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Medicinal Uses of Marijuana and Cannabinoids

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ABSTRACT

In the past two decades, there has been increasing interest in the therapeutic potential of cannabis and single cannabinoids, mainly cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). THC and cannabis products rich in THC exert their effects mainly through the activation of cannabinoid receptors (CB1 and CB2). Since 1975, 140 controlled clinical trials using different cannabinoids or whole-plant preparations for the treatment of a large number of disorders and symptoms have been conducted. Results have led to the approval of cannabis-based medicines [dronabinol, nabilone, and the cannabis extract nabiximols (Sativex®, THC:CBD = 1:1)] as well as cannabis flowers in several countries. Controlled clinical studies provide substantial evidence for the use of cannabinoid receptor agonists in cancer chemotherapy induced nausea and vomiting, appetite loss and cachexia in cancer and HIV patients, neuropathic and chronic pain, and in spasticity in multiple sclerosis. In addition, there is also some evidence suggesting a therapeutic potential of cannabis-based medicines in other indications including Tourette syndrome, spinal cord injury, Crohn's disease, irritable bowel syndrome, and glaucoma. In several other indications, small uncontrolled and single-case studies reporting beneficial effects are available, for example in posttraumatic stress disorder, attention deficit hyperactivity disorder, and migraine. The most common side effects of THC and cannabis-based medicines rich in THC are sedation and dizziness (in more than 10% of patients), psychological effects, and dry mouth. Tolerance to these side effects nearly always develops within a short time. Withdrawal symptoms are hardly ever a problem in the therapeutic setting. In recent years there is an increasing interest in the medical use of CBD, which exerts no intoxicating side effects and is usually well-tolerated. Preliminary data suggest promising effects in the treatment of anxiety disorders, schizophrenia, dystonia, and some forms of epilepsy. This review gives an overview on clinical studies which have been published over the past 40 years.

KEYWORDS

Cannabinoids; cannabis; CBD; endocannabinoids; interactions; side effects; THC; therapeutic use

I. Introduction

For hundreds of years cannabis has been used for therapeutic purposes in many cultures (Fankhauser, 2002). In 1830, the medical use of "Indian hemp," a former expression for cannabis rich in THC, was described for the first time in detail in Europe by Theodor Friedrich Ludwig Nees von Esenbeck, a professor for pharmacy and botany in Bonn, Germany. However, the most important pioneer for the introduction of cannabis into modern medicine was the Scottish physician, scientist, and engineer Sir William Brooke O'Shaughnessy, who published a summary describing his clinical experiences on the medical use of Indian hemp during his stay in India in 1839. This review attracted much attention in Europe and North America. He reported on the use of cannabis tinctures in rheumatism, tetanus, rabies, childhood epilepsy, and delirium tremens and described increased appetite and cheerfulness of his patients after intake of the drug.

Inspired by these reports many physicians started to use cannabis tinctures and other preparations for medical purposes and reported of successful treatments in a large number of medical conditions including chronic pain of different origin, inflammation of the joints, migraine, muscle cramps, loss of appetite, stomach pain, asthma, and sleeping disorders. In the second half of the 19th century, thus, cannabis was an accepted medicine in Western medicine.

At that time, cannabis preparations were produced by several pharmaceutical companies such as Merck in Germany, Bourroughs, Wellcome & Co. in the UK, and Squibb, Parke, Davis & Co., and Eli Lilly & Co. in the USA. In the first decades of the 20th century, however, the use of

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these preparations rapidly declined and they lost their place in medicine. This was mainly because at that time it was not possible to elucidate the chemical structure of the active ingredients of the cannabis plant (*Cannabis sativa* L.) and, therefore, standardization of cannabis preparations was not possible resulting in unreliable dosing. Currently, we see a re-awakened and extraordinary interest in the broad therapeutic potential of cannabis-based medicines on a worldwide scale.

II. Consequences of the late identification of THC

It was only in the 1930s and 1940s that the chemical structures of the first phytocannabinoids, for example cannabidiol, were characterized (Loewe, 1950). Due to the large number of cannabinoids with very similar chemical structures and their lipophilic nature, modern techniques of separation were necessary to elucidate their chemical structure. It was not before 1964 that delta-9-tetrahydrocannabinol (delta-9-THC or THC), also called dronabinol, was stereochemically defined and synthesized. Most of the psychological and many of the other pharmacological and therapeutic effects of the cannabis plant are caused by THC (Gaoni and Mechoulam, 1964).

The medicinal use of cannabis products decreased after their first flowering stage between 1880 and 1900 in Europe and North America. Most physicians did not want to further use plant-derived medications of unknown composition. In addition, for many uses of cannabis new synthetic pharmaceuticals were introduced, including chloralhydrat, paraldehyd, sulfonal, barbiturate, bromural and antipyrine.

It is not difficult to imagine the very different medical history of cannabis and cannabinoids, in case the chemical structure of THC would have been detected 50 or 100 years earlier. It is probable that there would not have been a decline in the medical use of medical cannabis preparations if they could have been standardized as it is possible today. In addition, it can be speculated that single natural and synthetic cannabinoids would have been introduced in the medical armamentarium of the second half of the 20th century similar to other plant compounds that have been successfully characterized in the 19th century. Those have been used for medicinal purposes since that time such as morphine and other opiates as well as salicylic acid and its derivative acetylsali-cylic acid.

A. The cannabis dilemma

Today, healthcare authorities in most countries handle cannabis and single cannabinoids as newly detected medicinal drugs without taking the long history of their therapeutic uses into account. Thus, cannabis preparations introduced by pharmaceutical companies have to undergo rigid and expensive approval procedures comparable to entirely new molecules from pharmaceutical laboratories. Currently, we are therefore confronted with a situation that can be called a "cannabis dilemma." On the one hand, many patients benefit from cannabinoids and doctors report of a variety of positive effects in seriously ill patients. These patients suffer from many different medical conditions including chronic pain of different types from neuropathic pain to migraine; in chronic inflammatory diseases such as Crohn's disease and rheumatism; from psychiatric conditions such as depression, obsessive compulsive disorders, and post-traumatic stress disorder; from neurological diseases such as multiple sclerosis, epilepsy, and Tourette syndrome; from appetite loss and nausea due to different origins; and many other illnesses such as irritable bowel syndrome, asthma, glaucoma, and hyperhidrosis (Hazekamp *et al.*, 2013; Grotenhermen and Müller-Vahl, 2012). On the other hand, only for a few indications reliable evidence is available based on randomized controlled clinical trials (RCTs) including a large number of patients. For most possible medicinal uses, evidence is weak because only small clinical studies and case reports have been published.

Today physicians and policymakers in different countries try to find reasonable ways to deal with this dilemma acknowledging not only our steadily increasing knowledge on the medical uses of cannabis-based medicines, but also the still existing lack of evidence. There is increasing awareness that seriously ill and otherwise treatment-resistant patients cannot be deprived from effective therapy with cannabinoids, although not officially approved. Considering the medicinal use of cannabis products, in any case risks and benefits have been weighted as with any other treatment.

In contrast to other molecules used as medicinal drugs, cannabinoids such as THC are effective not only in a limited number of medical conditions, but seem to have a unique and extraordinary broad therapeutic potential. In order to investigate the complete therapeutic spectrum of cannabis and cannabinoids, large RCTs have to be performed in several different medical conditions (possibly in 50 different indications or even more) and not only in two or three indications like with most other therapeutic agents. Thus, an enormous amount of time and cost would be necessary to assess the efficacy of cannabis-based medicines in all suggested indications to comply with the principles of evidence-based medicine.

III. The endogenous cannabinoid system

In 1988, it was demonstrated for the first time that the effects of THC are mediated by specific binding sites, of which the cannabinoid receptor type 1 (CB1 receptor) and the cannabinoid receptor type 2 (CB2 receptor) are best characterized today. The endocannabinoid system includes several different endogenous cannabinoids (endocannabinoids) as well as cannabinoid, vanilloid, and other receptors and enzymes for the biosynthesis and degradation of endocannabinoids and exerts important biological functions in the central nervous system and many other organs and tissues (Mechoulam and Parker, 2013; Maccarrone *et al.*, 2015). Today about 200 endocannabinoids and endocannabinoid-like substances have been identified, among them anandamide (arachidonoyl ethanolamine) and 2-arachidonoyl glycerol (AG) are the best studied.

The principal physiological function of the endocannabinoid system is the inhibition of the release of other neurotransmitters in the nervous system. A dysfunction of the endocannabinoid system, therefore, may result in several different neurological and physiological symptoms such as disturbances of cognition and movement. However, due to the wide distribution in the body several other functions might be impaired including reproduction, immune, and gastrointestinal functions. Therapeutically, different approaches may be beneficial and influence this system: (1) agents that influence the concentration of endocannabinoids, for example by inhibition of fatty acid amino hydrolase (FAAH), which is responsible for the degradation of anandamide; (2) direct stimulation of receptors using agonists such as synthetic or natural cannabinoids; and (3) substances that block the cannabinoid receptor. Psychotropic effects of cannabis products are mediated by CB1, but not CB2 receptors. Activation of the CB1 receptor results in an inhibition of the neuronal release of all neurotransmitters including acetylcholine, dopamine, gamma-aminobutyric acid (GABA), histamine, serotonin, glutamate, cholecystokinin, D-aspartate, glycine, and noradrenaline. This complex interaction may explain the manifold pharmacological actions of THC and medicinal drugs rich in THC and in other cannabinoid receptor agonists in the nervous system.

IV. Pharmacology of cannabinoids

Besides THC, C. *sativa* contains a large number of other cannabinoids and ingredients. Currently, 120 different cannabinoids have been identified (ElSohly, 2016). Most of the effects of cannabis preparations are based on the agonistic action of THC at the various cannabinoid receptors (Pertwee *et al.*, 2010). Some effects of THC, however, can also be attributed to actions at other receptor systems, for example at the nuclear receptor peroxisome proliferator-activated receptor (PPAR) gamma, than the endocannabinoid system. It is noteworthy that some effects of cannabis preparations are caused by the actions of cannabinoids other than THC. Following THC, cannabidiol (CBD) is the cannabinoid that occurs in the highest concentration in many strains of cannabis. There is evidence that CBD has antiemetic, neuroprotective, antiepileptic, antipsychotic, and anti-inflammatory properties. CBD possesses complex mechanisms of action that include antagonistic effects at CB1 receptors, agonistic effects at vanilloid receptors type 1 (VR1) and type 2 (VR2), inhibition of the hydrolysis of anandamide (resulting in increased concentration of anandamide), binding to the equilibrative nucleoside transporter-1 (leading to enhanced endogenous adenosine signaling), and binding to the G-protein coupled receptor (GPR55) (Grotenhermen *et al.*, 2015).

V. Therapeutic potential

The numerous therapeutic effects of cannabis-based medicines have been extensively reviewed only recently (Pertwee, 2014; Whiting *et al.*, 2015). The first RCT using a cannabis-based medicine was conducted in 1975 to investigate the effects of THC on chemotherapy-induced nausea and vomiting. About 140 controlled clinical studies with single cannabinoids, oral cannabis extracts and inhaled cannabis flowers have been conducted over the past 40 years. In Tables 1–23, a complete overview on available controlled studies is given. In the following paragraphs a selection of most important, recently performed, and most remarkable trials is presented.

However, until today cannabis-based medicines are approved only for a few indications. The cannabis extract nabiximols (Sativex®), an oromucosal spray, has been approved by regulatory bodies in several countries for the treatment of spasticity in multiple sclerosis (in the UK since 2010, followed by several other European countries). In the USA, dronabinol (THC), under the trade name Marinol®, has been licensed for the treatment of nausea and vomiting caused by cytostatic therapy (since 1985) and, in addition, for loss of appetite in HIV/AIDS-related cachexia (since 1992). In Great Britain, the USA and Canada, nabilone, under the trade name Cesamet®, has been sanctioned for the treatment

of the side effects caused by chemotherapy in patients with cancer (since 1985 in the USA).

A. Cancer chemotherapy induced nausea and vomiting

During the past 40 years, mainly in the 1970s and 1980s, 33 controlled trials including a total number of 1525 participants have been conducted to investigate the possible benefits of cannabinoids to improve side effects related to cancer chemotherapy (Table 1). In one of these clinical studies (n = 61), performed at the Bethesda Memorial Hospital in Boynton Beach, USA, it was demonstrated that THC was as effective as ondansetron, an established antiemetic medication, in the treatment of delayed nausea and vomiting following chemotherapy (Meiri *et al.*, 2007). Absence of nausea was significantly greater in active treatment groups (THC group in 71%; ondansetron group in 64%) versus placebo (15%; $p<0.05$ vs. placebo for both groups). The combination of both drugs had no additional effects (improvement in 53% of patients). Noteworthy, nausea intensity and vomiting/retching were lowest in patients treated with THC.

Several Spanish scientific institutions participated in a small RCT using the cannabis extract Sativex® in the treatment of nausea and vomiting caused by different forms of chemotherapy (Duran *et al.*, 2010). In this study, only patients who still suffered from nausea despite prophylaxis with standard antiemetic treatment were included. Patients received the cannabis extract (n = 7) or placebo (n = 9) in addition to standard antiemetic treatment during chemotherapy and in the 5 days post-chemotherapy period. Compared to placebo (22.2%), a non-significantly higher proportion of patients in the Sativex® group (71.4%) experienced a complete remission of adverse effects during the observation period. The authors concluded that Sativex® "added to standard antiemetic therapy was well tolerated and provided better protection" against delayed nausea and vomiting.

B. Appetite loss and cachexia in cancer or HIV/AIDS patients

So far, ten controlled studies including a total number of 973 patients have been performed investigating the effect on appetite loss and cachexia in cancer or HIV/AIDS patients (Table 2). At the Department of Agricultural, Food and Nutritional Science in the University of Alberta, Canada, for example, the effects of THC on taste and smell perception, appetite, caloric intake, and quality of life have been investigated in adult patients with advanced cancer and poor appetite and disturbed chemosensory perception. 46 patients were randomized and received either 2.5 mg THC twice daily or identical placebo capsules over a time period of 18 days (Brisbois *et al.*, 2011). Compared with placebo, THC-treated patients reported significantly improved ($p = 0.026$) and enhanced chemosensory perception ($p <0.001$), and "tasted better" food ($p = 0.04$). Pre-meal appetite ($p = 0.05$) and proportion of calories consumed as protein ($p = 0.008$) increased significantly compared with placebo. Furthermore, THC-treated patients reported increased quality of sleep ($p = 0.025$) and relaxation ($p = 0.045$).

Researchers at the Columbia University in New York investigated the effects of 10, 20, or 30 mg of oral THC (dronabinol) compared to those of cannabis cigarettes containing different amounts of THC (1.8%, 2.8%, and 3.9%) on food intake in 30 HIV positive cannabis smokers in eight 7-h sessions (Haney *et al.*, 2005). In addition, effects were compared depending on the presence of clinically significant loss of muscle mass. All three different cannabis cigarettes as well as the two lower THC doses (10 and 20 mg) were well-tolerated, usually causing only mild physical symptoms and significant increases in ratings of "good drug effect," while the highest dose of THC (30 mg) caused significant side effects in some participants. Both THC and cannabis cigarettes resulted in increased caloric intake, but only in the group of HIV-positive patients with weight loss ($n = 15$) and not in those without ($n = 15$). Authors concluded that "for experienced marijuana smokers with clinically significant muscle mass loss, both dronabinol (at acute doses at least four to eight times the current recommendation) and marijuana produce substantial and comparable increases in food intake without producing adverse effects."

C. Neuropathic and chronic pain

We identified 35 controlled studies with a total of 2046 patients investigating the effects of cannabis-based medications in the treatment of neuropathic and chronic pain (Table 3). In patients with peripheral neuropathic pain, it could be demonstrated that the cannabis extract Sativex® may cause clinically important improvements in pain and sleep quality (Serpell *et al.*, 2014). In this study at Gartnavel General Hospital at the University of Glasgow, the United Kingdom, 246 patients were included and randomized to either Sativex® ($n = 128$) or placebo ($n = 118$) in addition to their on-going analgesic therapy. Compared to the placebo, in the Sativex® group a

Table 1. Studies on cancer chemotherapy and radiotherapy induced nausea and vomiting.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Sallan *et al.* (1975)	USA	20	Various tumors (ages: 18–76)	Randomized, double-blind, cross-over, placebo-controlled	THC (oral)	Antiemetic effect of THC superior to placebo
Chang *et al.* (1979)	USA	15	Osteogenic sarcoma (ages: 15–49)	Randomized, double-blind, cross-over, placebo-controlled	THC (oral), cannabis (smoked)	Oral THC alone or the combination of oral and smoked THC had an antiemetic effect superior to placebo
Frytak *et al.* (1979)	USA	116	Gastrointestinal tumors (median age: 61 years)	Randomized, double-blind, placebo-controlled, parallel groups	THC (oral), prochlorperazine (oral)	Antiemetic effect equivalent with THC and prochlorperazine and superior to placebo
Kluin-Neleman *et al.* (1979)	The Netherlands	11	Hodgkin or non-Hodgkin lymphoma (ages: 21–53)	Randomized, double-blind, cross-over, placebo-controlled	THC (oral)	Antiemetic effect of THC superior to placebo
Herman *et al.* (1979)	USA	113	Various tumors (ages: 15–74)	Randomized, double-blind, cross-over	Nabilone (oral),prochlorperazine (oral)	Antiemetic effect of nabilone superior to prochlorperazine
Orr *et al.* (1980)	USA	55	Various tumors (ages: 22–71)	Randomized, double-blind, cross-over, placebo-controlled	THC (oral), prochlorperazine (oral)	Antiemetic effect of THC superior to prochlorperazine
Sallan *et al.* (1980)	USA	73	Various tumors (ages: 9–70)	Randomized, double-blind, cross-over	THC (oral), prochlorperazine (oral)	Antiemetic effect of THC superior to prochlorperazine
Colls *et al.* (1980)	New Zealand	35	Solid tumors	Randomized, double-blind, cross-over, placebo-controlled	THC (oral), thiethylperazine (oral), metoclopramide	Antiemetic effect equivalent with all three products
Steele *et al.* (1980)	USA	37	Various tumors (ages: 19–65)	Randomized, double-blind, cross-over	Nabilone (oral), prochlorperazine (oral)	Antiemetic effect of nabilone superior to prochlorperazine
Chang *et al.* (1981)	USA	8	Various tumors (ages: 17–58)	Randomized, double-blind, cross-over, placebo-controlled	THC (oral or smoked)	No antiemetic effect of THC in this group of patients receiving cyclophosphamide or doxorubicin
Neidhart *et al.* (1981)	USA	36	Various tumors (median age: 45 years)	Randomized, double-blind, cross-over	THC (oral), haloperidol (oral)	Antiemetic effect equivalent with THC and haloperidol
Einhorn *et al.* (1981)	USA	80	Various tumors (ages: 15–74)	Randomized, double-blind, cross-over	Nabilone (oral), prochlorperazine (oral)	Antiemetic effect of nabilone superior to prochlorperazine
Ungerleider *et al.* (1982)	USA	172	Various tumors (ages: 18–82)	Randomized, double-blind, cross-over	THC (oral), prochlorperazine (oral)	Antiemetic effect equivalent with THC and prochlorperazine
Johansson *et al.* (1982)	Finland	18	Various tumors (ages: 18–70)	Randomized, double-blind, cross-over	Nabilone (oral), prochlorperazine (oral)	Antiemetic effect of nabilone superior to prochlorperazine
Wada *et al.* (1982)	USA	84	Various tumors (ages: 18–81)	Randomized, double-blind, cross-over, placebo-controlled	Nabilone (oral)	Antiemetic effect of nabilone superior to placebo
Jones *et al.* (1982)	USA	24	Various tumors	Randomized, double-blind, cross-over, placebo-controlled	Nabilone (oral)	Antiemetic effect of nabilone superior to placebo
Levitt (1982)	Canada	36	Various tumors (ages: 17–78)	Randomized, double-blind, cross-over, placebo-controlled	Nabilone (oral)	Antiemetic effect of nabilone superior to placebo
George *et al.* (1983)	France	20	Advanced gynecological tumors (median age: 54 years)	Randomized, double-blind, cross-over	Nabilone (oral), chlorpromazine	Antiemetic effect equivalent but insufficient with nabilone and chlorpromazine at doses used

Ahmedzai *et al.* (1983)	Great Britain	26	Lung cancer (ages: 27–72)	Randomized, double-blind, cross-over	Nabilone (oral), prochlorperazine (oral)	Antiemetic effect of nabilone superior to prochlorperazine
Hutcheon *et al.* (1983)	Great Britain	108	Various tumors (ages: 17–80)	Randomized, single-blind, parallel groups	Levonantradol (i.m.), chlorpromazine	Antiemetic effect of levonantradol superior to chlorpromazine
Gralla *et al.* (1984)	USA	30	Various tumors (ages: 39–72)	Randomized, double-blind, parallel groups	THC (oral), metoclopramide	Antiemetic effect of metoclopramide superior to THC
Levitt *et al.* (1984)	Canada	20	Various tumors (ages: 28–78)	Randomized, double-blind, cross-over, placebo-controlled	Cannabis (smoked), THC (oral)	The treatments were effective only in 25% of the patients
Niiranen and Mattson (1985)	Finland	24	Lung cancer (ages: 48–78)	Randomized, double-blind, cross-over	Nabilone (oral), prochlorperazine (oral)	Antiemetic effect of nabilone superior to prochlorperazine
Dalzell *et al.* (1986)	Great Britain	18	Various tumors (ages: 10 months to 17 years)	Randomized, double-blind, cross-over	Nabilone (oral), domperidone (oral)	Antiemetic effect of nabilone superior to domperidone
Pomeroy *et al.* (1986)	Ireland	38	Various tumors (ages: 21–66)	Randomized, double-blind, parallel groups	Nabilone (oral), domperidone (oral)	Antiemetic effect of nabilone superior to domperidone
Niederle *et al.* (1986)	Germany	20	Testicular cancer (ages: 19–45)	Randomized, double-blind, cross-over	Nabilone (oral), alizapride (oral)	Antiemetic effect of nabilone superior to alizapride
Crawford and Buckman (1986)	Great Britain	32	Ovarian cancer or germ cell tumors	Randomized, double-blind, cross-over	Nabilone (oral),metoclopramide	Antiemetic effect equivalent but insufficient with nabilone and metoclopramide
Chan *et al.* (1987)	Canada	30	Various tumors (ages: 35–178)	Randomized, double-blind, cross-over	Nabilone (oral), prochlorperazine (oral)	Antiemetic effect of nabilone superior to prochlorperazine
McCabe *et al.* (1988)	USA	36	Various tumors (ages: 18–69)	Randomized, cross-over	THC (oral), prochlorperazine (oral)	Antiemetic effect of THC superior to prochlorperazine
Lane *et al.* (1991)	USA	54	Various tumors (ages: 20–68)	Randomized, double-blind, parallel groups	THC (oral), prochlorperazine (oral)	Antiemetic effect of THC superior to prochlorperazine; the combination of THC and prochlorperazine was more effective as an antiemetic than monotherapy
Meiri *et al.* (2007)	USA	64	Receiving moderately to highly emetogenic chemotherapy	Double-blind, placebo-controlled	THC (oral), ondansetron	THC or ondansetron were similarly effective for the treatment of CINV. Combination therapy with THC and ondansetron was not more effective than either agent alone
Duran *et al.* (2010)	Spain	16	Cancer with CINV	Placebo-controlled, double-blind, between-groups	Cannabis extract (Sativex, sublingual)	Improved protection against delayed CINV when added to standard antiemetic therapy
Côté *et al.* (2015)	Canada	56	Head-and-neck carcinomas receiving radiotherapy	Placebo-controlled, double-blind, parallel group	Nabilone	Nabilone did not improve quality of life

Table 2. Studies on appetite and chemosensory perception in cancer or HIV/AIDS patients.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Regelson *et al.* (1976)	USA	54	Advanced cancer (ages: 21–73)	Randomized, double-blind, cross-over, placebo-controlled	THC (oral)	THC stimulated appetite and helped retard chronic weight loss associated with cancer
Struwe *et al.* (1993)	USA	12	Symptomatic HIV infection and weight loss of 23 kg or more	Randomized, double-blind, cross-over, placebo-controlled	THC (oral)	THC stimulated appetite but the weight variation observed on THC and on placebo was statistically insignificant
Beal *et al.* (1995)	USA	139	AIDS and weight loss of 23 kg or more	Randomized, double-blind, parallel groups, placebo-controlled	THC (oral)	THC induced a marked stimulation of appetite. It tended to stabilize weight, while patients on placebo continued to lose weight
Jatoi *et al.* (2002)	USA	469	Advanced cancers, weight loss of 23 kg or more over the past 2 months and/or intake of less than 20 calories/kg/day	Randomized, double-blind, parallel groups	THC (oral),megestrol	In monotherapy, megestrol stimulated appetite in 75% of the subjects and induced a weight gain in 11% of the subjects, while oral THC stimulated appetite in 49% of the patients and caused a weight gain in 3% of the patients
Abrams *et al.* (2003)	USA	67	HIV infection	Randomized, double-blind, parallel groups, placebo-controlled	Cannabis (smoked), THC (oral)	Weight gain equivalent with smoked cannabis and oral THC and superior to placebo
Haney *et al.* (2005)	USA	30	HIV-positive patients smoking cannabis	Randomized, within-subject, staggered, double-dummy design	THC (oral), cannabis (smoked)	THC and cannabis cause increased caloric intake
Strasser *et al.* (2006)	Switzerland	164	Advanced cancer, cancer-related anorexia/cachexia syndrome, and severe weight loss	Multicenter, phase III, randomized, double-blind, placebo-controlled	Cannabis extract (Cannador, oral), THC (oral)	Insufficient difference among Cannador, THC, and placebo on appetite or quality of life
Haney *et al.* (2007)	USA	10	Taking at least 2 antiretroviral medications and smoking cannabis at least twice weekly for the past 4 weeks	Placebo-controlled within-subjects	THC (oral), cannabis (smoked)	THC and cannabis caused an increase in caloric intake and weight
Brisbois *et al.* (2011)	Canada	21	Cancer with chemosensory alterations	Placebo-controlled, double-blind, between-groups	THC (oral)	Improvement of chemosensory perception and appetite
Riggs *et al.* (2012)	USA	7	HIV infection	Placebo-controlled, double-blind, cross-over	Cannabis (smoked)	Alterations in appetite hormones

Table 3. Studies on neuropathic or chronic pain.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Noyes *et al.* (1975a)	USA	36	Cancer pain	Randomized, double-blind, cross-over, placebo-controlled	THC (oral), codeine (oral)	Pain relief equivalent with 10 mg of THC and 60 mg of codeine, as well as with 20 mg of THC and 120 mg of codeine
Noyes *et al.* (1975b)	USA	10	Cancer pain	Randomized, double-blind, cross-over, placebo-controlled	THC (oral)	Pain relief with the 15 and 20 mg doses
Staquet *et al.* (1978)	Belgium, USA	30	Cancer pain	Randomized, double-blind, cross-over, placebo-controlled	Benzopyranoperidine (oral), codeine (oral)	Equivalent pain relief with benzopyranoperidine and codeine and superior to placebo
Staquet *et al.* (1978)	Belgium, USA	15	Cancer pain	Randomized, double-blind, cross-over, placebo-controlled	Benzopyranoperidine (oral), secobarbital (oral)	Superior pain relief with benzopyranoperidine compared to secobarbital and placebo; secobarbital did not exhibit analgesic properties
Jochimsen *et al.* (1978)	USA	35	Chronic pain due to malignancies	Randomized, double-blind, cross-over, placebo-controlled	Benzopyranoperidine (oral), codeine (oral)	No analgesic effect of benzopyranoperidine
Lindstrom *et al.* (1987)	Sweden	10	Chronic neuropathic pain	Randomized, double-blind, cross-over, placebo-controlled	Cannabidiol (oral)	No analgesic effect of cannabidiol
Holdcroft *et al.* (1997)	Great Britain	1	Severe chronic gastrointestinal pain (Mediterranean fever)	Double-blind, cross-over, placebo-controlled	Cannabis extract (oral)	Reduction in morphine consumption with THC intake
Karst *et al.* (2003)	Germany	21	Chronic neuropathic pain	Randomized, double-blind, cross-over, placebo-controlled	CT-3 (oral), THC	CT-3 in both doses was more effective than placebo in relieving pain
Notcutt *et al.* (2004)	Great Britain	34	Chronic pain	Randomized, double-blind, cross-over, placebo-controlled	THC (sublingual), THC + CBD (Sativex, sublingual), CBD (sublingual)	Pain relief and improvement of sleep quality with THC alone and the THC–CBD combination; CBD alone ineffective
Berman *et al.* (2004)	Great Britain	48	Central neuropathic pain associated with brachial plexus root avulsion	Randomized, double-blind, cross-over, placebo-controlled	THC (sublingual), THC + CBD (Sativex, sublingual)	Decrease in pain and improvement in sleep quality with THC alone and the THC–CBD combination
Svendsen *et al.* (2004)	Denmark	24	Multiple sclerosis	Randomized, double-blind, cross-over, placebo-controlled	THC (oral)	Decrease in central pain with oral THC compared to placebo
Rog *et al.* (2005)	Great Britain	66	MS with central neuropathic pain	Randomized, double-blind, placebo-controlled, parallel-group	Cannabis extract (Sativex, sublingual)	Improvement of pain and sleep by Sativex
Pinsger *et al.* (2006)	Austria	30	Chronic therapy-resistant pain of the skeletal and locomotor system	Placebo-controlled, double-blind	Nabilone (oral)	Nabilone caused a reduction in pain and improvement of quality of life
Blake *et al.* (2006)	Great Britain	58	Active arthritis not adequately controlled by standard medication	Placebo-controlled, randomized, double-blind, parallel-group	Cannabis extract (Sativex, sublingual)	Sativex produced improvements in pain and sleep
Ware *et al.* (2006)	Canada	8	Experienced and authorized (Canada) cannabis users with chronic pain	Randomized, controlled, cross-over	Cannabis (smoked)	Medical cannabis users can appreciate differences in herbal cannabis products
Wissel *et al.* (2006)	Austria	11	Chronic upper motor neuron syndrome (UMNS)	Double-blind, placebo-controlled, cross-over	Nabilone (oral)	Reduction of pain, but not of spasticity, motor function, or activities of daily living
Nurmikko *et al.* (2007)	Great Britain	125	History of unilateral peripheral neuropathic pain and allodynia	Randomized, double-blind, placebo-controlled, parallel-group	Cannabis extract (Sativex, sublingual)	Improvement in pain by Sativex
Abrams *et al.* (2007)	USA	50	HIV infection and symptomatic HIV-associated sensory neuropathy	Prospective, randomized, placebo-controlled	Cannabis (smoked)	

(*Continued on next page*)

Table 3. (*Continued*)

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
						Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain
Frank *et al.* (2008)	Great Britain	96	Chronic neuropathic pain	Randomized, double-blind, crossover	Nabilone (oral), dihydrocodeine (oral)	Dihydrocodeine provided better pain relief than nabilone
Narang *et al.* (2008)	USA	30	Severe chronic noncancer pain, taking stable doses of opioid analgesics	Phase I: randomized, single-dose, double-blind, placebo-controlled, cross-over; Phase II: extended open-label titrated	THC (oral)	THC (in combination with opioids) reduced pain and pain bothersomeness, and increased satisfaction
Wilsey *et al.* (2008)	USA	38	Complex regional pain syndrome (CRPS type I), spinal cord injury, peripheral neuropathy, or nerve injury	Double-blind, placebo-controlled, cross-over	Cannabis (smoked)	Improvement of neuropathic pain
Skrabek *et al.* (2008)	Canada	40	Fibromyalgia patients having continued pain despite the use of other oral medications	Randomized, double-blind, placebo-controlled	Nabilone (oral)	Nabilone improved symptoms and was well-tolerated
Ellis *et al.* (2009)	USA	28	Documented HIV infection and neuropathic pain refractory to a least two previous analgesics	Phase II, double-blind, placebo-controlled, cross-over	Cannabis (smoked)	Pain relief with cannabis
Conte *et al.* (2009)	Italy	18	Secondary progressive MS	Randomized, double-blind, placebo-controlled, cross-over	Cannabis extract (Sativex, sublingual)	Results provide objective neurophysiological evidence that cannabinoids modulate the nociceptive system in patients with MS
Johnson *et al.* (2010)	Great Britain	177	Chronic cancer pain	Placebo-controlled, double-blind, between-groups	Cannabis extract (Sativex, sublingual), THC (sublingual)	Reduction in pain severity when added to standard opioid therapy
Selvarajah *et al.* (2010)	Great Britain	30	Painful diabetic neuropathy	Placebo-controlled, double-blind, between-groups	Cannabis extract (Sativex, sublingual)	No significant improvement over placebo
Rintala *et al.* (2010)	USA	7	Neuropathic pain associated with spinal cord injury	Active-controlled, double-blind, cross-over	THC (oral), diphenhydramine (oral)	THC not more effective than diphenhydramine for pain relief
Ware *et al.* (2010)	Canada	21	Neuropathic pain	Placebo-controlled, double-blind, cross-over	Cannabis (smoked)	Pain reduction, improved sleep, and reduced anxiety
Portenoy *et al.* (2012)	USA	263	Chronic cancer pain	Placebo-controlled, double-blind, graded-dose, between-groups	Cannabis extract (Sativex, sublingual)	Analgesic effects in secondary pain analyses when added to standard opioid therapy
Wilsey *et al.* (2013)	USA	39	Central and peripheral neuropathic pain	Placebo-controlled, double-blind, cross-over	Cannabis (vaporized)	Reduction in pain
Langford *et al.* (2013)	Great Britain	339	Central neuropathic pain associated with MS	Placebo-controlled, double-blind, between-groups	Cannabis extract (Sativex, sublingual)	No significant difference between placebo and Sativex in Phase A; Phase B demonstrated an analgesic effect
Issa *et al.* (2014)	USA	30	Chronic noncancer pain patients	Placebo-controlled, double-blind, cross-over	Cannabis (smoked), THC (oral)	Oral THC had similar psychoactive effects to smoked marijuana
Lynch *et al.* (2014)	Canada	16	Patients with chemotherapy-induced neuropathic pain	Placebo-controlled, double-blind, cross-over	Cannabis extract (Sativex, sublingual)	Reduction in pain intensity
Serpell *et al.* (2014)	Great Britain	246	Peripheral neuropathic pain	Placebo-controlled, double-blind, between-groups	Cannabis extract (Sativex, sublingual)	Improvements in pain, sleep quality, and subjective evaluations of patients
Wallace *et al.* (2015)	USA	16	Painful diabetic peripheral neuropathy	Placebo-controlled, double-blind, cross-over	Cannabis (inhaled by vaporizer), containing 1%, 4%, or 8% THC	Dose-dependent improvement in spontaneous pain scores

Table 4. Studies on experimental or acute pain.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Raft *et al.* (1977)	USA	10	Healthy volunteers undergoing dental extractions (4 molars for each patient)	Randomized, double-blind, cross-over, placebo-controlled	THC (oral)	No analgesic effect of THC on postoperative pain
Jain *et al.* (1981)	USA	56	Postoperative or trauma pain	Randomized, double-blind, parallel groups, placebo-controlled	Levonantradol (i.m.)	Pain relief with the four doses; analgesia persisted for more than 6 h with the 2.5 and 3 mg doses
Buggy *et al.* (2003)	Great Britain	40	Postoperative pain (hysterectomy)	Randomized, double-blind, parallel groups, placebo-controlled	THC (oral)	No analgesic effect of THC on postoperative pain
Naef *et al.* (2003)	Switzerland	12	Healthy cannabis-naive volunteers under experimental pain conditions	Randomized, double-blind, cross-over, placebo-controlled	THC (oral), morphine (oral)	THC did not reduce pain in any test compared to placebo
Roberts *et al.* (2006)	USA	13	Healthy volunteers	Double-blind, four-treatment, four-period, four-sequence, cross-over	THC (oral), morphine (oral)	There was a synergistic effect between THC and morphine on the affective component of pain but not on the sensory component
Holdcroft *et al.* (2006)	Great Britain	65	Postoperative patients experiencing at least moderate pain, after stopping patient controlled analgesia	Randomized, dose-escalation, parallel-group	Cannabis extract (Cannador, oral)	The optimal dose was 10 mg Cannador, effectively reducing postoperative pain without serious side effects
Seeling *et al.* (2006)	Germany	100	Patients after radical prostatectomy	Randomized, double-blind	THC (oral)	No synergistic or additive interaction between THC and piritramide
Beaulieu *et al.* (2006)	Canada	41	Patients undergoing surgery	Double-blind, randomized, placebo-controlled, parallel-group	Nabilone (oral)	Nabilone did not reduce 24 h morphine consumption or improve effects of morphine
Wallace *et al.* (2007)	USA	15	Healthy volunteers	Randomized, double-blind, placebo-controlled, cross-over	Cannabis (smoked)	A medium dose of cannabis reduced pain, while a high dose increased pain induced by capsaicin
Kraft *et al.* (2008)	Austria	18	Healthy female volunteers without a history of cannabis use	Double-blind, placebo-controlled, cross-over	Cannabis extract (Cannador, oral)	No analgesic or antihyperalgesic activity observed for the cannabis extract
Redmond *et al.* (2008)	Canada	17	Healthy volunteers	Double-blind, placebo-controlled, cross-over	Nabilone (oral)	Nabilone failed to produce analgesic effect

significantly higher percentage of patients ($p = 0.034$; 95% confidence interval: 1.05–3.70) had an improvement of more than 30% in peripheral neuropathic pain (assessed by the numerical rating scale, 0–10). There was also a nonsignificant difference in the reduction in mean pain scores in the Sativex® group compared to the placebo group.

According to another clinical study performed at the University of California, both low (1.29% THC) and moderate (3.5% THC) doses of cannabis (inhaled by a vaporizer) were effective in reducing central or peripheral neuropathic pain compared to placebo ($n = 39$) (Wilsey *et al.*,2013). Patients were treatment-resistant to conventional analgesics. An average of about three patients had to be treated for one patient to benefit with a pain reduction of more than 30%. Specifically, the number needed to treat (NNT) to achieve 30% pain reduction was 3.2 for placebo versus low-dose and 2.9 for placebo versus medium-dose cannabis. Thus, inhaled cannabis resulted in a significant pain reduction compared to placebo, while there was no significant difference between low and medium doses of cannabis. Authors noted that these results "are compatible to those of traditional neuropathic pain medications" and that psychoactive effects were minimal, and cannabis was well tolerated.

Table 5. Studies on spasticity in multiple sclerosis.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Petro and Ellenberger (1981)	USA	9	Multiple sclerosis	Randomized, double-blind, cross-over, placebo-controlled	THC (oral)	Decrease in spasticity in four patients with both doses of THC (objective evaluation)
Ungerleider *et al.* (1987)	USA	13	Multiple sclerosis	Randomized, double-blind, cross-over, placebo-controlled	THC (oral)	Subjective improvement in spasticity from the 7.5-mg dose; 2.5- and 5-mg doses ineffective
Greenberg *et al.* (1994)	USA	10	Multiple sclerosis	Randomized, double-blind, parallel groups, placebo-controlled; control group of 10 healthy volunteers	Cannabis (smoked)	Subjective feeling of clinical improvement in some patients; impairment of posture and balance in the 10 patients with multiple sclerosis
Martyn *et al.* (1995)	Great Britain	1	Multiple sclerosis	Double-blind, cross-over, placebo-controlled	Nabilone (oral)	Improvement in muscle spasms, pain, general health status, and frequency of nocturia (objective evaluation)
Killestein *et al.* (2002)	The Netherlands	16	Multiple sclerosis	Randomized, double-blind, cross-over, placebo-controlled	THC (oral), cannabis extract (Cannador, oral)	No benefits on spasticity; treatment with THC or plant extract worsened the patients' global impression
Wade *et al.* (2003)	Great Britain	18	Multiple sclerosis	Randomized, double-blind, cross-over, placebo-controlled	Cannabis extract (Sativex, sublingual), THC (sublingual), CBD (sublingual)	Reduction in spasticity, muscle spasms, and pain with THC compared to the placebo; reduction in pain with CBD compared to placebo; reduction in muscle spasms and improvement in sleep quality with Sativex compared to placebo
Zajicek *et al.* (2003)	Great Britain	630	Multiple sclerosis	Randomized, double-blind, parallel groups, placebo-controlled, oral THC: 206 patients; oral cannabis extract: 211 patients; placebo: 213 patients	Cannabis extract (Cannador, oral), THC (oral)	No beneficial effects of cannabinoids on spasticity when evaluated by the Ashworth scale; objective improvement in mobility with oral THC; subjective improvement in muscle spasms, pain, sleep quality, and general condition with both types of cannabinoids
Vaney *et al.* (2004)	Switzerland	50	Multiple sclerosis	Randomized, double-blind, cross-over, placebo-controlled	Cannabis extract (Cannador, oral)	No beneficial effects of cannabinoids on spasticity when evaluated by the Ashworth scale; reduction in spasm frequency; improvement in mobility and sleep quality
Wade *et al.* (2004)	Great Britain	160	Multiple sclerosis	Randomized, double-blind, parallel groups, placebo	Cannabis extract (Sativex, sublingual)	Reduction in spasticity with the cannabis extract compared to placebo, evaluated by the VAS scores (objective evaluation)

Collin *et al.* (2007)	Great Britain	189	MS with spasticity	Randomized, placebo-controlled	Cannabis extract (Sativex, sublingual)	Reduction in spasticity
Collin *et al.* (2010)	Great Britain	337	MS and spasticity	Placebo-controlled, double-blind, between-groups	Cannabis extract (Sativex, sublingual)	Reduction in treatment-resistant spasticity
Novotna *et al.* (2011)	Czech Republic	241	MS and spasticity	Placebo-controlled, double-blind, between-groups	Cannabis extract (Sativex, sublingual)	Reduction in spasticity in patients showing adequate response to Sativex in initial study phase
Corey-Bloom *et al.* (2012)	USA	30	MS and spasticity	Placebo-controlled, double-blind, cross-over	Cannabis (smoked)	Reduction in spasticity and pain
Notcutt *et al.* (2012)	Great Britain	36	MS and spasticity; benefit from cannabis extract (Sativex, sublingual) in ongoing study	Placebo-controlled, double-blind, parallel group, withdrawal study	Cannabis extract (Sativex, sublingual)	Time to treatment failure was significantly in favor of Sativex

Table 6. Studies on tremor in multiple sclerosis.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Clifford (1983)	USA	8	Multiple sclerosis	Single-blind, placebo	THC (oral)	Objective improvement in tremors and motor coordination in two patients; subjective improvement in tremors and well-being in five patients
Fox *et al.* (2004)	Great Britain	14	Multiple sclerosis	Randomized, double-blind, cross-over, placebo-controlled	Cannabis extract (Cannador, oral)	No beneficial effects on tremors

Table 7. Studies on bladder dysfunction in multiple sclerosis.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Freeman *et al.* (2006)	Great Britain	630	MS with muscle spasticity	Multicenter, randomized placebo-controlled	Cannabis extract (Cannador, oral); THC (oral)	Cannabis and THC caused a reduction in incontinence
Kavia *et al.* (2010)	Great Britain	135	MS and overactive bladder	Placebo-controlled, double-blind, between-groups	Cannabis extract (Sativex, sublingual)	No significant reduction in number of urinary incontinence episodes; Beneficial effects on other bladder symptoms

Table 8. Studies on disease progression, inflammation, and cognition in multiple sclerosis.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Katona *et al.* (2005)	Great Britain	100	MS with muscle spasticity	Randomized, placebo-controlled	Cannabis extract (Sativex, sublingual)	No evidence for cannabinoid influence on serum levels of cytokines
Aragona *et al.* (2009)	Italy	17	Cannabis-naïve MS patients	Double-blind, placebo-controlled, cross-over	Cannabis extract (Sativex, sublingual)	Cannabinoid treatment did not induce psychopathology and did not impair cognition in cannabis-naïve patients
Zajicek *et al.* (2013)	Great Britain	493	Progressive MS	Placebo-controlled, double-blind, between-groups	THC (oral)	No overall treatment effect on clinical disease progression

Table 9. Studies on spinal cord injury.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Hanigan *et al.* (1986)	USA	5	Spinal cord injury	Double-blind, cross-over, placebo-controlled	THC (oral)	Decrease in spasticity in two patients
Maurer *et al.* (1990)	Switzerland	1	Spinal cord injury	Double-blind, cross-over, placebo-controlled	THC (oral)	Pain relief, reduced vesical dysfunction, and improvement in sleep quality
Wade *et al.* (2003)	Great Britain	4	Spinal cord injury	Randomized, double-blind, cross-over, placebo-controlled	Cannabis extracts with THC or CBD or THC and CBD (Sativex, sublingual)	Decrease in spasticity, muscle spasms, and pain with THC; reduction in pain with CBD; reduction in muscle spasms; and improvement in sleep quality with the THC–CBD combination

Table 10. Studies on Tourette syndrome.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Müller-Vahl *et al.* (2002)	Germany	12	Tourette syndrome	Randomized, double-blind, cross-over, placebo-controlled	THC (oral)	Decrease in tics with THC compared to placebo; improvement in obsessive–compulsive behavior with THC compared to placebo
Müller-Vahl *et al.* (2003)	Germany	24	Tourette syndrome	Randomized, double-blind, parallel groups, placebo-controlled	THC (oral)	Decrease in tics with THC compared to placebo; THC reached efficacy after about 3 weeks of treatment; this efficacy persisted or increased after more than 4 weeks up to the end of the study (6 weeks)

Table 11. Study on epilepsy.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Cunha *et al.* (1980)	Brazil	15 patients with generalized epilepsy inadequately controlled by standard drugs (ages: 14–49)		Randomized, double-blind, parallel groups, placebo-controlled	Cannabidiol (oral)	Of the eight patients receiving cannabidiol, four subjects remained virtually convulsion-free for the duration of the study and three other subjects exhibited a clinical improvement

Table 12. Studies on glaucoma.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Merritt *et al.* (1980)	USA	18	Glaucoma (ages: 28–71)	Randomized, double-blind, cross-over, placebo-controlled	Cannabis (smoked)	Reduction in intraocular pressure
Merritt *et al.* (1981)	USA	8	Glaucoma and hypertension (average age: 65)	Randomized, double-blind, parallel groups, placebo-controlled	Eye drops containing THC	Reduction in intraocular pressure with 0.05% and 0.1% topical solutions of THC; no effect with the 0.01% topical solution of THC
Tomida *et al.* (2006)	Great Britain	6	Ocular hypertension or early primary open-angle glaucoma	Randomized, double-blind, placebo-controlled, 4-way cross-over	2 cannabis extracts rich in THC or CBD (Sativex, sublingual)	Reduction of intraocular pressure

Table 13. Study on dystonia.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Fox *et al.* (2002)	Great Britain	15	Generalized and segmental primary dystonia	Randomized, double-blind, cross-over, placebo-controlled	Nabilone (oral)	No significant reduction in dystonia with nabilone compared to placebo

D. Spasticity in multiple sclerosis

So far, 14 controlled studies with 1740 patients have been conducted to investigate efficacy and safety of cannabinoids in the treatment of spasticity in multiple sclerosis (Table 5). The effects of the cannabis extract Sativex® were investigated in a large multicenter phase III study conducted in several European countries in patients with otherwise treatment-refractory spasticity (Novotna *et al.*, 2011). The study consisted of two phases (so-called enriched-enrollment randomized-withdrawal design):

Table 14. Studies on intestinal dysfunction and irritable bowel syndrome.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Esfandyari *et al.* (2006)	USA	30	Healthy volunteers	Double-blind, randomized, placebo-controlled, parallel-group	THC (oral)	THC retards gastric emptying in humans; effects are gender-related; THC also increases fasting gastric volumes in males
Esfandyari *et al.* (2007)	USA	52	Healthy volunteers	Randomized, placebo-controlled	THC (oral)	THC relaxes the colon and reduces postprandial colonic motility
Klooker *et al.* (2011)	The Netherlands	22	Irritable bowel syndrome (IBS); healthy controls	Placebo-controlled, double-blind, cross-over	THC (oral)	No significant effects of THC on visceral hypersensitivity
Wong *et al.* (2011)	USA	75	Irritable bowel syndrome (IBS)	Placebo-controlled, double-blind, between-groups	THC (oral)	Reduction in fasting colonic motility in subgroup of patients
Wong *et al.* (2012)	USA	36	Irritable bowel syndrome (IBS)	Placebo-controlled, double-blind, between-groups	THC (oral)	No significant effects on gut transit

Table 15. Study on Crohn's disease.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Naftali *et al.* (2013)	Israel	21	Crohn's disease	Placebo-controlled, double-blind, between-groups	Cannabis (smoked)	Cannabis produced clinical benefits in 10 of 11 patients. Induction of remission was not achieved

Table 16. Study on pulmonary disease.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Pickering *et al.* (2011)	Great Britain	9	Patients with chronic obstructive pulmonary disease (COPD); healthy controls	Placebo-controlled, double-blind, cross-over	Cannabis extract (Sativex, sublingual)	No reduction in breathlessness, but reduction in unpleasantness of symptoms

Table 17. Studies on cannabis dependence.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Levin *et al.* (2011)	USA	156	*DSM-IV-TR* cannabis dependence	Placebo-controlled, double-blind, between-groups	THC (oral)	Improvement in treatment retention and withdrawal symptoms
Allsop *et al.* (2014)	Australia	51	*DSM-IV-TR* cannabis dependence	Placebo-controlled, double-blind, between-groups	Cannabis extract (Sativex, sublingual)	Reduction in severity and time course of cannabis withdrawal symptoms

participants were assigned to receive Sativex® for a period of 4 weeks in a single-blind, pre-randomization phase. They were randomly assigned to continue in the Sativex® group or to receive a placebo (second phase lasting 12 weeks), only if they benefited from Sativex®, achieved an improvement of spasticity of $\geq$ 20%, and tolerated the side effects. Of the 572 subjects enrolled, 272 achieved an improvement of at least 20% after 4 weeks, and 241 patients were randomized. Intention-to-treat (ITT) analysis showed a highly significant difference in favor of cannabis with respect to the reduction of spasticity ($p = 0.0002$). In addition, Sativex® resulted in a significant improvement in spasm frequency sleep, and global impression of change (assessed by both patients and

Table 18. Studies on anxiety and posttraumatic stress disorder.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Bergamaschi *et al.* (2011)	Brazil	36	Patients with social anxiety disorder; healthy controls	Placebo-controlled, double-blind, between-groups	CBD (oral)	Reduction in anxiety, discomfort, and cognitive impairment
Crippa *et al.* (2011)	Brazil	10	Social anxiety disorder	Placebo-controlled, double-blind, cross-over	CBD (oral)	Reduction in anxiety associated with altered activity in limbic and paralimbic brain areas
Das *et al.* (2013)	Great Britain	48	Healthy subjects	Placebo-controlled, double-blind, between-groups	CBD (vaporized)	CBD administered post-extinction enhanced consolidation of extinction No acute effects of CBD were found on extinction
Jetly *et al.* (2015)	Canada	10	Posttraumatic stress disorder (PTSD)	Placebo-controlled, double-blind, cross-over	Nabilone (oral)	Reduction of nightmares

Table 19. Studies on schizophrenia.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
D'Souza *et al.* (2005)	USA	13	Stable, antipsychotic-treated schizophrenia patients	Double-blind, randomized, placebo-controlled	THC (intravenous)	THC is associated with transient exacerbation in core psychotic and cognitive deficits in schizophrenia
Leweke *et al.* (2012)	Germany	42	Suffering from acute paranoid schizophrenia and schizophreniform psychosis	Double-blind, controlled	CBD (oral), amisulpride (oral)	CBD reduced psychopathological symptoms of acute psychosis. CBD was as effective as amisulpride, a standard antipsychotic

Table 20. Studies on Parkinson's disease.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Sieradzan *et al.* (2001)	Great Britain	7	Parkinson's disease	Randomized, double-blind, cross-over, placebo-controlled	Nabilone (oral)	Nabilone had no antiparkinsonian effect per se; nabilone had no effect on the antiparkinsonian action of levodopa; reduction in total levodopa-induced dyskinesia with nabilone compared to placebo
Carroll *et al.* (2004)	Great Britain	19	Parkinson's disease	Randomized, double-blind, cross-over, placebo-controlled	Cannabis extract (Cannador, oral)	The cannabis extract had no pro- or antiparkinsonian effect
Chagas *et al.* (2014)	Brazil	21	Idiopathic PD	Placebo-controlled, double-blind, between-groups	CBD (oral)	Improvement in well-being No effects on motor functioning or neuroprotection

Table 21. Study on dementia.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
van den Elsen *et al.* (2015)	The Netherlands	50	Dementia with neuropsychiatric symptoms (NPS)	Randomized, double-blind, parallel groups, placebo-controlled	THC (oral)	No reduction in NPS by low-dose THC (3×1.5 mg), though it is well-tolerated

Table 22. Studies on interaction between cannabinoids.

Study	Country	Number of patients	Medical condition	Type of study	Study medication	Efficacy
Hindocha *et al.* (2015)	Great Britain	48	Healthy subjects	Randomized, double-blind, placebo-controlled, cross-over	THC (8 mg, oral), CBD (16 mg, oral), THC + CBD (8 + 16 mg, oral)	Improvement of recognition of emotional facial affect by CBD and attenuation of the impairment induced by THC
Englund *et al.* (2015)	Great Britain	10	Male healthy subjects	Randomized, double-blind, placebo-controlled, cross-over	Tetrahydrocannabivarin (THCV) (oral), THC (i.v.)	Inhibition of some of the well-known effects of THC by THCV and potentiation of other effects

physicians). Researchers concluded that the used study design provided a method of determining the efficacy and safety of cannabinoids "in a way that more closely reflects proposed clinical practice, by limiting exposure to those patients who are likely to benefit from it."

In another placebo-controlled cross-over study performed at the University of California in San Diego with 30 adult patients with multiple sclerosis, it was demonstrated that smoked cannabis is effective in the treatment of spasticity (Corey-Bloom *et al.*, 2012). Participants were randomly assigned to either the intervention group (where patients smoked cannabis once daily for 3 days) or the control group (where patients smoked identical placebo cigarettes). After an 11-day interval, participants crossed over to the other group. Treatment with smoked cannabis resulted in a reduction in muscle tone (as assessed by a modified Ashworth scale) by an average of 2.74 points more than placebo ($p < 0.0001$). In addition, treatment led to a pain reduction (measured by a visual analog scale) by an average of 5.28 points more than placebo ($p = 0.008$). Cannabis was generally well tolerated and had only mild negative effects on attention and concentration.

E. The therapeutic potential of THC and cannabis in other medical conditions

Only a small number of controlled studies have been conducted in other indications (Tables 6–23), among them are tremor and bladder dysfunction in multiple sclerosis, spinal cord injury, Tourette syndrome, glaucoma, dystonia, irritable bowel syndrome, Crohn's disease, pulmonary disease, and Parkinson's disease.

In a large number of further indications, only (small) uncontrolled studies or case reports are available. For

Table 23. Number of studies and patients reviewed in the years 1975–2015.

Pathology	Number of studies found	Total number of patients included
Cancer chemotherapy or radiotherapy induced nausea and vomiting	33	1525
Appetite and chemosensory perception in cancer or HIV/AIDS patients	10	973
Neuropathic or chronic pain	35	2046
Experimental or acute pain	11	387
Spasticity in multiple sclerosis	14	1740
Tremor in multiple sclerosis	2	22
Bladder dysfunction in multiple sclerosis	2	765
Disease progression, inflammation, and cognition in multiple sclerosis	3	610
Spinal cord injury	3	10
Tourette syndrome	2	36
Epilepsy	1	15
Glaucoma	3	32
Dystonia	1	15
Intestinal dysfunction and irritable bowel syndrome	5	215
Crohn's disease	1	21
Pulmonary disease	1	9
Cannabis dependence	2	207
Anxiety and posttraumatic stress disorder	4	104
Schizophrenia	2	55
Parkinson's disease	3	47
Dementia	1	50
Interaction between cannabinoids	2	58
Total*	140*	About 8,000**

*The study by Wade *et al.* (2003) is listed in 2 tables, so that the summation of all studies in the tables ($n = 140$) is higher than the sum of conducted controlled studies ($n = 139$).

**The summation of all participants in the studies is higher ($n = 8886$) than the real number of participants since a few studies have been conducted on the same subjects. For example, the study by Freeman *et al.* (2006) used the same study population as that by Zajicek *et al.* (2003).

example, an open clinical study ($n = 14$ females, mean age of 33 years) was performed at the Department of Psychiatry of the University of Minnesota in Minneapolis, USA, investigating the effect of oral dronabinol (THC) in patients suffering from trichotillomania (Grant *et al.*, 2011). Trichotillomania is a difficult-to-treat, impulse-control disorder characterized by the compulsive urge to pull out one's own hair leading to noticeable hair loss, distress, and social or functional impairment. Treatment with 2.5–15 mg THC daily over 12 weeks resulted in a significant reduction of hair pulling (as assessed by the Massachusetts General Hospital Hair Pulling Scale) (from 16.5 ± 4.4 at baseline to 8.7 ± 5.5, at study endpoint, $p = 0.001$). Nine subjects (64.3%) responded to the treatment with a symptom reduction of more than 35% and improved "much or very much" on a global impression scale.

1. Tourette syndrome

Two controlled studies with 36 patients suffering from Tourette syndrome, a chronic combined motor and vocal tic disorder, have been performed (Table 10). A double-blind placebo-controlled study with 24 patients was conducted at the Hannover Medical School, Germany (Müller-Vahl *et al.*, 2003). This 6-week trial confirmed results of a smaller single-dose cross-over trial by the same group (Müller-Vahl *et al.*, 2002) and demonstrated that THC is effective in the treatment of tics. Starting at 2.5 mg/day, the dosage was up-titrated by increments of 2.5 mg/day every 4 days to the target dosage of 10 mg THC. Tic severity was rated using several established rating scales. For example, using the Tourette Syndrome Symptom List (TSSL) at 10 treatment days (between days 16 and 41) there was a significant difference ($p < 0.05$) between both groups. Seven patients dropped out of the study or had to be excluded, but only one due to side effects. Authors concluded that the "results provide more evidence that THC is effective and safe in the treatment of tics." A large multicenter RCT including 96 participants is planned to start at the Hannover Medical School in 2017.

2. Spinal cord injury

In this indication, only 3 controlled studies with 10 patients could be identified (Table 9). One of these studies was conducted as consecutive series of double-blind, placebo-controlled, single-patient cross-over trials with 2-week treatment protocols at different hospitals in Oxford (Wade *et al.*, 2003). The authors compared the effects of a THC-rich cannabis extract, to a cannabidiol (CBD)-rich extract and a cannabis extract with a CBD/THC ratio of 1:1 (Sativex®) in symptom control of 24 patients, of whom four suffered from spinal cord injury and 20 from other disorders (n = 18 multiple sclerosis, n = 1 brachial plexus damage, and $n = 1$ limb amputation). Trials started with an open-label period where patients received the CBD/THC extract to get familiar with the procedure. Three patients withdrew from the study due to side effects during the open-label period and one other patient dropped out due to unknown reasons. In the remaining 20 patients treatment with the CBD-rich extract caused a significant improvement of pain compared to placebo (assessed by visual analog scales). Using the THC rich extract, a significant improvement not only of pain, but also of spasms, spasticity and appetite could be demonstrated, whereas treatment with the CBD/THC extract resulted in a significant improvement of spasms and sleep. In addition, some patients felt they had improved bladder control. The authors concluded that "cannabis medicinal extracts can improve neurogenic symptoms unresponsive to standard treatments. Unwanted side effects are predictable and generally well tolerated."

3. Crohn's disease

One controlled study with 21 patients was conducted at the Tel Aviv University, Israel (Table 15), demonstrating improved symptoms and disease activity in patients with Crohn's disease (CD) following inhalation of cannabis (Naftali *et al.*, 2013). Participants in this study did not respond to well-accepted therapy strategies such as steroids, immunomodulators, and anti-tumor necrosis factor-alpha agents. Patients received either cannabis cigarettes twice daily or placebo cigarettes for 8 weeks. Complete remission was achieved by 5 of 11 subjects in the cannabis group, but only 1 of 10 in the placebo group. A clinically significant improvement (defined as a decrease in Crohn's Disease Activity Index score of >100) was observed in 10 of 11 subjects in the cannabis group compared to 4 of 10 in the placebo group. Three patients in the cannabis group were weaned from steroid dependency. Subjects receiving cannabis, in addition, reported improved appetite and sleep. No significant side effects occurred. Authors concluded that "a short course (8 week) of THC-rich cannabis produced significant clinical, steroid-free benefits to 11 patients with active CD, compared to placebo, without side effects."

4. Irritable bowel syndrome

Our literature search resulted in the identification of 5 controlled studies with 215 patients suffering from irritable bowel syndrome (IBS) (Table 14). For example, researchers at the Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER) in

Rochester, USA, investigated the effects of THC on colonic motility and sensation in 75 patients with IBS (35 with IBS and constipation, 35 with IBS and diarrhea, and 5 with IBS and both). Patients were randomly assigned either to receive a single dose of placebo or 2.5 or 5.0 mg dronabinol (Wong *et al.*, 2011). The motility, tone, and sensation of the colon were assessed during fasting and after a meal. In all patients, 5 mg THC decreased motility of the large intestine during fasting compared with placebo (overall $p = 0.05$), whereas 2.5 mg THC had no effect. The effects of dronabinol were greatest in patients with IBS with diarrhea and in those alternating between both diarrhea and constipation. Dronabinol did not alter sensation or tone of the colon.

5. Glaucoma

To the best of our knowledge, so far only 3 controlled studies, including a total of 32 patients, investigating the effects of cannabinoids in the treatment of glaucoma have been conducted (Table 12). In all studies, beneficial effects were reported. British researchers, in addition, compared the effects of THC and CBD in 6 patients with ocular hypertension or glaucoma (Tomida, 2006). In a four-way crossover study participants received 5 mg THC, 20 mg CBD, 40 mg CBD, or a placebo. Substances were applied to the mucosa of the mouth. Two hours after sublingual administration of THC, the intraocular pressure (IOP) was significantly lower than after placebo (on average 23.5 mm Hg versus 27.3 mm Hg, $p = 0.026$). The IOP returned to baseline level after 4 h. CBD administration did not reduce IOP, but the higher dose caused a small increase in pressure after 4 h. Visual acuity remained unchanged.

VI. The therapeutic potential of cannabidiol (CBD)

Cannabidiol (CBD) is usually the primary cannabinoid of fiber or industrial hemp/cannabis and the second most prevalent cannabinoid in drug types of the cannabis plant. In fiber cannabis, CBD is present in concentrations in the range of about 0.5–2% in the upper third of the plant and the flowers. In Germany and many other countries of the world, farmers are allowed to grow fiber cannabis with high CBD and low THC concentrations (in the European Union below 0.2% THC) for the production of fiber, which serves as raw material for industrial and other applications, and hemp seeds for the production of hemp seed oil, a high-quality vegetable oil.

In recent years, however, there is increasing interest in the therapeutic potential of CBD, which does not cause intoxicating effects and relevant side effects even in high doses. Only a few clinical studies have been conducted so far, but basic research suggests a potential therapeutic use in a large number of diseases and symptoms.

A. Anxiety disorders and posttraumatic stress disorder

Four controlled studies with 104 patients have been conducted (Table 18). Scientists at the University of Sao Paulo, Brazil, investigated the effects of CBD in patients with generalized social anxiety disorder using a simulation public speaking test (Bergamaschi *et al.*, 2011). The following three groups were compared: 12 healthy controls without any medication; 12 patients with social anxiety disorder, who received a single dose of CBD (600 mg); and a group of 12 patients, who received a placebo. Pretreatment with CBD significantly reduced anxiety, cognitive impairment, and discomfort in the speech performance of patients with social anxiety disorder as assessed by the Visual Analog Mood Scale, and significantly decreased alert in their anticipatory speech compared to the placebo. No significant differences were observed between patients, who had received CBD and healthy controls in anxiety scores, cognitive impairment, discomfort, and alert factors. This study confirmed previous research of the same group involving 10 patients with social anxiety disorder (Crippa *et al.*, 2011).

B. Schizophrenia

Until today, only one RCT investigating the efficacy and safety of CBD in patients with acute schizophrenia has been conducted (Table 19) (Leweke *et al.*, 2012). At the University of Cologne, 42 patients received over 4 weeks of either treatment with 800 mg of oral CBD daily (4 × 200 mg) or treatment with the well-established antipsychotic drug amisulpride (4 × 200 mg). Both drugs demonstrated comparable efficacy in the treatment of psychopathological symptoms, but CBD caused significantly less adverse effects. In addition, as CBD resulted in a significant increase in serum levels of anandamide, the authors stated: "The results suggest that inhibition of anandamide deactivation may contribute to the antipsychotic effects of cannabidiol potentially representing a completely new mechanism in the treatment of schizophrenia."

C. Parkinson's disease

Three controlled studies on Parkinson's disease with 47 patients have been conducted (Table 20). According to a study by Brazilian researchers at the University of São Paulo, there may be a positive effect of CBD in improving quality of life in patients with Parkinson's disease (Chagas *et al.*, 2014). From a sample

of 119 consecutively patients evaluated in a specialized movement disorders outpatient clinic, they selected 21 patients without dementia or other comorbid psychiatric conditions. Participants were assigned to 3 groups of 7 subjects each and were treated with either placebo, 75 mg CBD daily, or 300 mg CBD daily. The administration of 300 mg CBD was associated with significantly different mean total scores in subjects' well-being and quality of life in the Parkinson's Disease Questionnaire (PDQ-39) ($p = 0.05$) compared to placebo. However, CBD did not mitigate general symptoms of the disease, nor was it shown to be neuroprotective, because brain-derived neurotrophic factor (BDNF) remained unchanged and no changes were observed using magnetic resonance spectroscopy.

D. Dystonia

CBD was given to 5 patients with different dystonic movement disorders in a preliminary open pilot study (Consroe *et al.*, 1986). Oral doses of CBD rising from 100 to 600 mg/day over a 6-week period were administered along with standard medication. Dose-related improvement in dystonia was observed in all patients and ranged from 20% to 50%. Side effects of CBD were mild and included hypotension, dry mouth, psychomotor slowing, light-headedness, and sedation. In 2 patients with coexisting Parkinsonian features, CBD at doses over 300 mg/day exacerbated hypokinesia and resting tremor.

E. Epilepsy

One RCT on epilepsy with 15 patients was conducted (Table 11). In phase 1 of this study, 3 mg/kg daily of CBD were given to 8 healthy human volunteers for 30 days compared to a placebo ($n = 8$) (Cunha *et al.*, 1980). Neurological and physical examinations, blood and urine analysis, ECG, and EEG were performed at weekly intervals. In phase 2 of the study, 15 patients suffering from secondary generalized epilepsy with temporal focus were randomly divided into two groups. Each patient received, in a double-blind procedure, 200–300 mg daily of CBD or a placebo. The drugs were administered for as long as 4.5 months. Throughout the trial the patients continued to take their usual antiepileptic drugs, although these drugs no longer controlled the symptoms of the disease. All patients and volunteers tolerated CBD very well and no signs of toxicity or serious side effects were detected. Four of the 8 patients treated with CBD remained almost free of convulsive crises throughout the experiment and other 3 patients demonstrated partial improvement. CBD was ineffective in 1 patient.

Currently, clinical studies investigating the efficacy and safety of a standardized CBD extract in children and adolescents with epilepsy are underway. Preliminary results of open studies have already been published showing promising effects mainly in certain serious, often treatment-resistant epilepsy forms, such as Dravet syndrome (Devinsky *et al.*, 2015).

VII. Side effects

Cannabis extracts or flowers and individual cannabinoid receptor agonists (THC/dronabinol, nabilone) show similar side effects, which are mainly mediated by the CB1 receptor (Grotenhermen, 2007). Psychoactive effects occur at doses above the individual consumer's psychotropic threshold. They are generally perceived as pleasurable and relaxing. However, the feeling of increased well-being can give way to dysphoria and anxiety or even panic. Further acute psychoactive effects of cannabinoids are impairment of memory, reductions in psychomotor and cognitive performance, and disordered perception of the passage of time.

Cannabis consumption may induce schizophrenic psychosis in vulnerable individuals. Current data indicate that consumption of cannabis may double the risk of schizophrenia in adolescents (Moore *et al.*, 2007). Psychosis is therefore regarded as a contraindication to a treatment with cannabinoid medications, but may be of therapeutic value in some cases (Schwarcz and Karajgi, 2010).

Frequent physical effects of cannabinoids are tiredness, dizziness, tachycardia, orthostatic hypotension, dry mouth, reduced lacrimation, muscle relaxation, and increased appetite (Grotenhermen, 2014). The vascular effects of cannabinoids may increase the risk of myocardial infarction in persons so predisposed. Tolerance develops to many of these undesired effects of cannabinoids—particularly tiredness, dizziness, and cardiovascular and psychoactive effects—over a period of days or weeks. The severity of withdrawal symptoms depends on the intensity and duration of use. They are similar in character and intensity to those experienced after sudden cessation of cigarette smoking and include uneasiness, irritability, sleeplessness, increased perspiration, and loss of appetite (Vandrey *et al.*, 2008).

VIII. Interactions

Because THC is metabolized mainly in the liver by cytochrome P-450 isoenzymes (principally CYP2C), it may interact with other substances metabolized in the same

way (Grotenhermen, 2005). Cannabis smoking can reduce the plasma concentration of certain antipsychotics. However, neither in patients with AIDS nor those with cancer, the plasma levels of various antiretroviral drugs or cytostatics were found to be altered by simultaneous treatment with THC, although they are also metabolized by CYP2C (Kosel *et al.*, 2002; Engels *et al.*, 2007). Most often interactions occur, when both THC and the other substances share the same effector systems, leading to mutual enhancement or attenuation of effect (Hollister, 1999). The principal clinically relevant interactions are increased tiredness when THC is taken together with other psychotropic agents or interactions with substances that also act on the cardiovascular system such as amphetamines. However, some of these additive effects may be desirable, e.g. when THC is administered together with analgesics and antiemetics.

CBD inhibits the activity of the enzymes cytochrome CYP2C19 and CYP2D6, two enzymes of the cytochrome P450 complex (Jiang *et al.*, 2013). Substances that are degraded by the 2C19 and the 2D6 isoenzymes of this complex, including many proton pump inhibitors, the antiepileptic drugs clobazam and the neuroleptic risperidone, may be degraded slower if given together with CBD. This may be of great importance for the use of CBD in epilepsy and psychosis, respectively.

IX. Conclusions and outlook

We identified 140 controlled clinical studies conducted since 1975 including about 8000 participants with different cannabis preparations and single cannabinoids, which were administered by inhalation or the oral route. These studies were conducted in a variety of medical conditions. However, a good scientific basis for the therapeutic use of cannabis preparations exists only for a limited number of symptoms and diseases. On the other hand, small studies, controlled or open-label, and sometimes very impressing case reports underline the notion that THC and other cannabinoids are unique with regard to their broad therapeutic potential. In contrast to other medicinal compounds, large controlled trials would have to be carried out in more than 50 indications or maladies to elucidate the full therapeutic potential according to the requests of modern evidence-based medicine. However, it is not realistic to fulfill these criteria within the next decades.

In an increasing number of countries, policymakers try to find pragmatic ways to deal with this situation by both being rational and compassionate with their citizens and open possibilities to get relief from their suffering by the use of cannabis-based medicines. In recent years there is an increasing dynamic on this issue in North America, Europe, and South America. In parallel to the increasing use of cannabinoid receptor agonists such as THC and nabilone as well as natural cannabinoids with different mechanisms of action, mainly cannabidiol, large pharmaceutical companies such as Sanofi, Pfizer, Merck, and Johnson & Johnson are developing synthetic compounds, which modulate the endocannabinoid system in other ways. The most advanced of these substances are inhibitors of enzymes responsible for the degradation of endocannabinoids, mainly of FAAH, resulting in an increase of endocannabinoid concentration and enhancement of their effects. Several different FAAH inhibitors already have been tested in humans.Thus, the future will open the way to new medicines, which influence the endocannabinoid system. In addition, laws which inhibit access to potential natural remedies for serious diseases, are increasingly changed by jurisdictions of many countries to facilitate and allow an increasing number of physicians and patients to find new ways to deal with many severe, often treatment-resistant ailments.

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