Medical cannabis in the treatment of cancer pain and spastic conditions and options of drug delivery in clinical practice

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The use of cannabis for medical purposes has been recently legalised in many countries including the Czech Republic. As a result, there is increased interest on the part of physicians and patients in many aspects of its application. This mini review briefly covers the main active substances of the cannabis plant and mechanisms of action. It focuses on two conditions, cancer pain and spasticity in multiple sclerosis, where its effects are well-documented. A comprehensive overview of a few cannabis-based products and the basic pharmacokinetics of marijuana's constituents follows. The review concludes with an outline for preparing cannabis (dried inflorescence) containing drug dosage forms that can be produced in a hospital pharmacy.

Key words: cannabis, pain, cancer, spasms, multiple sclerosis, mechanism of action, THC, cannabinoids

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INTRODUCTION

Cannabis is an annual dioecious plant containing over 1,300 natural compounds[1]. It diverged around 27.8 million years ago from *Humulus*, the hop plant[2] and botanic taxonomy classifies cannabis as follows: order *Urticales*, family *Cannabaceae*, genus *Cannabis* (hemp), species *sativa* Linné[3]. There is continuing debate whether cannabis is one species (*Cannabis sativa*, with several subspecies and varieties) or if there are several distinct species (*Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*) (ref.[2]). Marijuana was domesticated thousands of years ago and the two most frequently cited hypotheses on the origin of cannabis domestication locate the centre to either China or Central Asia[4,5].

Cannabis was used therapeutically for almost 5.000 years (first noted in China 2737 B.C.) (ref.[6,7]). In ancient and medieval cultures it was predominantly used for the treatment of various somatic disorders including headache, fever, bacterial infections, diarrhoea, rheumatic pain and malaria, apart from its psychoactive uses[6,8,9]. Western medicine also used cannabis, particularly in the 19th century. It was a common analgesic drug before the introduction of Aspirin[10].

Naturally occurring phytochemicals of the species *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis* comprise nearly 1,300 chemical entities. Of these, more than 140 are classified as phytocannabinoids[11] – substances able to bind to cannabinoid receptors. These compounds are present in the highest amounts in the viscous resin produced by the glandules of female cannabis inflorescence[12]. Eleven chemical classes of phytocannabinoids were defined by Elsohly et al.[12]. These include: 1) cannabigerol type, 2) cannabichromene type, 3) cannabidiol type, 4) (-)-Δ9-trans-tetrahydrocannabinol type, 5) (-)-Δ8-trans-tetrahydrocannabinol type, 6) cannabicyclol type, 7) cannabielsoin type, 8) cannabinol type, 9) cannabinodiol type, 10) cannabitriol type, and 11) miscellaneous type. The (-)-Δ^9-trans-tetrahydrocannabinol type, cannabinol type, and cannabidiol type are the most abundant and best known. They are also the most studied and used/tested in clinical trials as therapeutic agents.

The main psychoactive ingredient is Δ^9-tetrahydrocannabinol (THC) (ref.[13]). The other compounds of non-cannabinoid nature involve among others, nitrogenous compounds, amino acids, proteins, enzymes, glycoproteins, sugars, alcohols, aldehydes, ketones, fatty acids, esters, lactones, steroids and terpenes, thus the profile of the *Cannabis* plant is very complex[12]. Its characteristic aroma is due to volatile terpenoids, not cannabinoids[14].

From the medical point of view, cannabinoids are the best studied components of cannabis. Herbal cannabinoids or phytocannabinoids are compounds produced especially by female plants of *Cannabis sativa* and found in the resin of the herb. The first substance isolated from *Cannabis sativa* was cannabinol at the end of the 19th century[15]. The major psychoactive substance is THC, which was isolated in 1964 (ref.[16-18]) and the majority of the phytocannabinoids were isolated shortly afterwards. The best explored phytocannabinoids are THC, cannabidiol (CBD), tetrahydrocannabivarin, tetrahydrocannabiorcol, cannabichromene and cannabigerol[19,20]; the first real cannabinoid compound in cannabis plant (cannabidiolic acid) was isolated and identified by Krejci and Santavy

in 1955 (ref.[20]). Cannabis plant varieties differ greatly in their content of THC. The concentration of THC in industrial hemp is less than 0.3% and according to legal bodies is not considered a substance of abuse and thus its possession is not restricted in the Czech Republic. On the other hand, strains producing higher amounts of THC or CBD have been recently cultured and these may contain up to 25% of THC in the dried inflorescence[21].

The effects of phytocannabinoids are mostly associated with their ability to influence the function of the endocannabnoid system. This consists of endocannabinoids, cannabinoid receptors and enzymes involved in endocannabinoid biosynthesis and degradation[22]. Thus, actions of both endocannabinoids and phytocannabinoids are mediated by cannabinoid receptors CB_1 and CB_2. Both types of receptors are coupled with the G protein[23]. CB_1 receptors are found particularly in the central nervous system (CNS) in regions of the brain responsible for movement, pain modulation, and memory[24,25]. They are also expressed in smaller amounts in some peripheral tissues such as immune cells, reproductive tissues, pituitary gland, gastrointestinal tissues, sympathetic ganglia, heart, lung, urinary bladder and adrenal gland[26]. In contrast, CB_2 receptors are found especially in the peripheral tissues, with the highest density in immune cells[26], tonsils and spleen[27]; however, they have also been found within the CNS (ref.[28]). Besides the two "classical" receptors, cannabinoids can act on $TRPV_1$ receptors (transient receptor potential cation channels subfamily V member 1, also known as the "capsaicin receptor" and "vanilloid receptor" 1) (ref.[29]) and the existence of other G-protein cannabinoid receptors (putative cannabinoid receptors) has also been suggested – GPR12, GPR18, GPR55 and GPR119 (ref.[30-32]).

APPROVED CANNABIS-BASED PRODUCTS AVAILABLE IN THE CZECH REPUBLIC AND EUROPE

Two categories of cannabinoid medicines are currently approved in the Czech Republic: ready-made products containing standardized extract of cannabis sold under the trade name Sativex® and crude medical cannabis (marijuana) available as a pharmaceutical compound with a standardized content of 19% THC and 6% CBD, 16% THC and 0.1% CBD or 10% THC and 10% CBD. Crude medical cannabis is intended for use as individually prepared preparations. Sativex® (GWPharmaceuticals, Salisbury, Wiltshire, UK) is an oromucosal spray containing 38-44 mg/mL and 35-42 mg/mL of two extracts (as soft extracts) of *Cannabis sativa, folium cum flore* (Cannabis leaf and flower) corresponding to 2.7 mg Δ^9-tetrahydrocannabinol and 2.5 mg cannabidiol per mL. According to SmPC, Sativex® is indicated for the treatment of adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded to other anti-spasticity medication and who showed clinically significant improvement in spasticity related symptoms during an initial treatment trial.

The term "medical marijuana" is in general related to the cannabis that healthcare providers recommend for therapeutic purposes[33]. The State Agency for Medical Cannabis in the Czech Republic defines medical cannabis as dried female flowers of *Cannabis sativa* L. or *Cannabis indica* Lam. plants. It contains a range of active substances, among others Δ^9-tetrahydrocannabinol and cannabidiol. Cannabis issued in pharmacies meets qualitative requirements defined in the Decree No 236/2015 Coll. It is indicated as supportive treatment to moderate symptoms accompanying serious diseases. According to the definition, the expressed content of THC as percentage is in the range 0.3% - 21.0% and expressed content of CBD as percentage is in the range 0.1% - 19.0%. The actual content of both THC and CBD in medical cannabis must not differ more than ± 20% from the value given by the producer. As mentioned above, currently available medical cannabis contains 19% of Δ^9-THC and 6% of CBD, 10% Δ^9-THC and 10% CBD or 16% Δ^9-THC and 0.1% CBD.

It can be seen, that despite the tremendous number of compounds present in cannabis, the greatest attention is being paid to two substances – THC and CBD. Δ^9-tetrahydrocannabinol, the main psychotropic substance in cannabis is a partial agonist of cannabinoid CB_1 and CB_2 receptors. Cannabidiol (possessing no psychotropic effects) is referred to as an antagonist of CB_1/CB_2 receptor agonists in CB_1- and CB_2- receptor expressing cells or tissues[26]. This mechanism could lead to the assumption that CBD decreases the effects of THC, however it has been shown that it may conversely potentiate the pharmacological effects of THC via a CB_1 receptor-dependent mechanism – by increasing CB_1 receptor density[34]. Moreover, it has been also shown that CBD can stimulate vanilloid pain receptors (VR1), inhibit uptake of anandamide, and weakly inhibit its degradation[35].

In compliance with the legal rules mentioned, medical cannabis can be prescribed by physicians of the following professional competences: clinical oncology, radiation oncology, neurology, palliative medicine, pain treatment, rheumatology, orthopaedics, infectious medicine, internal medicine, ophthalmology, dermatovenerology, geriatrics and psychiatry. Indications involve among others: chronic persistent pain – especially in association with cancer, neuropathic pain, pain associated with glaucoma, pain associated with degenerative disease of the musculoskeletal system, spasticity and pain in multiple sclerosis, tremor caused by Parkinson's disease, nausea and vomiting particularly following cancer treatment, stimulation of appetite in cancer and HIV patients, Tourette syndrome and superficial treatment of dermatosis and mucosal lesions.

Besides Sativex® and medical cannabis, there are two other cannabinoids approved for use in other countries – nabilone (Cesamet®, Cesamet, Valeant Pharmaceuticals, Aliso Viejo, CA, USA) and dronabinol (Marinol®, Solvay Pharmaceuticals, Brussels, Belgium) (ref.[36]). Both nabilone and dronabinol are available in capsules and are used to treat chemotherapy-induced nausea and vomiting, particularly in oncologic patients who have not responded

to standard means for control of these conditions[37]. Dronabinol is also used to treat anorexia associated with AIDS (ref.[38]). Dronabinol is synthetic THC, nabilone is synthetic THC analogue; each of these substances has partially agonistic effect at the cannabinoid CB_1 and cannabinoid CB_2 receptors[37].

CLINICAL EXPERIENCE WITH CANNABIS IN CANCER PAIN AND MULTIPLE SCLEROSIS

Cancer pain

It is generally accepted that smoking cannabis ameliorates the perception of pain in healthy volunteers[39-41]. However, it is questionable, whether the effect is of antinociceptive or rather psychotropic nature and possibly both components may play a role[42]. From the pathophysiological point of view, cancer pain comprises both nociceptive and neuropathic components. Hence, all the clinical studies assessing the role of cannabis in this condition are relevant. Unfortunately, there is a lack of studies evaluating the therapeutic effectiveness of pure cannabis in cancer pain exclusively.

Importantly, the analgesic efficacy of cannabinoids (THC 5–20 mg orally and levonantradol 1.5–3.0 mg i.m.) was confirmed in a meta-analysis of 9 clinical trials, where these substances were administered in patients with cancer, chronic non-cancer, and acute postoperative pain (total n = 222). Their effects were very similar to codeine (50–120 mg), which is commonly referred to as a weak opioid analgesic (The Number Needed to Treat, NNT for codeine 60 mg for acute pain: 16.7; 11.0–48.0) (ref.[43]). This conclusion is somewhat contradictory as NNT values for THC in the treatment of distal sensory predominant polyneuropathy are 3.5 and 3.6 according to Abrams et al.[44] and Ellis et al.[45], respectively.

Considering cannabis smoking effects in pain, several studies have been published so far. Abrams et al. observed the superior effectiveness of smoking cannabis over placebo (three times a day for 5 days) in experienced smokers suffering from the neuropathic pain of HIV-associated sensory neuropathy (n = 50). When compared to placebo, it significantly reduced daily pain (-34% vs. -17%; P = 0.03). Reduction in pain greater than 30% was achieved in 52% and 24% subjects on cannabis and placebo, respectively (P = 0.04). Importantly, smoked cannabis (3.56 % tetrahydrocannabinol) also reduced hyperalgesia to both brush and von Frey hair stimuli ($P \leq 0.05$) (ref.[43]). The beneficial effects of smoked cannabis in HIV-patients with distal sensory neuropathy (both in terms of the total pain relief and the proportion of patients with at least 30% pain relief versus placebo) were additionally achieved in another placebo-controlled trial (n = 28) (ref.[45]).

Also, the other published trials on smoked cannabis assessed its effects in neuropathic pain. Wilsey et al. in his double-blinded, placebo-controlled, cross-over study evaluated its effects in thirty-eight patients with central and peripheral neuropathic pain. An analgesic response to cannabis with good tolerance was achieved[46]. Smoked cannabis of four different potencies (0%, 2.5%, 6% and 9.4% tetrahydrocannabinol) was additionally evaluated in 21 adults with post-traumatic or postsurgical neuropathic pain over four 14-day periods in a double-blind, placebo-controlled, four-period crossover trial. Only cannabis with a potency of 9.4% THC administered three times a day for five days significantly reduced the intensity of pain, improved sleep and was well tolerated[47]. Lower doses possessed only insignificant trend. All these studies are reflected in the latest guideline for the treatment of neuropathic pain published by NICE (ref.[48]).

Smoking cannabis was reported to be effective also in patients with non-cancer pain (i.e. post-traumatic pain, osteoarthritic pain etc.) as presented and discussed in several papers[49-52], however, the extent of its use in this indication might be limited by adverse effects[53].

To our knowledge, there has been no well-designed clinical trial with cannabis monotherapy in the treatment of cancer pain. It is also demanding to perform such a study and thus, the evidence of antinociceptive effect of cannabis is only indirect. Nonetheless, as mentioned above, some its antinociceptive effects were recorded in various types of pain. Importantly, cannabis/cannabinoids are well recognized antiemetic agents, hence an additional benefit of their use in oncologic patients undergoing chemotherapy might be expected[54].

Multiple sclerosis

The therapeutic efficacy of medical cannabis in managing symptoms of MS was evaluated in several case-studies and clinical trials with relatively heterogeneous results. Probably in the first clinical trial evaluating 10 adults with spasticity and 10 healthy volunteers found that smoking cannabis impairs posture and balance in patients with spasticity[55] During the late 90's., Schon et al. described beneficial effect of smoking cannabis resin in one patient with MS. He substantially improved in terms of dramatic suppression of acquired pendular nystagmus. Surprisingly, he did not respond adequately either to oral nabilon or capsules containing cannabis oil[56]. The typically mentioned problem with the use of cannabis in any therapeutic indication, including MS, is the side-effects (namely, central nervous system disorders – drowsiness, anxiety, paranoia etc.) as well as the attitudes of the society to any use of marijuana. Therefore, the evaluation of attitudes of MS-patients in this relation was very important to establish. Page et al. published a work, where MS-patients were asked to describe their own beliefs with cannabis (n = 420). The majority of them (96%) considered cannabis as potentially useful. Forty-three percent had their own experience with this plant, however, only 16% of these cases were related to MS. These patients reported especially an improvement in general symptoms of MS (e.g. anxiety/depression, spasticity and chronic pain) (ref.[57]). This corresponds with results published by Clark et al. one year later, where stress, sleep, mood, stiffness/spasm, and pain were substantially improved in medicinal cannabis users (n = 34; orally or smoked; THC content not specified; the single dose size varied from 1–2 puffs to the entire joint in smokers and mostly up to 1 g when given orally) trying to alleviate their MS-related symptoms[58].

Since then, several studies were published. Fox et al. did not observe any significant improvement in any of the objective measures of upper limb tremor with oral cannador (cannabis extract) at the mean dose of 0.107 mg/kg twice a day of THC compared to placebo in 14 patients with MS; only a weak subjective relief of symptoms was reported[59]. Vaney et al. also provided no convincing evidence of cannabis benefits in this illness. In total, 50 subjects were involved in a prospective, randomized, double-blind, placebo-controlled cross-over study, where cannabis-extract capsules, standardized to 2.5 mg tetrahydrocannabinol and 0.9 mg cannabidiol (maximal daily dose was 30 mg of THC after dose-escalation phase) were used. Only a statistically insignificant trend in favour of these capsules was observed in terms of improving spasm frequency, mobility and getting to sleep in the intention-to-treat analysis. However, as shown in per-protocol analysis (n = 37), a significant improvement in spasm frequency ($P = 0.01$), and mobility was recorded. Hence, the authors conclude that a standardized cannabis extract might lower spasm frequency and increase mobility with tolerable side effects in patients with persistent spasticity not responding to other drugs[60]. Nevertheless, the MUSEC trial shows significant superiority of oral cannabis extract to placebo (n = 279) in terms of muscle stiffness after twelve weeks of administration. Similar results were also obtained after four and eight weeks of the treatment[61]. The most recently published review covering the role of encodannabinoid system in the multiple sclerosis was presented by Chiurchiu et al.[62].

PHARMACOKINETICS OF MEDICAL CANNABIS CONSTITUENTS

The medical use of cannabis exploits oral and inhalation routes of administration. Both have considerable benefits and also pitfalls, with different pharmacokinetic features as clinically the most relevant consequence. There are available registered products with synthetic THC and/or CBD, such as synthetic THC (dronabinol – Marinol, Syndros) or nabilone – synthetic analogue of THC (Cesamet). Other options of oral use include standardized extracts and cannabis-derived formulations with content of both THC and CBD (Sativex, Cannador). This combination is claimed to improve tolerability for medical uses by reducing the psychoactive effects of THC (ref.[63]). There may be considerable differences between pharmacokinetics of pure THC and/or CBD in tablets, extracts and raw material in oral drug dosage forms - possibly due to matrix effects on absorption.

The general features of cannabinoids, such as protein binding and volume of distribution are apparently little influenced by the route of administration. The protein binding of THC is reported to be 95-99% and volume of distribution of 5.7-10.0 L/kg. The volume of distribution is reported to increase with chronic administration[64].

Inhalation

Medical cannabis may be principally smoked or vaporized and inhaled. Vaporization or smoking of medical cannabis apparently seems to be most effective way of administration. The main reasons for greater bioavailability are the lipophilic nature of major constituents (partition coeff. octanol/water between $6x10^3$ and $9 x10^6$) and effective conversion of THC-A and CBD-A to their decarboxylated forms when smoked. In contrast, smoking is also not recommended due to the adverse effects of smoking due to the possible toxic effects of other compounds formed at high temperatures of raw material[63].

The technique of smoking considerably affects the absorption and therefore there is great variability in bioavailability, estimated as 2–56%. Absorption is very fast, with C_{max} reached within several minutes[65]. To the best of our knowledge, no pharmacokinetic studies with vaporization of medical cannabis have been published.

Oral ingestion

Oral administration comprises variety of oral drug dosage forms with the oromucosal spray and tablets as the most used. Others include crude medical cannabis in capsules, chocolate bars, cookies, but also herbal infusions, tinctures and oils. Various kinds of extracts may be encapsulated (dry extracts) or used as oral liquid ethanolic or oily extracts. The pharmacokinetic features of THC and CBD after oral intake may be greatly influenced by the drug dosage form, excipient, intake with/without food, physiological factors (motility, constipation), pathophysiology (liver functions) and co-medication (e.g. administration of antiemetics – metoclopramide, itopride) (ref.[64]).

Even though the oral route may look safer than inhalation (toxic compounds originated during cannabis combustion, more precise dosing), it may result in more frequent central adverse effects[66-68] possibly due to greater proportion of active metabolite 11-OH THC to parent THC (ref.[69,70]).

The absorption of THC and CBD is very rapid upon oromucosal administration with T_{max} reported to vary from 15 min to 1 h, and variable half-life increasing with the dose – from 1.9 to 3.72 and 5.2 h in case of THC and from 5.3 to 6.4 and 9.4 h in case of CBD after 2,4 and 8 inhalations, which corresponds to 5.4 mg THC/5.0 mg CBD, 10.8 mg THC/10.0 mg CBD and 21.6 mg THC/20.0 mg CBD, respectively[71,72]. There is huge inter- and intra-individual variability of the pharmacokinetic parameters with CV ranging from 57 to 74% (ref.[71]). No significant drug accumulation was found after repeated doses (up to 21.6 mg THC and 20.0 mg CBD) (ref.[72]).

The pharmacokinetics of THC and CBD in oral tablets shows lower absorption rate with THC T_{max} of approx. 0.6 to 2.6 h after ingestion, depending on the dose and drug dosage form[66,73,74]. Interestingly, slower absorption was reported in sublingual (crushed tablet) administration of 5 mg THC than after normal oral use, in study of Klumpers et al.[74]. The elimination of cannabinoids after conventional oral administration is believed to be biphasic, with a distribution half-life of about 4 hours and terminal elimination half-life of 24 to 38 h[71,75], which may even be prolonged in chronic users[64]. Elimination parameters do not seem to be affected by the route of administration,

with terminal half-life of 24-36 h observed after inhalation[76], which is comparable to half-life reported by Ahmed and Heuberger after oral, inhalation or intravenous administration[73,75]. Interestingly, a close correlation of serum ALT levels and elimination rate constant was found[76], which could make ALT an important predictive marker of THC elimination and co-variate in pharmacokinetic models. Similar profile as THC show also major metabolites 9-hydroxy- and 1-hydroxy-THC (ref.[64,77]). On contrary, the plasmatic levels of major secondary metabolite, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (THC-COOH) exerts much slower increase (T_{max} approx. 3 h) (ref.[66]) with sustained plasmatic levels, especially in chronic administration[64,77,78]. Overall bioavailability after oral administration varies from 4 to 20% (ref.[64]). Interestingly, some studies reported two peaks in plasma after single dose administration which occurs due to entero-hepatic circulation[64,65]. In older subjects, there could be observed greater bioavailability due to decreased liver metabolic activity and also lower elimination rate due to larger volume of distribution[79]. In general, oral administration exerts slower absorption, lower bioavailability and delayed peak in plasma compared to inhalation[64].

To date, there were not published pharmacokinetic studies with non-extracted medical cannabis in capsules.

There are few studies on rectal administration of cannabinoids. T_{max} of THC after rectal administration of 2.5 and 5 mg of THC were 2−8 h. The bioavailability of THC after rectal administration was considerably higher (about twice) than after oral route, possibly due to greater extent of absorption and lower pre-systemic elimination[80]. Recently, the pharmacokinetic interactions of cannabinoids, including THC and CBD, have been reviewed elsewhere[81].

PRODUCTION OF INDIVIDUALLY PREPARED PREPARATIONS WITH CANNABIS IN ST. ANNE'S FACULTY HOSPITAL PHARMACY IN BRNO

Following legalisation of medical cannabis use in the Czech Republic since 2013, pharmacists had to solve the issue, what drug dosage forms are suitable for production of customised preparations. It has been shown that for oral use, capsules are very convenient and this final section briefly describes production of casules in St. Anne's Faculty Hospital. The main reasons for the issue of individual preparationswere: cancer pain, spasticity and antiemetic purposes.

Cannabis is supplied to the pharmacy in the form of dried female flowers. It is well known, that apart from THC and CBD, carboxylated forms (tetrahydrocannabinolic acid, THC-A and cannabidiolic acid, CBD-A) are also present in significant amounts in raw plant material. These carboxylated cannabinoids are spontaneously converted to THC and CBD at high temperatures (approx. 100-140 °C). Moreover, THC-A may be converted to cannabinolic acid (CBN-A) when exposed for long time to oxygen in the air. CBN-A may be also decarboxylated to CBN at high temperatures[82,83].

Thus, in order to increase the effect of oral ingestion the first step involves cannabis decarboxylation. The plant is first of all weighed out into suitable containers. Decarboxylation is carried out using a sterilisation procedure: temperature 121 °C for 30 min. After this, the material must be allowed to cool down. Cannabis is then treated in a splintery grinder and homogenized. Following homogenization, adjuvant substances are added (suitable filling mass such as lactose or starch) and finally the required volume is produced. This mass is subsequently adjusted to gelatinous capsules; size 2 is commonly used. The amount of dried cannabis is usually 125 mg per capsule, but 250 and 375 mg per capsule are also produced.

Raw medical cannabis, even if available as standardized extract, is considered instable and the content of active components can vary with storage condition. Hence, capsules are stored in tightly closed plastic containers kept at – 18 °C to prevent excessive evaporation of volatile oils.

Capsules containing medical cannabis of Czech origin (Elkoplast) were produced in the pharmacy of St. Anne's Faculty Hospital from April 2016 until February 2017. Cannabis was not available from March 2017 till June 2017. Capsules were produced again from July 2017 to August 2017 and contained cannabis of Dutch origin (Bedrocan). Currently, there is available cannabis of Canadian origin with 16% of THC and 0.1% CBD or with 10% of both THC and CBD, and of Czech origin containing 19% of THC and 6% of CBD.

Capsules with medical cannabis produced in the period April 2016-August 2017 were prepared for approximately 20 patients predominantly from Southern and Northern Moravia. These patients described in general, pain relief and consequent improvement of sleep.

CONCLUSION

Despite the long history, the current use of cannabis in practical medicine is still rather limited. This situation however soon became subject to change. Interestingly, despite the huge number of substances that have been identified in the plant, attention is only paid to THC and CBD, and other compounds that could also play a role in the mechanism of action of medical cannabis are not in the centre of interest. Studies declare only amounts of THC and CBD, and regulatory authorities control medical cannabis for the content of these two substances. Recently however, promising neuroprotective properties of cannabigerol (CBG) in Huntington's disease have been reported[84]. Thus, it can be concluded, that further research will provide other facts and this will contribute to larger introduction of medical cannabis into practical use.

Search strategy and selection criteria

Literature was searched using the databases: Medline, EBSCO, EMBASE, Cochrane Library, and OVID. The mesh words used during searching were: "cannabis"/ "cannabinoid"/"nabilon"/"dronabinol" both alone and

in combination with words "pharmacokinetics", "pharmacodynamics", "pain", "analgesia", "cancer pain", "spasticity", "multiple sclerosis", "toxicity", "safety", "interactions", "effectiveness" and "efficacy". The most relevant published studies are discussed in the presented article.

ABBREVIATIONS

ALT, alanine aminotransferase; CB, cannabinoid; CBD, cannabidiol; CBN-A, cannabinolic acid; CBG, cannabigerol; CNS, central nervous system; THC, Δ^9-tetrahydrocannabinol; HIV, human immunodeficiency virus; MS, multiple sclerosis; NICE, National institute for health and care excellence; NNT, the number needed to treat; $TRPV_1$, transient receptor potential cation channels subfamily V member 1; VR1, vanilloid pain receptors.

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