REVIEW ARTICLE

The Therapeutic Potential of Cannabis and Cannabinoids

Franjo Grotenhermen, Kirsten Müller-Vahl

SUMMARY

Background: Cannabis-based medications have been a topic of intense study since the endogenous cannabinoid system was discovered two decades ago. In 2011, for the first time, a cannabis extract was approved for clinical use in Germany.

Methods: Selective literature review

Results: Cannabis-based medications exert their effects mainly through the activation of cannabinoid receptors (CB1 and CB2). More than 100 controlled clinical trials of cannabinoids or whole-plant preparations for various indications have been conducted since 1975. The findings of these trials have led to the approval of cannabis-based medicines (dronabinol, nabilone, and a cannabis extract [THC:CBD=1:1]) in several countries. In Germany, a cannabis extract was approved in 2011 for the treatment of moderate to severe refractory spasticity in multiple sclerosis. It is commonly used off label for the treatment of anorexia, nausea, and neuropathic pain. Patients can also apply for government permission to buy medicinal cannabis flowers for self-treatment under medical supervision. The most common side effects of cannabinoids are tiredness 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.

Conclusion: There is now clear evidence that cannabinoids are useful for the treatment of various medical conditions.

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Knowledge about the therapeutic potential of cannabis products has been greatly improved by a large number of clinical trials in recent years (1–5). In October 2008, the German Medical Association, the National Association of Statutory Health Insurance Physicians, and the Drug Commission of the German Medical Association issued the following statement at a hearing of the Health Committee of the German Federal Parliament (*Bundestag*): "The benefit of treatment with cannabinoids for a number of medical indications has been shown in controlled trials in which predominantly standardized and/or synthetic cannabinoid preparations were used. The use of such preparations may therefore be reasonable for patients in whom conventional treatment does not achieve adequate relief of symptoms such as spasticity, pain, nausea, vomiting, or loss of appetite" (6). The first cannabis-based medication was approved for use in Germany in 2011. In this article we present the current state of knowledge on the therapeutic application of cannabinoid medications.

Method

This review covers publications identified by a search of the medical database PubMed (January 2000 to December 2011) using the terms "cannabi* OR marijuana OR THC OR endocannabinoid". Reviews from standard references (1–5) and the study database of the International Association for Cannabinoid Medicines (IACM) were also analyzed. With regard to therapeutic potential, exclusively data from randomized controlled trials were considered.

History

Medications based on cannabis have been used for therapeutic purposes in many cultures for centuries (7). In Europe, they were used at the end of the 19th century to treat pain, spasms, asthma, sleep disorders, depression, and loss of appetite. In the first half of the 20th century cannabinoid medications fell into almost complete disuse, partly because scientists were unable to establish the chemical structure of the ingredients of the cannabis plant (*Cannabis sativa L.*). It was only in 1964 that (-)-trans-delta-9-tetrahydrocannabinol (THC, dronabinol), the principal active ingredient of cannabis, was stereochemically defined (8). This, followed by the discovery of the body's own cannabinoid system with specific receptors and endogenous ligands, marked the

BOX 1

Definitions and medications

- **THC** is the acronym for tetrahydrocannabinol. When not otherwise specified, THC is used to refer to the naturally occurring (-)-trans isomer of delta-9-tetrahydrocannabinol from the cannabis plant (*Cannabis sativa L.*). It is responsible for most of the pharmacological actions of cannabis, including the psychoactive effects.

- **Dronabinol** is the international non-proprietary name (INN) for (-)-trans-delta-9-tetrahydrocannabinol and is used synonymously with THC. In Germany, dronabinol is classified in Appendix III of the Narcotics Act (BtMG) and can be supplied on prescription as a prepacked commercial product or as drops or capsuled prepared by the pharmacist using raw dronabinol. Prepacked dronabinol is available in capsules containing 2.5 mg, 5 mg, or 10 mg of active substance. In the USA, dronabinol is licensed for the treatment of nausea in cancer chemotherapy and of loss of appetite in Aids patients with weight loss.

- **CBD** or cannabidiol is the most important non-psychotropic cannabinoid found in the cannabis plant. It is not a cannabinoid receptor agonist.

- **Nabilone** is a synthetic derivative of THC. In Great Britain, it is licensed for the treatment of nausea in chemotherapy. A quantity of 1 mg nabilone has about the same effect as 7–8 mg dronabinol.

- **Cannabis extract** nabiximols. In 2011, regulatory approval was granted for an alcoholic cannabis extract that is standardized to contain dronabinol and CBD in a ratio of 1:1 and is sprayed under the tongue using a dose pump. To date, nabiximols is the only medication based on cannabinoids that has been licensed (for the treatment of spasticity in MS) in Germany. Spraying once delivers 2.7 mg THC and 2.5 mg CBD.

beginning of intensive research into the function of the endocannabinoid system and the clinical relevance of cannabis-based medications.

Cannabinoid receptors and endocannabinoids

To date, two endogenous cannabinoid receptors have been identified. The predominantly centrally located CB_1 receptor was cloned in 1990; the predominantly peripheral CB_2 receptor, expressed principally by cells of the immune system, 3 years later (9). Meanwhile, CB_1 receptors have also been demonstrated not only in the CNS but also in many peripheral organs and tissues, e.g., immune cells, spleen, adrenals, sympathetic ganglia, pancreas, skin, heart, blood vessels, lung, and parts of the urogenital tract and gastrointestinal tract. Only activation of the CB_1 receptor—not of the CB_2 receptor—leads to the well-known psychotropic effects. Endogenous cannabinoid receptor agonists were demonstrated in 1992. The two most important endocannabinoids are anandamide (arachidonoyl ethanolamide) and 2-arachidonoyl glycerol (10). Since the discovery of this complex endogenous cannabinoid receptor system it has been evident that cannabinoids have numerous physiological actions.

There are a wide variety of interactions between the CB_1 receptor system and many different neurotransmitters and neuromodulators in the central and peripheral nervous system (10). For instance, activation of CB_1 receptors leads to retrograde inhibition of the neuronal release of acetylcholine, dopamine, GABA, histamine, serotonin, glutamate, cholecystokinin, D-aspartate, glycine, and noradrenaline. The CB_1 receptor is the most widely distributed G-protein-coupled receptor in the CNS. These complex interactions explain not only the large number of physiological actions of cannabinoids, but also the pharmacological effects of cannabis preparations.

Pharmacology of cannabis and cannabinoids

Besides THC, the strongest psychotropically active component, cannabis contains numerous other cannabinoids and phytochemicals (11). Most of the effects of cannabis preparations are based on the agonistic action of THC on the various cannabinoid receptors (12). Some effects, however, can also be attributed to actions on other receptor systems. It is assumed, for example, that the alleviation of nausea and vomiting is due partly to an antagonistic action on the serotoninergic 5-hydroxytryptamine $(HT)_3$ receptor.

Some effects of cannabis preparations are caused by the actions of cannabinoids other than THC. For instance, cannabidiol (CBD)—after THC, the cannabinoid that occurs in the highest concentration in many strains of cannabis—possesses antiemetic, neuroprotective, and anti-inflammatory properties. CBD's complex mechanisms of effect include an antagonistic action on the CB_1 receptor, stimulation of the vanilloid-1 receptor, inhibition of the hydrolysis of anandamide (10), and activation of the nuclear receptor PPAR-gamma (13).

TABLE

Overview of controlled trials of cannabis medications for established indications*[1]

Indication	Number of randomized controlled trials (some three-armed)	Positive studies	Negative studies
Spasticity	n = 12 (dronabinol: [e1, e2, e4–e6]; cannabis: [e1–e3, e6–e12]) in multiple sclerosis	n = 9 (e4–e12)	n = 3 (e1–e3)
	n = 3 (dronabinol: [e13–e14]; nabilone: [e15] in paraplegia)	n = 3 (e13–e15)	–
Nausea and vomiting due to cytostatics	n = 41 (dronabinol: [e16–e34]; cannabis cigarettes: [e25]; cannabis extract: [e35]; nabilone: [e36–e52]; levonantradol: [e53–e56])	n = 40	n = 1 (e18)
Loss of appetite/weight loss	n = 7 (dronabinol: [e59–e65]; cannabis cigarettes: [e63–e65]) in HIV/Aids	n = 7	–
	n = 4 (dronabinol: [e66–e68]; cannabis extract: [e69]) in various tumor diseases	n = 3	n = 1 (e69)
	n = 1 (dronabinol: [e70]) in Alzheimer's disease	n = 1	–
Chronic pain	n = 14 (dronabinol: [e71–e74]; nabilone: [e75, e76]; cannabis extract: [e73, e74, e77–e79]; cannabis cigarettes: [e80–e83]; CT3 (ajulemic acid): [e84]) in neuropathic pain or pain in MS	n = 12 (e71, e73–e75, e77–e84)	n = 2 (e72, e76)
	n = 12 (dronabinol: [e85–e87, e93]; NIB: [e88]; benzopyranoperidine: [e89]; cannabis extract: [e87, e90, e94]; nabilone: [e91, e92, e96]; cannabis cigarettes: [e95]) in chronic pain (cancer, rheumatism, fibromyalgia)	n = 11 ([e85, e86, e87] cannabis extract, [e88, e90–e96])	n = 2 ([e87] dronabinol, [e89])

*[1] A complete list of clinical trials of cannabis medications can be found on the website of the IACM (24)

Therapeutic potential

Cannabis preparations exert numerous therapeutic effects. They have antispastic, analgesic, antiemetic, neuroprotective, and anti-inflammatory actions, and are effective against certain psychiatric diseases. Currently, however, only one cannabis extract is approved for use. It contains THC and CBD in a 1:1 ratio and was licensed in 2011 for treatment of moderate to severe refractory spasticity in multiple sclerosis (MS). In June 2012 the German Joint Federal Committee (JFC, Gemeinsamer Bundesausschuss) pronounced that the cannabis extract showed a "slight additional benefit" for this indication and granted a temporary license valid up to 2015.

The cannabis extract, which goes by the generic name nabiximols, has been approved by regulatory bodies in Germany and elsewhere for use as a sublingual spray. In the USA, dronabinol has been licensed since 1985 for the treatment of nausea and vomiting caused by cytostatic therapy and since 1992 for loss of appetite in HIV/Aids-related cachexia. In Great Britain, nabilone has been sanctioned for treatment of the side effects of chemotherapy in cancer patients *(Box 1)*.

In addition to these confirmed indications, there is solid evidence from a large number of small controlled trials that cannabinoid receptor agonists have an analgesic action, particularly in neuropathic pain; however, no country has yet approved their use for this purpose. The published controlled trials of cannabinoids for the indications spasticity, nausea and vomiting induced by cytostatics, anorexia in HIV/Aids, and chronic pain are summarized in the *Table*.

Spasticity

Novotna et al.'s large study on the treatment of spasticity in MS, published in 2011, led to the approval of the cannabis extract for this indication in Germany (e12). Of the 572 patients enrolled in the study, 272 (47.6%) responded to the treatment during an initial 4-week single-blind period of therapy (with response defined as a >20% decrease in spasticity) and went on to take part in the second phase of the study, a 12-week, double-blind, placebo-controlled trial (enriched design). Compared with placebo, the cannabis extract significantly reduced spasticity and the frequency of spasms and significantly improved sleep quality *(Table)*.

Cytostatic-induced nausea and vomiting

Numerous studies, most of them carried out in the 1970s and 1980s, demonstrated that cannabinoids were just as effective against chemotherapy-related nausea and vomiting as were the then standard antiemetics (e.g., phenothiazines such as prochlorperazine and dopamine antagonists such as metoclopramide), or even more so (e16–e56) *(Table)*. Moreover, it seems that low-dose dronabinol (2 × 2.5 mg) may have an additive effect when given with modern antiemetics (e34). In the treatment of delayed-onset nausea (2 to 5 days after cytostatic administration), dronabinol was just as effective as the antiemetic ondansetron (e34). Overall,

BOX 2

Contraindications and precautions

- **Contraindications:**
  - Abnormal sensitivity to individual components of the preparations
  - Severe personality disorders and psychoses
- **Strict precautions in:**
  - Pregnant and breast-feeding women, because of possible developmental disorders in the child
  - Children and adolescents (before puberty): the manufacturer of the registered cannabis extract recommends it not be used in those under the age of 18, because the data on safety and efficacy are inadequate
  - The elderly, because they are more vulnerable to central nervous and cardiovascular side effects
  - Severe cardiovascular diseases
  - Hepatitis C
  - Addictive disorders

cannabinoids are now considered reserve medications in the treatment of nausea and vomiting induced by cytostatics (e57, e58).

Anorexia and cachexia in HIV/Aids

All studies reported to date (n = 7) have shown a positive effect of dronabinol and cannabis cigarettes in the treatment of poor appetite in HIV patients (e59, e65) *(Table)*. In a 6-week double-blind, placebo-controlled trial with 139 patients, dronabinol was significantly superior to placebo: while the body weight of the patients taking dronabinol (2 × 2.5 mg) remained constant, those in the placebo group lost weight (mean 0.4 kg) (e60). In a three-armed study, low-dose dronabinol (2 × 2.5 mg) was inferior to high-dose megestrol acetate (750 mg) (e61). Cannabinoids were effective in the treatment of lack of appetite and weight loss in patients with tumor diseases (e66–e69) and Alzheimer's disease (e70).

Chronic pain

Cannabinoids are particularly effective against (chronic) neuropathic pain and pain in MS (e71–e84) *(Table)*, but have little or no effect in patients with acute pain (e97–e104). In a parallel group study of cannabis cigarettes in 50 patients with HIV-associated neuropathic pain, smoking cannabis reduced pain by a mean 34% (versus 17% for placebo). Fifty-two percent of the patients in the cannabis group experienced reduction in pain >30% (versus 24% for placebo) (e80). In a crossover trial (n = 24), dronabinol (up to 10 mg/day) reduced MS-related pain by a mean of 3 points (on a scale of 1 to 10), compared with 0 points for placebo (e71). Small controlled studies have indicated that cannabinoids may also be effective against chronic pain of other causes (tumor pain, rheumatism, fibromyalgia) (e85–e96).

Other indications

Small randomized controlled trials have shown positive effects of cannabis preparations in, for example, the following diseases and symptoms:

- Bladder dysfunction in MS (e105–e107)
- Tics in Tourette syndrome (e108, e109)
- Levodopa-induced dyskinesia in Parkinson's disease (e110).

Positive effects of cannabinoids against many other diseases and symptoms have been reported, but only in case reports and small open, non-controlled studies, so no firm conclusions can be drawn.

Side effects

Cannabis and individual cannabinoid receptor agonists (dronabinol, nabilone) show very similar, albeit not identical, side effects (14). Drug users smoke cannabis principally because of the psychoactive effects that occur at doses above the individual consumer's psychotropic threshold. These acute effects are generally perceived as pleasurable and relaxing. Sensory perception is often heightened. However, the feeling of increased wellbeing can give way to dysphoria, and anxiety or panic may occur. Further acute psychoactive effects of cannabinoids are impairment of memory, reductions in psychomotor and cognitive performance, disordered perception of the passage of time, and euphoria.

The debate continues as to whether high consumption of cannabis has long-term consequences on cognitive performance. On the basis of the current data it can be assumed that only extremely high consumption at levels hardly ever used for therapeutic purposes leads to irreversible cognitive impairments (15, 16). It seems quite clear, however, that the risk is much higher in children and adolescents (particularly before puberty). Therefore, the advisability of (long-term) treatment of patients in this age group with cannabinoids must be weighed up very carefully *(Box 2)*.

Cannabis consumption may induce schizophrenic psychosis in vulnerable individuals. Current data indicate that consumption of cannabis doubles the risk of schizophrenia in adolescents (17). Psychosis is therefore regarded as a contraindication to treatment with cannabinoid medications, although two case series have shown a positive effect of THC in the treatment of refractory schizophrenia (e111, e112).

Frequent physical effects of cannabinoids are tiredness, dizziness, tachycardia, orthostatic hypotension, dry mouth, reduced lacrimation, muscle relaxation, and increased appetite. According to small epidemiological studies, regular consumption of cannabis may accelerate the development of cirrhosis in patients with hepatitis C (18). No acute deaths have been described that could be unequivocally attributed solely to cannabis consumption or treatment with cannabinoids.

Nevertheless, the vascular effects of cannabinoids may increase the risk of myocardial infarction in persons so predisposed.

Tolerance develops to many of the undesired effects of cannabinoids—particularly tiredness, dizziness, and cardiovascular and psychoactive effects—over a period of days or weeks (e113–e116). Withdrawal symptoms only ever occur in heavy users of cannabis after abrupt cessation of consumption. 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 (19). Withdrawal symptoms seldom represent a problem, however, in the controlled medical administration of cannabinoids (20). Information on fitness to drive vehicles and operate machinery is provided in *Box 3*.

Interactions

Because THC is metabolized mainly in the liver by cytochrome P-450 isoenzymes (principally CYP2C), it may interact with other medications metabolized in the same way (10). Cannabis smoking can reduce the plasma concentration of individual antipsychotics (clozapine, olanzapine). However, neither in Aids patients nor in cancer patients was the plasma level of various antiretroviral drugs or cytostatics altered by simultaneous treatment with cannabinoids (21, 22).

Cannabinoids interact most often with substances that share the same effector systems, leading to mutual enhancement or attenuation of effect (23). The principal clinically relevant interactions are increased tiredness when cannabinoids are taken together with other psychotropic agents (e.g., alcohol and benzodiazepines) or interactions with medications that also act on the cardiovascular system (such as amphetamines, atropine, and beta-blockers). Additive effects may also be desirable, however, e.g., when cannabinoids are administered concurrently with antispastic drugs, broncholytics, analgesics, and antiemetics, as well as in the treatment of glaucoma.

Practical tips on the use of cannabis preparations in Germany

In Germany, medically supervised treatment with cannabis or individual cannabinoids can take one of two forms: 1.) prescription of the active substance dronabinol (THC)—prepacked or mixed specially for the patient—, the synthetic THC derivative nabilone, or the cannabis extract (in the form of a sublingual spray), using the special prescription form for narcotic substances; or 2.) treatment with herbal cannabis. The latter, however, requires special exemption according to § 3 para. 2 of the German Narcotics Act (*Betäubungsmittelgesetz*, BtMG) *(Boxes 4, 5)*.

Prescription of cannabinoid medications

Commercial preparations of nabilone and dronabinol are available in the USA, Great Britain, and other countries and can be prescribed in Germany according

BOX 3

Driving vehicles and operating machinery

- During a course of cannabinoids the patient's ability to drive vehicles and operate machinery safely may be impaired. The greatest risk is at the outset of treatment, during the dose-finding phase, and if the dose is changed.
- Patients who take cannabinoids at a constant dosage over an extensive period of time often develop tolerance to the impairment of psychomotor performance, so that they can drive vehicles safely (e117).
- Because of the alleviation of symptoms, treatment with cannabinoid medications may actually distinctly improve the patient's ability to drive motor vehicles (compared with no treatment) (e118, e119).

BOX 4

Options for treatment with cannabis in Germany

- Prescription of dronabinol, nabilone, or the cannabis extract by a physician, using the special prescription form for narcotic substances
- A prescription for dronabinol to be prepared by the pharmacist could read as follows: "Oil-based dronabinol drops 2.5%, 10 mL (corresponding to 250 mg dronabinol), start with 2 × 3 drops (2 × 2.5 mg) and increase gradually."
- Application to the Federal Opium Agency for an exemption according to § 3 para. 2 of the Narcotics Act (BtMG), permitting a patient to self-administer cannabis under medical supervision.

BOX 5

Dosage of cannabinoids

- Begin with a low dose and increase gradually.
- Start with 1 to 2 × 2.5 mg dronabinol, 1 × 1 mg nabilone, or 1 spray dose of cannabis extract daily.
- Increase by one unit (2.5 mg dronabinol, 0.5 mg nabilone, 1 spray dose of cannabis extract) every 1 to 2 days until the desired effect is achieved or side effects occur.
- If side effects occur, reduce by one unit.
- The maximum licensed daily dosage of the cannabis extract is 12 spray doses.
- Therapeutic dosages of dronabinol usually range between 5 and 30 mg per day, depending on indication and individual response and tolerance.
- The daily dosage of nabilone is usually 1 to 4 mg and does not normally exceed 6 mg.

to § 73 para. 3 of the Medicinal Products Act (*Arzneimittelgesetz*). Pharmacists obtain these medications from specialist importers. However, these dronabinol-containing agents are more expensive than individually mixed preparations.

The German Medicinal Products Code (*Deutscher Arzneimittelkodex*) of the Federal Union of German Associations of Pharmacists has published regulations for the production of a preparation containing dronabinol. Using an active substance manufactured by two companies in Germany, the pharmacist can prepare oil-or alcohol-based drops or capsules.

In principle, physicians of any discipline without additional qualifications can prescribe dronabinol (prepacked or individually mixed), nabilone, and the cannabis extract, even beyond the licensed indications (off-label), to any individual patient. The most frequent off-label uses of cannabis-based medications are as follows:

- In palliative medicine, to increase appetite and alleviate nausea
- To treat chronic pain (often together with opiates)
- To treat spasticity of causes other than MS (e.g., in paraplegic patients)
- To treat tics in patients with Tourette syndrome.

Off-label treatment with cannabinoid medications is difficult in everyday clinical practice, however, because statutory health insurers usually refuse to assume the costs. To avoid possible subsequent recourse claims, the question of assumption of costs should therefore be clarified with the relevant insurer before writing a prescription. A private prescription, where the patient will bear the costs, can be issued at any time.

Treatment with cannabis on the basis of an exemption according to the Narcotics Act

Alternatively, the patient can apply to the Federal Opium Agency, a body of the Federal Institute for Drugs and Medical Devices (BfArM), for an exemption according to BtMG § 3 para. 2. If granted, this exemption permits acquisition of medicinal cannabis flowers for use in medically supervised self-treatment. To simplify the procedure, the website of the BfArM contains information for physicians and patients and the necessary application forms. In the application, the patient must state that other therapies were not effective and explain why treatment with other, prescribable cannabinoid medications is not possible, e.g., because the health insurer will not assume the costs. The application must be accompanied by a physician's statement. The costs of this treatment must be borne by the patient.

Information on the Internet:
Federal Opium Agency: www.bfarm.de

Conflict of interest statement
Dr. Grotenhermen acts as consultant for the companies Bionorica Ethics and THC Pharm. He is chairman of the German Association for Cannabinoid Medicines (*Arbeitsgemeinschaft Cannabis als Medizin e. V.*; ACM) and chief executive officer of the International Association for Cannabinoid Medicines (IACM).

Prof. Müller-Vahl has received reimbursement of congress attendance fees and travel and accommodation costs from Astra-Zeneca und Lundbeck. She has received honoraria for conducting commissioned clinical studies and funds for a research project of her own initiation from Böhringer Ingelheim.

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KEY MESSAGES

- The clinical effect of the various cannabis-based medications rests primarily on activation of the endogenous cannabinoid receptor system with predominantly centrally situated CB_1 receptors and peripherally located CB_2 receptors.
- In 2011 the German regulatory authorities approved a cannabis extract for the treatment of moderate to severe refractory spasticity in multiple sclerosis.
- Medically supervised treatment may involve prescription of the cannabis active substance dronabinol (THC)—prepacked or individually prepared—, the synthetic THC derivative nabilone, or the cannabis extract in the form of a sublingual spray.
- Alternatively, patients can apply to the Federal Opium Agency for a permit allowing treatment with medicinal cannabis flowers.
- The established indications for treatment with cannabinoid medications are spasticity in multiple sclerosis, nausea and vomiting following chemotherapy, loss of appetite in HIV/Aids, and neuropathic pain.

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