying quality – with shared, fully disclosed medical documents, semi-anonymous, or also entirely anonymous – report successful use of the cannabis plant and its derivatives in various forms of administration, from inhalation and oral administration to suppositories [e.g., 115]. Case reports of cancer treatment with the entire cannabis plant and its derivatives occasionally appear in the scientific literature as well [116].

For now, the mechanism of the effect is not very well known; the hypothesis intuitively emerges for the selective influencing of apoptosis (cellular death), in whose control the endocannabinoid system plays a key role [117] and has been verified many times over in *in vitro* cancer cells [118, 119]. It is nevertheless probable that because of the complex role of the endocannabinoid system in controlling homeostasis, substantially more mechanisms are at play. Neither is it clear that the antitumor effect is limited to specific types of cancer (the most promising ones on the basis of *in vivo* trials, animal studies, and very rare human studies seem to be gliomas and other nerve cell tumors, prostate tumors, and estrogen-negative carcinomas of the breast (cited in Barnes & Barnes, 2016)). For now, the most recent

reviews containing plausible hypotheses on how modulation of the endocannabinoid system could be effective for the treatment of a series of sub-types of cancer have come from Nikan, Nabavi (103) and Velasco et al. [102].

Despite a strong theoretical basis for the anti-cancer effects of cannabis and its derivatives, only precious few official medical human studies exist. In one of them [120], Liang and his team studied the correlation between cancer of squamous cells in the neck and head and cannabis use. They came to the convincing conclusion that a ten-to-twenty-year history of marijuana use substantially reduces the risk of this cancer. In Spain, Guzmán et al. [121] performed a first pilot phase of a clinical trial with recurrent glioblastoma multiforme on nine patients whom all available therapy had failed, including aggressive chemo- and radiotherapy, and they reported unambiguous signs of progress of the tumor. THC was administered directly into the tumor – testing the safety of this form of administration was the main aim of the study, and in this regard the study was a total success. One of the secondary findings was also proof of the anti-tumor effects of THC on an *in vivo* tumor.

For reasons stated at the start of this chapter, clinically applicable results of research in treating cancer using cannabinoids and the entire cannabis plant and its derivatives make up one of the most fervently sought-after products of contemporary "cannabis science". The authors of this review believe that the theoretical basis and frequent case reports should orient medical research – and its sponsors – towards this direction on a much greater scale than is the case today. The problems that prevent this to a certain extent are explored in the *Discussion*.

Nevertheless, until clinical research is significantly developed in this area, the introduction of (curative) treatment of tumors in human medicine will be as distant as it is now, when causal treatment with cannabis and cannabinoids is not considered an official medical procedure founded upon the principles of EBM.

## Discussion

### Limitation of the selective review

The scientific literature dealing with cannabis and its derivatives aimed at clarifying the potential for its use in human medicine or routinely introducing them suffers from a series of weaknesses: a large number of studies have taken place and are still on very small or small samples, a significant quantity of isolated case studies exists, but only very few are double-blinded placebo controlled clinical trials of high quality and relevance for positively identifying causality.

This is caused in particular by the economic, logistical, and ethical demands of these studies, and in the first place the illegality of cannabis – including its use for treatment – in most of the countries of our world today.

The indications stated in our selection are far from covering all the indications recommended and/or researched in the available original research or scientific review papers; we tried to summarize only those most relevant for the Czech environment, and in them mainly for the work of the general practitioner. Barnes and Barnes (2016) list in their extensive review further indications for which valid

and reliable bases in scientific literature exist, but which still do not meet the requirements of EBM: ADHD, glaucoma, trichotillomania, tinnitus, pruritus, nocturnal paroxysmal anxiety, asthma, respiratory disorders, dystonia, neuroprotective effects after traumatic brain injury or spinal cord injury and after stroke, Huntington's disease, dementia (especially Alzheimer's disease), amyotrophic lateral sclerosis, psychosis and other psychiatric illnesses, (substitutive) treatment of dependencies on other psychotropic substances, and persistent hiccups.

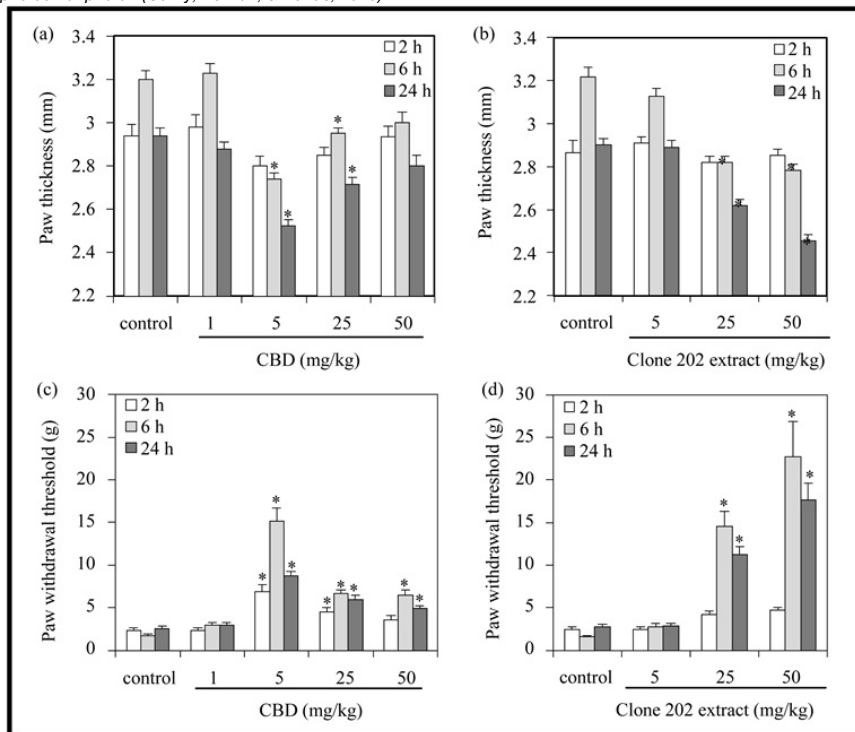
### Limitations of traditional scientific studies and the need to change the paradigm: the effect of individual cannabinoids vs. the complex "entourage" effect of the cannabis plant

The entourage effect, which one might describe as the "complex effect of substances from the entire cannabis plant" can be defined as a *complex mutual effect of biologically active – but also biologically inactive – chemical substances derived from cannabis, which modify their effect so that it is unique, and differs from the effect of isolated substances derived from cannabis, and from combinations of only certain of its substances; "substances" include mainly phytocannabinoids, terpenoids, and flavonoids, but also other compounds.*

The term "entourage effect" in the given context was first discovered in the works of Ben-Shabbat and Mechoulam [122, 123]; in their second paper, the authors point out that the effect they described (relatively simple potentiation of the bond of one acylglycerol ester to both known endocannabinoid receptors in the presence of two different biologically inactive acylglycerol esters) can have a more general impact: "This type of synergy could play a role in the frequently shared (but experimentally unconfirmed) opinion that in certain cases, plants are a better medicine than natural chemical substances that have been isolated from them."

Meanwhile, one of the co-authors of this review took part in a study [124] which experimentally proved the *entourage effect*: while the dependency curves of anti-inflammatory and analgesic effects for a dose of pure CBD exhibit a bell shape (the effects decrease rapidly after a certain dose has been achieved), when the extract from an entire plant with a high CBD content was used, these curves exhibited the classic dependency of the effect on a dose up to achieving a *plateau* – the effect did not decrease upon a further increase in the dose. The same differences in curves were observed in the same study for inhibition of the signaling protein of a systemic inflammation. What is also extraordinary is the fact that to achieve the same anti-inflammatory and analgesic effects, a much smaller dose of CBD contained in the standardized cannabis extract was needed than when purified CBD was used.

Image: anti-inflammatory and painkilling effects of intraperitoneally injected (isolated) CBD (graphs (a) and (c)) and of an extract from a cannabis clone with high CBD content (graphs (b) and (d)).  
 Graphs (a) and (b) indicate the level of prevention of swelling induced by injecting Zymosan into the left rear paw of a mouse. Statistical significance of the differences is  $p < 0.001$ .  
 Graphs (c) and (d) indicate the painkilling (analgesic) effect measured by von Frey by a nociceptive test: the higher the threshold for withdrawing the paw, the higher the antinociceptive (painkilling) effect of the drug. The results had statistical significance at a level of  $p < 0.001$  or  $p = 0.01$  (Gallily, Yekhtin, & Hanus, 2015).



Cannabis contains a large number of chemical substances; as of December 27, 2016, a total of 1,269 compounds were known, of which 144 were phytocannabinoids, 150 were terpenes and terpenoids, and 50 were flavonoids and flavonoid glycosides, and an entire further series of other substances such as amino acids, phenols, glycosides, amines, sugars, hydrocarbons, alcohols, ketones, esters, acids, fatty acids, vitamins, heavy metals, and others [125, 126].

In the light of this number of compounds and the quantity of their possible combinations (if we only take phytocannabinoids into account, there are up to  $5.5 \times 10^{249}$ ), it can be expected with significant certainty that the research methods of medicine, bio/chemistry, and other areas of the natural sciences that use quantitative research approaches will not be able, in the historically predictable period, to describe the *entourage effect* in comprehensive fashion – or even deeply enough for us to understand the potential modifications of the effect of the cannabis plant or products derived from it upon a change in the content of one or several substances, and be able to control such an intricate yet fragile complex by outside intervention without the risk of adverse side effects, even with the ever more

steadily-growing computing power that exists. The situation is further complicated by the inability described below "to patent" a natural compound or even the plant as such (though valid patents do exist for certain specially bred cultivars and genetic profiles of *Cannabis* – e.g., those used by the British pharmaceutical company GW Pharmaceuticals for their own mass-produced product).

Despite this, we are confident that thousands of case studies being shared by ill persons (often with their own medical documentation) on widely varying social networks on specialized and publicly accessible websites (one of thousands can be found, e.g., at <http://www.cureyourowncancer.org/>) represent a potential basis for methodically solid experimental verification of the complex *entourage effect* of cannabis, not achieved by mono- or double- and multiple-component pharmaceutical products.<sup>4</sup> If this expectation of ours is confirmed, it will mean an important challenge for the methodology of clinical and sub-clinical trials – because a conventional ambition of biomedical research is the isolation of a "molecule", a detailed description of its effect, and experimental verification of its (potential) therapeutic use while taking into account potential secondary (in the absolute majority binary) interactions with other "molecules," generally with other medicines that are already known or used.

If it can be proven through further studies that the *complex effect of substances derived from cannabis* systematically differs qualitatively from the effect of isolated substances and their combination, and that at this time we do not know how to reliably "break them down into prime factors and the system of their interrelationships", it may be essential to change the paradigm for the effective and ethical development of research on the treatment effects of cannabis and its derivatives – even for human clinical research. In a certain sense, it would concern a return to a functional approach, which brought humankind, for example, Acylpyrin (aspirin): since 1832 this has saved at least millions, if not hundreds of millions of lives – but the mechanism of the effect of acetylsalicylic acid only became known later, in 1971. So it was used for 140 years before it became clear "how it worked". This is the most extreme case – but dozens of much more modern drugs exist whose "molecular mechanism" was not or is not yet known, and despite this they are used successfully – from lithium to Methocarbamol.

Also acting for the benefit of clinical research, which would preferably take into account the *entourage effect*, is the huge gap between an effective and a lethal dose of all the known active substances derived from cannabis.<sup>5</sup> Upon appropriate identification or "typing" (metabolomic,<sup>6</sup> genosequential,

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<sup>4</sup> Medications available in the EU and in Anglo-Saxon countries include "Dronabinol/Marinol" (orally administered pure THC, produced synthetically); "Nabilone/Cesamet" (a synthetic cannabinoid with effects identical to those of THC, administered orally), and Sativex® – a two-component product – a sublingual spray, containing THC and CBD gained by extraction from specially bred cultivars of cannabis; for the mixture of these two substances in a vehicle (usually sesame oil), the generic term "nabiximol" is often used. Also pharmaceutically manufactured are certain synthetic cannabinoids for the treatment of pain, spasticity, and inflammation; the synthetic cannabinoid Ribonamant, acting as an CB1 antagonist and used in 2006-2009 as a drug against obesity, was withdrawn because of its serious side effects, which included severe depression and increased suicide rates.

<sup>5</sup> There has never been a single case recorded in history of a lethal dose of marijuana or hashish or any other product derived from cannabis, even despite the long, massive, and, in the last three decades, rapidly rising global popularity of these products as "recreational drugs". Even in laboratory conditions, it was never possible to achieve a systematic lethal effect among larger animals – even, e.g., after administering three grams of THC per kilogram of body weight; trials derived from smaller animals – mice, rats, etc. – report LD50<sup>5</sup> at 700-1200 mg THC/kg; this means that a man weighing 70 kilograms would have to ingest or otherwise get into his body in a few dozen minutes around six kilograms of pure THC or smoke around 30 kg of highly potent ("strong, with high THC content") psychotropic cannabis. Both can be considered technically absolutely ruled out.

<sup>6</sup> metabolom: characteristics of the complete group of low-molecular substances in a biological sample



other) a specific cultivar, or cannabis plant, or possibly a routinely manufactured product derived from it, with all safety measures preserved, it is possible to perform clinical experiments using such typed products not only as symptomatic medicines but also as causal (curative) medicines fully in compliance with all the ethical requirements of clinical research. Similarly as for acetylsalicylic acid 185 years ago, for cannabis and its derivatives it must apply that "first we examine what functions, and in the second (or third) place how it functions". Meanwhile, no reason exists for not spreading this paradigm from single-component medicines to metabolically or otherwise characterized mixtures, or specifically to mixtures that represent cannabis plants and products derived from them.

### Economic and regulatory problems influencing research on cannabis and cannabinoids and their introduction into routine treatment

It is with some wonder that the authors note how little interest – with the exception of enthusiasts and narrowly focused specialists – appears globally among the wider medical community in researching cannabinoids and their introduction into treatment, and how little activity physicians – especially in Europe – exert in this area.

At least a partial explanation lies, in the authors' opinion, in the fact that the factual [to some extent and in some countries only, though - see 127] impossibility of effective international patenting of natural molecules or molecular complexes or even entire plants or other organisms (and the consequent commercial monopoly on them) substantially reduces the willingness of pharmaceutical companies (which are easily the largest global sponsors of pharmacological research) to invest in researching cannabis and cannabinoids – and particularly to pay for the escalating requirements for the multiple and extremely costly testing of the "absolute safety" of a medicine.

It appears almost unbelievable that 25 years after the discovery of the endogenous cannabinoid – anandamide – and description of a series of its effects even a single clinical (and according to our knowledge even a preclinical) study has yet to be performed with it. Let us recall that insulin, which Frederick Banting discovered with his colleagues in 1921, was practically clinically tested just a few months thereafter. In 1948, Edward Kendall discovered the antirheumatic properties of cortisone (which he had isolated in the 1930s), the following year he administered it experimentally to ill persons, and the Merck company introduced it into clinical practice in 1950 [128]. Countless similar examples can be found in both the older and more recent history of modern medicine.

Research on cannabinoids and further cannabis derivatives – either in the complex of the entire plant or isolated – and the initiation of research on anandamide and other endocannabinoids are thus being massively hindered by the current worldwide practice of exceptionally demanding processes in terms of time and money, which were introduced – at least declaratively – in the interest of increasing the safety of new drugs and the protection of patients. One can object that the safety profile of phytocannabinoids is entirely exceptional, and in the case of anandamide, it concerns a human endogenous substance – but these too, according to today's rules, must be tested repeatedly, and not only in terms of toxicology.

This status, of course, and specifically in the case of cannabinoids, paradoxically increases the number of those who tend towards self-treatment cannabis, which is often of dubious quality and contains a

series of admixtures – mainly sprays and molds – which could pose a risk to ill persons.

According to unofficial information (and targeted "leaks", which are a usual part of the PR strategy of global companies), there does not exist among the "Big Ten" pharmaceutical and biotechnology firms a single one which, to a certain extent, would not perform its own research on the possibility of influencing the endocannabinoid system, mainly at the level of mono- and oligo-nucleotide synthetic products. However, this research, of course, occupies only a "low profile" in the strategies of these firms – especially because despite the interest of natural scientists, physicians, pharmacists, and biochemists, the marketing departments of these companies have yet to find a reliable method of capitalizing on the potential results of such research. It is possible to expect that in a time when even mammoth pharmaceutical corporations rely ever more on income from generics, and are investing an ever smaller portion of their profits into research, the most probable strategy will be "to wait, assess, and possibly purchase a successful 'ready-made' product" – which is the model that these same corporations have successfully tried in certain biotechnologies.

So if any appreciable progress is to occur in understanding the potential for influencing the endocannabinoid system with the aim of treating not just the symptoms, but also the causes of a series of (varying) diseases, whose pathogenesis is demonstrably influenced by the cannabinoid system, room opens up in the situation of insufficient stimuli for the corporate sector in part for agile small businesses with a high degree of flexibility – startups, which we know primarily from the IT sector and which are spreading successfully as an investment model across various economic sectors – but mainly for public (thus state, international, or multinational) support for academic, public, and private entities.

It is also necessary to emphasize that because of the long-persisting illegality of a demonstrably effective medicine, we have arrived at an unusual and perhaps unique state in which patients using cannabis for treatment "illegally" are, along with their "healers", in terms of knowledge of it, of the interactions with other medicines, and of dosage and other aspects of successful therapy, at least several steps ahead of physicians – and in the medical profession this is an unlikely and extremely uncomfortable state of affairs.

At the same time, however, these same patients often do not have any idea what cultivar they used and what substances it contained, and so their possibly successful treatment – and again it is necessary to refer to hundreds of known case reports of healing both the symptoms of many illnesses and the illnesses themselves – has nearly no benefit for the treatment of other patients with the same illness. If we are to move forward towards successful use, it will be essential to have the sincere multilateral cooperation of analysts, patients (including those who have been or are being treated outside the medical system), and physicians, and this cooperation must state and follow rules that will satisfy all the participating groups, not just one of them.

The discoverer of the structure and synthesis of THC, Raphael Mechoulam, declared during the first International Conference on Cannabis and Cannabinoids in Prague in 2015 that if and when medicine realizes how to purposefully influence the endocannabinoid system, it will be capable of treating tens and hundreds of incurable diseases at the causal level (see [www.medical-cannabis-conference.com](http://www.medical-cannabis-conference.com)). The authors of this review identify with this opinion and deduce that since the endocannabinoid system is a part of homeostatic mechanisms at all known levels – from system-wide to subcellular – even its "only" functional control (without deep and perfect insight into the complex interactions – see

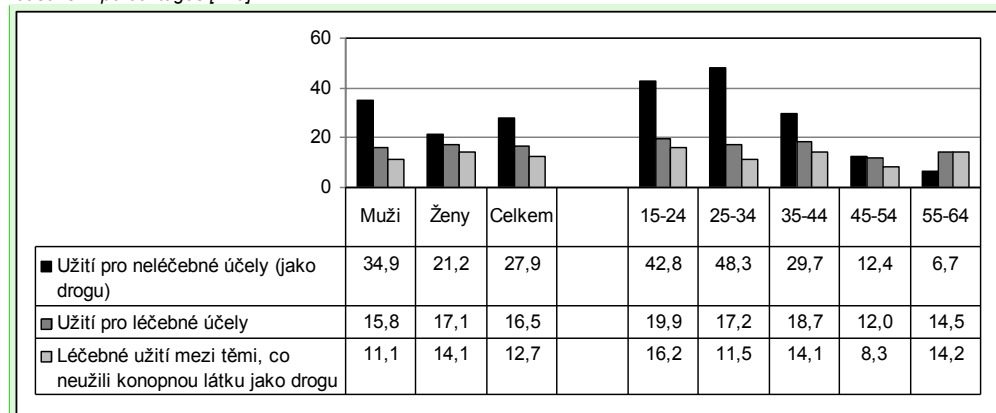
the previous chapter) can represent a revolution comparable with the discovery of antibiotics, if not greater.

### Status of the use of cannabis and cannabinoids in medicine in the Czech Republic

In 2012, 28% of the population of the Czech Republic (CR) aged 15 to 64 stated they had at least one personal experience of cannabis use. The use of cannabis-based substances for treatment purposes was reported by a total of 16.5% of those questioned (15.8% of the men and 17.1% of the women), and 10.7% of those questioned (10.4% of the men and 11.0% of the women) reported such use within the last year.

It is necessary to emphasize that at least 13% of the whole Czech population – and thus, nearly half of those who have experience of cannabis – used cannabis with the aim of improving their health condition, and they considered the psychotropic effect of cannabis as undesirable.

Image: Comparison of life-long prevalence of use of cannabis-based substances for non-treatment and treatment reasons in percentages [129]



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Comment [2] : opět bude třeba pro web přesázet / překreslit

Czech	English
Užití pro neléčebné účely (jako drogu)	Use for non-treatment purposes (as a drug)
Užití pro léčebné účely	Use for treatment purposes
Léčebné užití mezi těmi, co neužíli konopnu látku jako drogu	Therapeutic use among those not using cannabis substances as a drug
Muži	Men
Ženy	Women
Celkem	Total

In other words: in the CR there are around 950,000 people aged 15 to 64 who have used or use cannabis exclusively with the aim of improving their health condition.

Meanwhile, the official medical use of cannabis in the CR – i.e., as a result of a medical diagnosis' and under the supervision of a physician – was or is being used by just over 100 patients, i.e., roughly

0.001% of the population; on the website of the State Agency for Medical Cannabis, 16 physicians working with this medicine published their contact information, and according to unofficial information, there are around 25 such physicians altogether in the CR; according to current legal and sub-legal norms, around 15,000 physicians working in the CR are authorized to do so.

These two comparisons – (i) the interest of ill persons in using cannabis treatment for their ailments versus the number of those to whom such care is provided on an official medical basis, and (ii) the number of physicians authorized to provide treatment using medical cannabis compared to those who actually do so – serve as convincing proof that in this area the Czech medical community is failing to fulfill the patient demand to administer a drug that presents minimum danger and proven effectiveness – while it quite eagerly embraces areas such as “Chinese medicine”, “homeopathy”, or other dubious healing methods, whose effectiveness was never proven by any of the methods required by EBM.

That is rather alarming, as the treatment effect of cannabis and its derivatives for a series of wide-ranging symptoms of serious illnesses that are highly prevalent in the CR is utterly indisputable – as shown by this review and thousands of scientific papers published in highly prestigious periodicals and monographs.

A detailed analysis of why, since April 2013 (when treatment using medical cannabis was legalized), the Czech Republic has not been able to utilize the relatively favorable legislative environment and at least approach the advanced countries where this treatment has also been introduced, and which have comparable or more favorable demographic and public health profiles according to the number of officially medically indicated patients,<sup>7</sup> lies outside the focus and scope of this review. It is irrefutable, however, that this is not the fault of insufficient interest among patients or the inadequacy of this treatment for the Czech Republic's most widespread diseases or their symptoms.

## Conclusion

Cannabis and its derivatives constitute, in line with the principles of Evidence-based Medicine, safe and effective treatment for widespread pathologic symptoms: pain, loss of appetite, vomiting, and spastic conditions. Weaker evidence in terms of quality and quantity exists for its use to treat the symptoms of Parkinson's disease, Tourette syndrome, the treatment of dementia among the elderly (especially Alzheimer's disease), epilepsy (especially frequent [not reacting to other treatment] childhood epilepsy), insomnia and other sleep disorders, fibromyalgia, post-traumatic stress disorder, anxiety, and certain other maladies.

Much hope is held about the potential of medical cannabis and its derivatives for (causal) treatment of a series of diseases, among which clearly the ones most discussed by laypersons and professionals alike are the various types of cancer.

While other clinical research on isolated endo-, phyto-, and synthetic cannabinoids can and will continue to use the standard battery of research designs determined primarily for research on

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<sup>7</sup> e.g. Israel (0.6% of the population), 24 states of the USA (of these states an average of 0.8% of the population and 0.5% of the nation as a whole), Canada (0.2%), the Netherlands, and others.

intermolecular interaction with the organism, it is highly probable that studying the effects of the entire plant will require a shift in the research paradigm in order to take into account the complex "entourage effect" both for symptomatic and for causal treatment.

Although since the spring of 2013 a relatively favorable legislative environment has existed in the CR for treatment by cannabis in a relatively wide range of indications, Czech medicine and the state administration have not yet been able to tap into this potential to at least approach the level in the most advanced countries in the field. Thus, in the CR, the vast majority of *lege artis* indicated patients are flocking towards illegal sources of cannabis of unknown quality, with all the legal and health risks accompanying such behavior exhibited in the name of one's health.

This is caused not least by the low level of attractiveness of cannabis and its derivatives for large pharmaceutical companies as the major sponsors of pharmacological research; the authors of this review believe that these are just the kinds of cases where states and supranational non-commercial structures should and must enter into play, as the purpose of their existence and primary aim is not and cannot be to generate profit, but rather the wellness of citizens and fulfillment of their human rights, including the right to health and quality of life.

### **Statutory Declaration**

The authors of this paper hereby declare that in relation to the topic, origin, and publication of this article, there is any conflict of interest, and that neither the origin nor the publication of this article was supported by any pharmaceutical company. This declaration concerns all the co-authors.

The first concept of this review arose in late November/early December of 2015 as accompanying material for submission to the State Institute for Drug Control ([www.sukl.cz](http://www.sukl.cz)) with the aim of achieving the repeal of the Measure of a General Nature of SÚKL 004/2013, which banned any payment *magistra liter* for medicines containing medical cannabis or its derivatives under medical insurance.

The authors prepared it within the framework of their *pro bono* membership in the supervisory board of the non-governmental organization KOPAC, z. s. ([www.kopac.cz](http://www.kopac.cz)), associating patients in the CR who are being treated or want to be treated with medical cannabis and its derivatives. For the purposes of journal publication, this concept has been thoroughly updated and expanded.

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