

## 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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**K**nowledge 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 19<sup>th</sup> century to treat pain, spasms, asthma, sleep disorders, depression, and loss of appetite. In the first half of the 20<sup>th</sup> 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

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**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 capsules 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-psycho-tropic 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<sub>1</sub> receptor was cloned in 1990; the predominantly peripheral CB<sub>2</sub> receptor, expressed principally by cells of the immune system, 3 years later (9). Meanwhile, CB<sub>1</sub> 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<sub>1</sub> receptor—not of the CB<sub>2</sub> 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<sub>1</sub> receptor system and many different neurotransmitters and neuromodulators in the central and peripheral nervous system (10). For instance, activation of CB<sub>1</sub> receptors leads to retrograde inhibition of the neuronal release of acetylcholine, dopamine, GABA, histamine, serotonin, glutamate, cholecystokinin, D-aspartate, glycine, and noradrenaline. The CB<sub>1</sub> 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 serotonergic 5-hydroxytryptamine (HT)<sub>3</sub> 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, neuro-protective, and anti-inflammatory properties. CBD's complex mechanisms of effect include an antagonistic action on the CB<sub>1</sub> 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\*<sup>1</sup>

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]; benzopyrrolone: [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])

\*<sup>1</sup> 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](http://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 and 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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**REFERENCES**

1. Grotenhermen F: Cannabis und Cannabinoide. Pharmakologie, Toxikologie und therapeutisches Potential. 2<sup>nd</sup> edition. Göttingen: Hans Huber 2004.
2. Lambert DM: Cannabinoids in Nature and Medicine. Weinheim: Wiley-Vch. Verlag GmbH & Co. KGaA 2009.
3. Mechoulam R: Cannabinoids as Therapeutics. Basel: Birkhäuser Verlag 2005.
4. Radbruch L, Nauck F: Cannabinoide in der Medizin. Bremen: Unimed 2006.
5. Guy G, Whittle BA, Robson PJ: Medicinal Uses of Cannabis and Cannabinoids. London: Pharmaceutical Press 2004.
6. Stellungnahme der Bundesärztekammer, der Kassenärztlichen Bundesvereinigung und der Arzneimittelkommission der deutschen Ärzteschaft zu den Anträgen der Fraktion Bündnis 90/Die Grünen „Medizinische Verwendung von Cannabis erleichtern“ vom 27. 11. 2007 und der Fraktion Die Linke „Cannabis zur medizinischen Behandlung freigeben“ vom 25.06.2008. Ausschussdrucksache 16(14)0420(9). Deutscher Bundestag, Ausschuss für Gesundheit.
7. Fankhauser M: Cannabis in der westlichen Medizin. In: Grotenhermen F (ed.): Cannabis und Cannabinoide. Pharmakologie, Toxikologie und therapeutisches Potential. 2<sup>nd</sup> edition. Göttingen: Hans Huber 2004; 57–71.
8. Gaoni Y, Mechoulam R: Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc 1964; 86: 1646–7.

**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<sub>1</sub> receptors and peripherally located CB<sub>2</sub> 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.

9. Pertwee RG: Emerging strategies for exploiting cannabinoid receptor agonists as medicines. *Br J Pharmacol* 2009; 156: 397–411.
10. Grotenhermen F: Cannabinoids. *Curr Drug Targets CNS Neurol Disord* 2005; 4: 507–30.
11. ElSohly M: Chemische Bestandteile von Cannabis. In: Grotenhermen F (ed.): Cannabis und Cannabinoide. Pharmakologie, Toxikologie und therapeutisches Potential. 2<sup>nd</sup> edition. Göttingen: Hans Huber 2004; 45–55.
12. Pertwee RG, Howlett AC, Abood ME, et al.: Cannabinoid receptors and their ligands: beyond CB1 and CB2. *Pharmacol Rev* 2010; 62: 588–631.
13. O'Sullivan SE, Kendall DA: Cannabinoid activation of peroxisome proliferator-activated receptors: potential for modulation of inflammatory disease. *Immunobiology* 2010; 215: 611–6.
14. Grotenhermen F: The toxicology of cannabis and cannabis prohibition. *Chem Biodivers* 2007; 4: 1744–69.
15. Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T: Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. *J Int Neuropsychol Soc* 2003; 9: 679–89.
16. Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL: Dose-related neurocognitive effects of marijuana use. *Neurology* 2002; 59: 1337–43.
17. Moore TH, Zammit S, Lingford-Hughes A, et al.: Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007; 370: 319–28.
18. Hézode C, Zafrani ES, Roudot-Thoraval F, et al.: Daily cannabis use: a novel risk factor of steatosis severity in patients with chronic hepatitis C. *Gastroenterology* 2008; 134: 432–9.
19. Vandrey RG, Budney AJ, Hughes JR, Liguori A: A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. *Drug Alcohol Depend* 2008; 92: 48–54.
20. Beal JE, Olson R, Lefkowitz L, et al.: Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *J Pain Symptom Manage* 1997; 14: 7–14.
21. Kosel BW, Aweeka FT, Benowitz NL, et al.: The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. *AIDS* 2002; 16: 543–50.
22. Engels FK, de Jong FA, Sparreboom A, et al.: Medicinal cannabis does not influence the clinical pharmacokinetics of irinotecan and docetaxel. *Oncologist* 2007; 12: 291–300.
23. Hollister LE: Interactions of marijuana and 9-THC with other drugs. In: Nahas G, Sutin KM, Harvey DJ, Agurell S (eds.): Marijuana and Medicine. Totowa, NJ: Humana Press 1999: 273–7.
24. IACM: Studies and case reports. Available at: [www.cannabis-med.org/english/studies.htm](http://www.cannabis-med.org/english/studies.htm).

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For eReferences please refer to:  
[www.aerzteblatt-international.de/ref2912](http://www.aerzteblatt-international.de/ref2912)

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**eReferences**

- e1. Killestein J, Hoogervorst EL, Reif M, et al.: Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002; 58: 1404–7.
- e2. Zajicek J, Fox P, Sanders H, et al.: Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003; 362: 1517–26.
- e3. Centonze D, Mori F, Koch G, et al.: Lack of effect of cannabis-based treatment on clinical and laboratory measures in multiple sclerosis. *Neurol Sci* 2009; 30: 531–4.
- e4. Petro DJ, Ellenberger C: Treatment of human spasticity with 9-tetrahydrocannabinol. *J Clin Pharmacol* 1981; (Suppl 21): 413–6.
- e5. Ungerleider JT, Andrysiak T, Fairbanks L, Ellison GW, Myers LW:  $\Delta$ 9-THC in the treatment of spasticity associated with multiple sclerosis. *Adv Alcohol Substance Abuse* 1987; 7: 39–50.
- e6. Zajicek JP, Sanders HP, Wright DE, et al.: Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry* 2005; 76: 1664–9.
- e7. Vaney C, Heinzel-Gutenbrunner M, Jobin P, et al.: Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Multiple Sclerosis* 2004; 10: 417–24.
- e8. Wade DT, Makela P, Robson P, House H, Bateman C: Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler* 2004; 10: 434–41.
- e9. Wade DT, Makela PM, House H, Bateman C, Robson P: Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler* 2006; 12: 639–45.
- e10. Collin C, Davies P, Mutiboko IK, Ratcliffe S, for the Sativex Spasticity in MS Study Group: Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurology* 2007; 14: 290–6.
- e11. Conte A, Bettolo CM, Onesti E, et al.: Cannabinoid-induced effects on the nociceptive system: a neurophysiological study in patients with secondary progressive multiple sclerosis. *Eur J Pain* 2009; 13: 472–7.
- e12. Novotna A, Mares J, Ratcliffe S, et al.: A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols\* (Sativex), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2011; 18: 1122–31.
- e13. Hanigan WC, Destree R, Truong XT: The effect of D9-THC on human spasticity. *Clin Pharmacol Ther* 1986; 39: 198.
- e14. Hagenbach U, Luz S, Ghafoor N, et al.: The treatment of spasticity with delta-9-tetrahydrocannabinol in persons with spinal cord injury. *Spinal Cord* 2007; 45: 551–62.
- e15. Pooyania S, Ethans K, Szturm T, Casey A, Perry D: A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. *Arch Phys Med Rehabil* 2010; 91: 703–7.
- e16. Artim R, DiBella N: Tetrahydrocannabinol (THC) plus prochlorperazine (PCZ) for refractory nausea and vomiting (NV). *Proc Am Soc Clin Oncol* 1983; 2: 84.
- e17. Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky I: Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. *Ann Int Med* 1979; 91: 819–24.
- e18. Chang AE, Shiling DJ, Stillman RC, et al.: A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. *Cancer* 1981; 47: 1746–51.
- e19. Colls BM, Ferry DG, Gray AJ, Harvey VJ, McQueen EG: The antiemetic activity of tetrahydrocannabinol versus metoclopramide and thiethylperazine in patients undergoing cancer chemotherapy. *N Z Med J* 1980; 91: 449–51.
- e20. Ekert H, Waters KD, Jurk KH, Mobilia J, Loughnan P: Amelioration of cancer chemotherapy-induced nausea and vomiting by  $\Delta$ 9-tetrahydrocannabinol. *Med J Aust* 1979; 2: 657–9.
- e21. Frytak S, Moertel CG, O'Fallon JR, Rubin J, Creagan ET, O'Connell MJ: Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy. A comparison with prochlorperazine and a placebo. *Ann Int Med* 1979; 91: 825–30.
- e22. Gralla RJ, Tyson LB, Bordin LA, Clark RA, Kelsen DP, Kris MG: Antiemetic therapy: a review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. *Can Treat Rep* 1984; 68: 163–72.
- e23. Kluin-Nelemans JC, Nelemans FA, Meuwissen OJATH, Maes RAA:  $\Delta$ 9-tetrahydrocannabinol (THC) as an antiemetic in patients treated with cancer chemotherapy; a double-blind crossover trial against placebo. *Vet Hum Toxicol* 1979; 21: 338–40.
- e24. Lane M, Vogel CL, Ferguson J, Krasnow S, Saiers JL, Hamm J: Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. *J Pain Sym Manag* 1991; 6: 352–9.
- e25. Levitt M, Faiman C, Hawks R, Wilson A: Randomized double blind comparison of delta-9-tetrahydrocannabinol (THC) and marijuana as chemotherapy antiemetics. *Proc Am Soc Clin Oncol* 1984; 3: 91.
- e26. Levitt M, Wilson A, Bowman D, Faiman C, Kemel S, Krepart G: Dose vs response of tetrahydrocannabinol (THC) vs prochlorperazine as chemotherapy antiemetics. *Proc Am Soc Clin Oncol* 1981; 22: 422.
- e27. McCabe M, Smith FP, Goldberg D, Macdonald J, Woolley PV, Warren R: Efficacy of tetrahydrocannabinol in patients refractory to standard anti-emetic therapy. *Invest New Drugs* 1988; 6: 243–6.
- e28. Neidhart JA, Gagen MM, Wilson HE, Young DC: Comparative trial of the antiemetic effects of THC and haloperidol. *Int J Clin Pharmacol Res* 1981; 21: 38–42.
- e29. Orr LE, McKernan JF, Bloome B: Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Arch Int Med* 1980; 140: 1431–33.
- e30. Sallan SE, Cronin C, Zelen M, Zinberg NE: Antiemetics in patients receiving chemotherapy for cancer. A randomized comparison of



- delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med* 1980; 302: 135–8.
- e31. Sallan SE, Zinberg NE, Frei E: Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N Engl J Med* 1975; 293: 795–7.
- e32. Ungerleider JT, Andrysiak T, Fairbanks L, Goodnight J, Sarna G, Jamison K: Cannabis and cancer chemotherapy. A comparison of oral delta-9-THC and prochlorperazine. *Cancer* 1982; 50: 636–45.
- e33. Ungerleider JT, Sarna G, Fairbanks LA, Goodnight J, Andrysiak T, Jamison K: THC or compazine for the cancer chemotherapy patient – the UCLA study. Part II: patient drug preference. *Am J Clin Oncol* 1985; 8: 142–7.
- e34. Meiri E, Jhangiani H, Vredenburg JJ, et al.: Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opin* 2007; 23: 533–43.
- e35. Duran M, Pérez E, Abanades S, et al.: Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol* 2010; 70: 656–63.
- e36. Ahmedzai S, Carlyle DL, Clader IT, Moran F: Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. *Br J Cancer* 1983; 48: 657–63.
- e37. Chan HS, Correia JA, MacLeod SM: Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. *Pediatrics* 1987; 79: 946–52.
- e38. Crawford SM, Buckman R: Nabilone and metoclopramide in the treatment of nausea and vomiting due to cisplatin: a double blind study. *Med Oncol Tumour Pharmacother* 1986; 3: 39–42.
- e39. Cunningham D, Bradley CJ, Forrest GJ, et al.: A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues. *Eur J Can Clin Oncol* 1988; 24: 685–9.
- e40. Dalzell AM, Bartlett H, Lilleyman JS: Nabilone: An alternative antiemetic for cancer chemotherapy. *Arch Dis Child* 1986; 61: 502–5.
- e41. Einhorn LH, Nagy C, Furnas B, Williams SD: Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. *J Clin Pharmacol* 1981; 21(8–9 Suppl): 64–9.
- e42. George M, Pejovic MH, Thuairé M, Kramar A, Wolff JP: Randomized comparative trial of a new anti-emetic: nabilone, in cancer patients treated with cisplatin. *Biomed Pharmacother* 1983; 37: 24–7.
- e43. Herman TS, Einhorn LH, Jones SE, et al.: Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. *N Engl J Med* 1979; 300: 1295–7.
- e44. Johansson R, Kilku P, Groenroos M: A double-blind, controlled trial of nabilone vs prochlorperazine for refractory emesis induced by cancer chemotherapy. *Can Treat Rev* 1982; 9: 25–33.
- e45. Jones SE, Durant JR, Greco FA, Robertone A: A multi-institutional phase III study of nabilone vs placebo in chemotherapy-induced nausea and vomiting. *Can Treat Rev* 1982; 9: 45–8.
- e46. Levitt M: Nabilone vs placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. *Can Treat Rev* 1982; 9(suppl B): 49–53.
- e47. Nagy CM, Furnas BE, Einhorn LH, Bond WH: Nabilone: antiemetic crossover study in cancer chemotherapy patients. *Proc Am Soc Can Res* 1978; 19: 30.
- e48. Niederle N, Schutte J, Schmidt CG: Crossover comparison of the antiemetic efficacy of nabilone and alizapride in patients with nonseminomatous testicular cancer receiving cisplatin therapy. *Klin Wochenschr* 1986; 64: 362–5.
- e49. Niiranen Aila, Mattson K: A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. *Am J Clin Oncol* 1985; 8: 336–40.
- e50. Pomeroy M, Fennelly JJ, Towers M: Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. *Can Chemother Pharmacol* 1986; 17: 285–8.
- e51. Steele N, Gralla RJ, Braun Jr DW, Young CW: Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. *Can Treat Rep* 1980; 64: 219–24.
- e52. Wada JK, Bogdon DL, Gunnell JC, Hum GJ, Gota CH, Rieth TE: Double-blind, randomized, crossover trial of nabilone vs. placebo in cancer chemotherapy. *Cancer Treatment Rev* 1982; 9(Suppl B): 39–44.
- e53. Citron ML, Herman TS, Vreeland F, Krasnow SH, Fossieck BE Jr: Antiemetic efficacy of levonantradol compared to delta-9-tetrahydrocannabinol for chemotherapy-induced nausea and vomiting. *Cancer Treat Rep* 1985; 69: 109–12.
- e54. Higi M, Niederle N, Bremer K, Schmitt G, Schmidt CG, Seeber S: Levonantradol bei der Behandlung von zytostatika-bedingter Übelkeit und Erbrechen. *Dtsch Med Wochenschr* 1982; 107: 1232–4.
- e55. Hutcheon AW, Palmer JB, Soukop M, et al.: A randomised multicentre single blind comparison of a cannabinoid anti-emetic (levonantradol) with ychlorpromazine in patients receiving their first cytotoxic chemotherapy. *Eur J Can Clin Oncol* 1983; 19: 1087–90.
- e56. Stambaugh Jr JE, McAdams J, Vreeland F: Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapy-induced emesis. *Int J Clin Pharmacol Res* 1984; 24: 480–5.
- e57. American Society of Clinical Oncology, Kris MG, Hesketh PJ, et al.: American Society of Clinical Oncology guideline for antiemetics in oncology: Update 2006. *J Clin Oncol* 2006; 24: 2932–47.
- e58. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Antiemesis, V.3.2008. Available at: [www.nccn.org/professionals/physician\\_gls/PDF/antiemesis.pdf](http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf).
- e59. Struwe M, Kaempfer SH, Geiger CJ, et al.: Effect of dronabinol on nutritional status in HIV infection. *Ann Pharmacother* 1993; 27: 827–31.
- e60. Beal JE, Olson R, Laubenstein L, et al.: Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Sympt Manag* 1995; 10: 89–97.
- e61. Timpone JG, Wright DJ, Li N, et al.: The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Res Hum Retroviruses* 1997; 13: 305–15.
- e62. Bedi G, Foltin RW, Gunderson EW, et al.: Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: a controlled laboratory study. *Psychopharmacology* 2010; 212: 675–86.
- e63. Abrams DI, Hilton JF, Leiser RJ, et al.: Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Ann Intern Med* 2003; 139: 258–66.
- e64. Haney M, Rabkin J, Gunderson E, Foltin RW: Dronabinol and marijuana in HIV(+) marijuana smokers: acute effects on caloric intake and mood. *Psychopharmacology* 2005; 181: 170–8.
- e65. Haney M, Gunderson EW, Rabkin J, et al.: Dronabinol and marijuana in HIV-positive marijuana smokers. Caloric intake, mood, and sleep. *J Acquir Immune Defic Syndr* 2007; 45: 545–54.
- e66. Jatoi A, Windschitl HE, Loprinzi CL, et al.: Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002; 20: 567–73.
- e67. Regelson W, Butler JR, Schulz J, et al.: Delta-9-tetrahydrocannabinol as an effective antidepressant and appetite-stimulating agent in advanced cancer patients. In: Braude MC, Szara S (eds.): *Pharmacology of marijuana*. Vol 2. New York: Raven Press 1976; 763–76.

- e68. Brisbois TD, de Kock IH, Watanabe SM, et al.: Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol* 2011; 22: 2086–93.
- e69. Cannabis-In-Cachexia-Study-Group, Strasser F, Luftner D, et al.: Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol* 2006; 24: 3394–400.
- e70. Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ: Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 1997; 12: 913–9.
- e71. Svendsen KB, Jensen TS, Bach FW: Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004; 329: 253.
- e72. Rintala DH, Fiess RN, Tan G, Holmes SA, Bruel BM: Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. *Am J Phys Med Rehabil* 2010; 89: 840–8.
- e73. Wade DT, Robson P, House H, Makela P, Aram J: A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil* 2003; 17: 18–26.
- e74. Berman JS, Symonds C, Birch R: Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004; 112: 299–306.
- e75. Wissel J, Haydn T, Müller J, et al.: Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. *J Neurol* 2006; 253: 1337–41.
- e76. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D: Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ* 2008; 336: 199–201.
- e77. Rog DJ, Nurmikko TJ, Friede T, Young CA: Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005; 65: 812–9.
- e78. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D: Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007; 133: 210–20.
- e79. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S: Randomised Placebo Controlled Double Blind Clinical Trial of Cannabis Based Medicinal Product (Sativex) in Painful Diabetic Neuropathy: Depression is a Major Confounding Factor. *Diabetes Care* 2010; 33: 128–30.
- e80. Abrams DI, Jay CA, Shade SB, et al.: Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. *Neurology* 2007; 68: 515–21.
- e81. Wiley B, Marcotte T, Tsodikov A, et al.: A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 2008; 9: 506–21.
- e82. Ellis RJ, Toperoff W, Vaida F, et al.: Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology* 2009; 34: 672–80.
- e83. Ware MA, Wang T, Shapiro S, et al.: Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ* 2010; 182: 694–701.
- e84. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U: Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA* 2003; 290: 1757–6.
- e85. Noyes R, Brunk SF, Baram DA, Canter A: Analgesic effects of delta-9-THC. *J Clin Pharmacol* 1975; 15: 139–43.
- e86. Noyes R, Brunk ST, Avery DH, Canter A: The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther* 1975; 18: 84–9.
- e87. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT: Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD Extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* 2010; 39: 167–79.
- e88. Staquet M, Gantt C, Machin D: Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. *Clin Pharmacol Ther* 1978; 23: 397–401.
- e89. Jochimsen PR, Lawton RL, VerSteeg K, Noyes Jr R: Effect of benzopyranoperidine, a delta-9-THC congener, on pain. *Clin Pharmacol Ther* 1978; 24: 223–7.
- e90. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS: Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* 2006; 45: 50–2.
- e91. Skrabek RQ, Galimova L, Ethans K, Perry D: Nabilone for the treatment of pain in fibromyalgia. *J Pain* 2008; 9: 164–73.
- e92. Ware MA, Fitzcharles MA, Joseph L, Shir Y: The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg* 2010; 110: 604–10.
- e93. Narang S, Gibson D, Wasan AD, et al.: Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain* 2008; 9: 254–64.
- e94. Notcutt W, Price M, Miller R, et al.: Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. *Anaesthesia* 2004; 59: 440–52.
- e95. Ware MA, Ducruet T, Robinson AR: Evaluation of herbal cannabis characteristics by medical users: a randomized trial. *Harm Reduct J* 2006; 3: 32.
- e96. Pinsger M, Schimetta W, Volc D, Hiermann E, Riederer F, Polz W: Nutzen einer Add-On-Therapie mit dem synthetischen Cannabinomimetikum Nabilone bei Patienten mit chronischen Schmerzzuständen – eine randomisierte kontrollierte Studie. *Wien Klin Wochenschr* 2006; 118: 327–35.
- e97. Raft D, Gregg J, Ghia J, Harris L: Effects of intravenous tetrahydrocannabinol on experimental and surgical pain: psychological correlates of the analgesic response. *Clin Pharmacol Ther* 1977; 21: 26–33.
- e98. Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, Rowbotham DJ: Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. *Pain* 2003; 106: 169–72.
- e99. Seeling W, Kneer L, Buchele B, et al.: Delta-9-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative pain. *Anaesthesist* 2006; 55: 391–400.
- e100. Holdcroft A, Maze M, Dore C, Tebbs S, Thompson S: A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. *Anesthesiology* 2006; 104: 1040–6.
- e101. Beaulieu P: Effects of nabilone, a synthetic cannabinoid, on postoperative pain. *Can J Anaesth* 2006; 53: 769–75.
- e102. Jain AK, Ryan JR, McMahon FG, Smith G: Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol* 1981; 21(suppl 8–9): 320–6.
- e103. Kantor TG, Hopper M: A study of levonantradol, a cannabinol derivative, for analgesia in post operative pain. *Pain* 1981; (suppl): S37.
- e104. Ostenfeld T, Price J, Albanese M, et al.: A randomized, controlled study to investigate the analgesic efficacy of single doses of the cannabinoid receptor-2 agonist GW842166, ibuprofen or placebo in patients with acute pain following third molar tooth extraction. *Clin J Pain* 2011; 27: 668–76.
- e105. Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J: The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). *Int Urogynecol J Pelvic Floor Dysfunct* 2006; 17: 636–41.

- e106. Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ: An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Multiple Sclerosis* 2004; 10: 425–33.
- e107. Kavia RB, De Ridder D, Constantinescu CS, Stott CG, Fowler CJ: Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. *Mult Scler* 2010; 16: 1349–59.
- e108. Müller-Vahl KR, Schneider U, Koblenz A, et al.: Treatment of Tourette's syndrome with  $\Delta$ 9-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry* 2002; 35: 57–61.
- e109. Müller-Vahl KR, Schneider U, Prevedel H, et al.:  $\Delta$ 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry* 2003; 64: 459–65.
- e110. Sieradzan KA, Fox SH, Dick J, Brotchie JM: The effects of the cannabinoid receptor agonist nabilone on L-DOPA induced dyskinesia in patients with idiopathic Parkinson's disease (PD). *Movement Disorders* 1998; 13(Suppl 2): 29.
- e111. Schwarcz G, Karajgi B, McCarthy R: Synthetic delta-9-tetrahydrocannabinol (dronabinol) can improve the symptoms of schizophrenia. *J Clin Psychopharmacol* 2009; 29: 255.
- e112. Schwarcz G, Karajgi B: Improvement in refractory psychosis with dronabinol: four case reports. *J Clin Psychiatry* 2010; 71: 1552–3.
- e113. Jones RT, Benowitz N, Bachman J: Clinical studies of cannabis tolerance and dependence. *Ann N Y Acad Sci* 1976; 282: 221–39.
- e114. Stefanis C: Biological aspects of cannabis use. *NIDA Res Monogr* 1978; 19: 149–78.
- e115. Elsner F, Radbruch L, Sabatowski R: Tetrahydrocannabinol zur Therapie chronischer Schmerzen. *Schmerz* 2001; 15: 200–4.
- e116. Hirvonen J, Goodwin RS, Li CT, et al.: Reversible and regionally selective down regulation of brain cannabinoid CB(1) receptors in chronic daily cannabis smokers. *Molecular Psychiatry* 2012; 17, 642–49.
- e117. Kurtzthaler I, Bodner T, Kemmler G, et al.: The effect of nabilone on neuropsychological functions related to driving ability: an extended case series. *Hum Psychopharmacol* 2005; 20: 291–3.
- e118. Brunnauer A, Segmiller FM, Volkamer T, Laux G, Müller N, Dehning S: Cannabinoids improve driving ability in a Tourette's patient. *Psychiatry Res* 2011; 190: 382.
- e119. Strohecker-Kuehner P, Skopp G, Mattern R: Fahrtüchtigkeit trotz (wegen) THC. *Arch Kriminol* 2007; 220: 11–9.