

## CANNABIS IN ONCOLOGY

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### Summary

Although today among oncology patients use of various preparations of complementary and alternative medicine is more and more frequent, there is unequivocal scientific base for their use. Among the often used preparations, especially in the treatment of cancer pain, is cannabis and its derivatives. Cannabinoids act on the endogenous cannabinoid system, with widespread receptors in the central nervous system and peripheral tissues. Although the pharmacology of the cannabinoids is still largely unknown, numerous of their effects were investigated. In oncology, studies have been conducted on the effect of cannabinoids on nausea and vomiting during the oncological treatment, the cancer pain and neuropathy, on appetite and weight loss, and the impact on mood, depression and anxiety. It is also observed that some of the cannabinoids have antitumor, but also protumorous activity. There have been many different side effects of cannabinoids detected, and in a smaller percentage also the development of addiction. Best known preparations nowadays are dronabinol, nabilon and nabiximol. At the moment, the evidence lack strength, and large randomized clinical trials are required, which would confirm predominantly positive results of the research.

KEY WORDS: *CAM, cannabis, cannabinoids, CB1, CB2, cancer pain, cancer cachexia, chemotherapy induced nausea and vomiting, adverse effects, anticancer activity, protumorous effect, dronabinol, nabilon, nabiximol*

### MEDICINSKA KONOPLJA U ONKOLOGIJI

#### Sažetak

Iako je danas među onkološkim bolesnicima sve učestalija uporaba različitih pripravaka komplementarne i alternativne medicine, za njihovu uporabu nema nedvojbene znanstvene potvrde. Među češće primjenjivanim pripravcima, osobito u liječenju karcinomske boli, je i kanabis i njegovi derivati. Kanabinoidi djeluju u organizmu preko endokanabinoidnog sustava, s rasprostranjenim receptorima u središnjem živčanom sustavu i perifernim tkivima. Iako je farmakologija kanabinoida još uvijek uglavnom nepoznata, do sada su istraživani njihovi brojni učinci. U onkologiji su provedena istraživanja utjecaja na mučninu i povraćanje prilikom onkološkog liječenja, na karcinomsku bol te neuropatiju, na apetit i gubitak tjelesne mase te utjecaj na raspoloženje, depresiju i tjeskobu. Također je opažen antitumorski, ali i protumorski učinak nekih kanabinoida. Zabilježeni su brojni različiti neželjeni učinci kanabinoida, a u manjem postotku i razvoj ovisnosti. Najpoznatiji pripravci danas jesu dronabinol, nabilon i nabiximol. Sveukupno, za sada nisu osigurani dovoljno snažni i nedvojbeni dokazi i potrebne su velike randomizirane kliničke studije, koje bi potvrdile do sada opažene pozitivne rezultate istraživanja.

KLJUČNE RIJEČI: *CAM, kanabis, medicinska konoplja, kanabinoidi, CB1, CB2, karcinomska bol, kaheksija, kemoterapijom uzrokovana mučnina i povraćanje, neželjeni učinci kanabisa, protutumorski učinak, protumorska aktivnost, dronabinol, nabilon, nabiximol*

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**ARTICLE****CAM in oncology**

Use of complementary and alternative medicine (CAM) is nowadays all the more frequent among cancer patients. Research results speak for variable range of application, 7-64% (1). Even though the use increases, there is no satisfactory evidence in studies on the effectiveness of CAM. Level of evidence for different types of interventions (acupuncture, reflexology, massage, TENS, psychosocial support, education, Chinese herbal medicine, music therapy, homeopathy) is small to moderate. In the reduction of malignant pain in cancer patients acupuncture in combination with drugs, Chinese herbal medicine, homeopathy, reflexology and cannabis have proven to have some effect (2). Studies on CAM are difficult to compare, because the samples are very different, there are many methodological weaknesses and a high probability of systematic errors, and there are many nonstandardized methods of application of CAM (3). According to the study from 2014, on 27 systematic reviews, it is not advisable to apply the CAM in any way in the treatment of adult patients with malignant disease who suffer pain (2).

**Cannabinoids**

Cannabinoids are the active components of the plant *Cannabis sativa*, and there are about 60 of them known so far. Pharmacology of cannabinoids is mostly unknown. The two best known derivatives are tetrahydrocannabinol (THC) and cannabidiol (CBD), as weak derivative and derivative without any cannabimimetic activity. Cannabinoids act on the endogenous cannabinoid system and its role in brain neuromodulation via two types of receptors, CB1 and CB2 (4). CB1 receptors are associated with central and peripheral effects. They are permanently expressed in the part of the brain responsible for motor activity, memory and understanding, emotions, sensory and autonomic functions and endocrine function, as well as in peripheral nerve endings, but also in different extra-neural parts, such as the testes, eyes, spleen, etc., CB2 receptors are exclusively present in the immune system, associated with the cells (T and B lymphocytes, macrophages) or with organs (liver, tonsils, lymph nodes) (5). Beside endocannabinoids, there are three basic structural groups of

cannabinoid agonists/ ligands, such as classical cannabinoid THC analogs, nonclassical bicyclic and tricyclic cannabinoid analogues of THC and aminoalkylindols. All of them served for thorough pharmacological research and as design models for clinically useful substances (6).

**Cannabis - panacea or psychoactive drug?**

Cannabis' use in medicine began in the 19th century, when it was recognized as analgesic, sedative, anti-inflammatory, antispasmodic and anti-convulsant agent. In the 20th century cannabis has been removed from the US pharmacopoeia and in the 1970's marijuana was listed as group I substance, substance with a high potential for abuse, along with drugs such as LSD, heroin, mescaline, etc. (7). According to some opinion, cannabis is like medicine for all, yet, according to many, dangerous illegal drug with psychogenic effects. It is known that cigarette smoke is carcinogenic, and that THC has psychoactive effects. Today, some cannabis derivatives are approved as prescription drugs, while the plant itself (hemp, other than industrial) remains to be a prohibited drug.

Out of drugs based on cannabis, nabiximol is the only natural extract of the whole plant, in spray formulation, and is commonly used in patients with multiple sclerosis. It was tested also as a pain releasing therapy among cancer patients (8). Most studies have investigated dronabinol, which according to the composition equals synthetic THC. The third most frequently used composition is nabilone, also synthetic analog of THC, which is investigated, same as dronabinol, as an antiemetic agent. Cannabis-based preparations may be in the form of oils, sprays, capsules or in the form of cigarettes.

**Anti-tumor effect**

Numerous studies in animal models and cell lines have shown that there is a potential for anti-tumor effect of cannabis and there was a kind of anti-tumor effect detected, which is not unequivocally proven at this time. However, it is found that cannabis interferes in key cell signaling pathways and thus can directly induce cessation of cell growth and cell death. Also, it has been shown to prevent tumor angiogenesis and metastasis (9). The question of influence on normal cells is also not completely elucidated, but it is possible that

it's all about different pathways and regulatory mechanisms of cell survival and death in tumor and non-tumor cells (10).

According to the research conducted so far it has been shown that cannabis affects invasion and cell proliferation in human breast cancer (11), due to the large number of CB receptors it may represent a potential therapeutic target to slow the growth of tumor cells in lung cancer (12), and a Spanish pilot clinical study applied the THC intracranially, through an infusion catheter and in patients with recurrent glioblastoma it showed slowing growth in 2/9 of patients undergoing treatment (13). However, despite the large number of pre-clinical studies, as well as sporadic individual examples, in which a certain effect was detected, there is no sufficient evidence in the clinic. Therefore, there is no hard evidence for counseling patients to stop the standard treatment and use highly potent extracts of cannabis. The arguments in favor of this are based on the testimonies of patients with skin cancer, which topically applied oil composition of cannabis on the skin.

### **Cannabis in oncology**

Cannabis has been studied in cancer patients as possible antiemetic therapy, to improve appetite, as an analgesic, to relieve neuropathy and in anxiety, depression and for the improvement of sleep.

### **Antiemetic effect**

The studies of antiemetic effect were usually conducted with dronabinol. Based on the results of these studies, dronabinol is as an antiemetic approved in the United States. A systematic review of 30 randomized trials comparing cannabis to placebo and the standard antiemetic therapy from 2001, over 1360 patients showed significantly greater antiemetic effect of cannabinoids nabilone and dronabinol, compared to the control group (14). A similar conclusion was conducted in a small study in 2010, that gave rise to nabiximol (15). Analysis of the 15 controlled studies that have compared the antiemetic effect of nabilone to placebo and standard antiemetic, in over 600 patients showed a greater effect of nabilone, and it was even preferred by patients (16). Analysis of studies investigating smoking cannabis proved positive antiemetic effect, but patients mostly preferred oral preparation. The results of these stud-

ies were sometimes contradictory, but if a positive effect was determined, it should have been considered as a substitute for dronabinol, if the patients can not tolerate it (7). A small study in 2007, comparing cannabis to newer antiemetics, such as ondansetron, showed similar efficacy and the lack of additive effect of the combination of these products (17). That gave a hint about potential economic benefit of cannabis in this indication, but also the need for further research and larger studies comparing cannabis and these preparations.

### **Effect on appetite and weight loss**

Among studies of the impact of cannabis on appetite there are very few adequate ones, and they also most frequently tested the effect of dronabinol. In two small studies, conducted in the past decade, it has been shown that oral THC stimulates appetite and that it can slow down the loss of appetite in advanced cancer. One large randomized double-blind study in almost 470 cancer patients with advanced cancer and loss of body weight (BW) compared the daily administration of THC to a standard agent in this indication, megestrol acetate, and both preparations together, and it appears that significantly better results were seen in the group of the megestrol acetate, and a combination therapy showed no additional effect, the two compositions are not therefore to have any additive effects (7). It appears that the endogenous cannabinoid system is actually responsible for the regulation of eating habits (18).

### **Analgesic effect**

In the studies of the analgesic effect of cannabis it has been proven that a possible way of endogenous cannabinoid system activity in pain modulation works through the anti-inflammatory mechanism via CB2 receptors, by releasing of anti-inflammatory substances and increased release of the opioid analgesics (19). Central action of cannabinoids is different from opioid, it is not blocked by opioid antagonists. This positions marijuana as a potential adjunctive therapy with opioids. Early studies on the impact of cannabinoids on (experimental) pain in healthy volunteers have been inconclusive. Some have shown no effect, some have even shown hiperalgesic effect, and analysis determined the existence of a number of methodological errors in the performance of the research

(20). The three pivotal studies of the effect of THC on cancer pain, from the mid-1970's, have shown that THC efficiency is comparable to that of codeine (21, 22, 23). In the study on effect of adding THC to chronic opioid therapy it has been shown that the best effect on pain relief was in a group on a proportionate amount of THC and CBD (24).

### **Effect on neuropathy**

Patients receiving chemotherapy with vinca alkaloids, taxanes or platinum compounds often present with painful sensory peripheral neuropathy. In studies with smoking cannabis it has been shown that it has twice the effect on the reduction of neuropathic pain (52% vs. 24%, 30% reduction of pain) compared to placebo, and the effect is specially expressed in the first cigarette of cannabis (effect up to 70%) (25). The two studies on the impact of cannabinoids on central neuropathic pain in patients with multiple sclerosis have shown that THC sublingual spray, alone or in combination with the CBD has a double effect on pain reduction, in comparison to placebo. CBD monotherapy showed no effect (26). Chronic administration of the CBD in animal models prevented the occurrence of chemotherapy-induced neurotoxicity (27). Despite the promising results, in order to prove unambiguous clinically significant effect of cannabinoids on neuropathy, further large prospective randomized clinical studies are needed.

### **Effect on mood changes**

In studies with cannabis often as a side effect occurs euphoria, which among other things depends on the patient's previous experience with cannabis. In some patients dysphoria with or without paranoia is recorded, and in these patients, cannabis and cannabis derivatives remain without clinical effect. In studies of nabiximol and inhaled cannabis the improvement of the quality of sleep and falling asleep is detected (28, 29). Analyses often concluded that cannabis is useful to consider in patients with cancer and anorexia, nausea, pain, depression, anxiety and insomnia, because it established effect on all of these problems.

### **Indications for cannabis in oncology**

Indications for cannabis in oncology today are nausea and vomiting, cachexia and stimulating appetite, pain and psychological impact.

According to guidelines cannabinoids are a potential third or fourth line antiemetic therapy, when standard treatments are not effective (30). According to present knowledge, in this situation an independent application of dronabinol can be considered. The optimal dose of dronabinol is 5 mg / m<sup>2</sup> per day, to a maximum of six doses. The application of dronabinol starts before chemotherapy and then continues through several posttherapeutic days. If ineffective, the dose may be increased during application of chemotherapy (31). Today approved drugs for this indication are dronabinol and nabilone. They have been shown to be effective in delayed emesis, after first 24 hours after chemotherapy administration, in the phase in which the emesis is usually poorly controlled (32). As mentioned above, it is necessary once more, thoroughly, through large prospective randomized studies to compare in this indication the effect among different cannabinoids and cannabinoids and today's modern antiemetics, such as setrons and NK antagonists.

The problem of the appetite loss and loss of the body weight is present in over 50% of cancer patients. There are ongoing phase II studies, that aim to determine the relationship between increased appetite and prevention of body weight loss, after treatment with THC in cancer patients. The recent phase III study demonstrated the effect of THC in improving appetite in cancer patients with advanced disease, and it is administered at a dose of 5 mg daily (33). Dronabinol is indicated for the treatment of anorexia in patients suffering from AIDS, in a dosage of 2.5 - 5 mg per day (34). Future large studies have the role of proving a definite effect of cannabinoids in the treatment of anorexia and cachexia, through the comparison with the standard (megestrol acetate), which has not yet yielded unambiguous results.

As noted, the analgesic effect of cannabis and cannabinoids (dronabinol, nabiximol, nabilone, natural THC itself, CBD, smoked marijuana) was recorded in a number of studies with different designs and quality, especially in studies with animal models. A meta-analysis of studies of analgesia in humans is not applicable, because studies conducted so far are not comparable, due to differences in methodology, sampling, the method of application preparations etc. It is clear that chronic cancer pain consists of more components, thus pharmacological approach should include action



on peripheral nerves, as well as on the spinal cord and brain. The only product that has regulatory approval in some countries for use as pain releasing therapy in malignancies, and that in case of inefficiency of the strong opioids, as adjunct therapy, is nabiximol. It is used as a spray, at a dose of 12 activations daily (35). There are ongoing studies on antiodorous effect of cannabinoids in the terminal stage malignancies.

According to studies on animal models cannabinoids reduce anxiety (36). Only a few studies that have examined the effect of cannabinoids on the mood in cancer patients have indicated a positive effect, with many restrictions. THC and nabilone may lead to positive psychological effects, reduction of depression and anxiety and sleep improvement (37).

#### **Adverse effects**

Among the harmful effects of cannabis affective, sensory, somatic and cognitive type of adverse effects can be seen (38). Since the receptors for cannabinoids are ubiquitous in human organism, use of cannabinoids can cause symptoms in multiple organ systems: cardiovascular, respiratory, gastrointestinal and musculoskeletal. Fortunately, symptoms are generally rare, mild and disappear spontaneously. Chronic smokers may experience withdrawal syndrome, and there is also fatigue, insomnia, irritability and hot flashes (39). Tolerance on cannabinoids develops quickly. This is mainly due to pharmacodynamic changes, reducing the total and number of functional receptors on the cell. Less it is due to pharmacokinetic changes (biotransformation and excretion) (40). Central and peripheral effects of cannabinoids are different, sometimes amplified in recreational use of cannabis (41). The risk of addiction by prolonged use of cannabis is 9%, lower than for heroin or other opiates (42).

#### **(Pro)tumorous effect**

Research of (pro)tumorous effect of cannabis has not have offered unmistakable conclusion. Studies of associations between smoking marijuana and cancer are mostly studies of pairs (smoking / non-smoking). Those research are unreliable because of limitations in the studies' design. Smoking proved to be a confounding factor (43). One study showed a connection between marijuana

with cancer of the head and neck (44), while others have not observed positive correlation. Increased risk is neither unambiguously established in the lung cancer: one Swedish study showed long-term increased risk, but patients were tobacco smokers in the same time (45). Among other types of cancer, two studies have shown an increased risk of testicular cancer, increased risk of developing cancer of the urinary bladder (46, 47), but in these studies a confounding factor was also smoking tobacco in many subjects.

#### **Cannabis today**

As a result of the new regulatory rules today a number of products based on cannabinoids, as well as numerous ways of their use become more and more accessible. This is especially important for patients and their families, but also in the scientific community, especially after a long pause in studying of cannabis. The problem today is the fact that many health care workers do not have the basic knowledge on cannabis, cannabinoids, neither of the endocannabinoid system. In this way, an adequate flow of information from the doctor to the patient is disabled. This prevents the patient to reach valuable tips and thereby weakens the quality of relations between doctors and patients. It is the duty and obligation of all medical professionals to critically monitor and use information in this area.

It is clear that the development and acceptance of cannabis preparations in other formulations (except smoking) is very likely a longlasting process. However, at the same time a lot of patients can benefit greatly in disposing side effects of chemotherapy and malignancy itself (nausea, vomiting, decreased appetite, cachexia pain, anxiety, depression, insomnia), but there are also anti-cancer properties.

Health workers are more likely to prescribe much more expensive and certainly more harmful pharmaceutical preparations, leaving cannabis aside. However, it is recommended to assess the indication and use the cannabis in practice as any other medical product. It takes a structured approach to the patient and treatment plan, a well-kept medical records, and clearly evident reason for the application. As there is no clear universal recommendation on the application, it is necessary to build an individual paradigm of application and dose titration.

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