



Medical Use of Cannabis Products

Joachim Nadstawek

Case Example

- ♂ 44 years
- restless-legs-syndrom
- peripheral polyneuropathy
- terminal renal failure
- status post renal transplantation
- sclerosis of the carotid artery
- renal anemia
- renal osteopathy
- hyperparathyreoidism
- asiderosis
- herpes zoster
- spontaneous fracture
- weight problems (44kg)

Drugs

- Fentanyl patch 75µg/h
- Restex
- Bisoprolol
- Ondansetron
- Simvastatin
- Allopurinol
- Rantidin
- Fosrenol
- Dreisavit
- Pantoprazol
- Movicol, Laxoberal
- Domperidon
- Metamizol
- Mimpara
- Fermed Ampullen
- Retacrit

Therapy

- rotation to hydromorphone
- fluoxetine
- simeticone
- macrogol
- antihistamines
- severe side effects
- no sufficient effect level
- therapeutical trial with THC
- reduction of the opioids and improvement of the general condition
- Request at the health insurance

Questions of the Health Insurance

- Concrete listing of all medications used till that time
 - Taking the start of the drugs
 - Taking the end of the drugs
 - Duration of treatment
 - Dosage
 - Application scheme
 - Treatment successful??
 - Side effects and treatment of the side effects

Questions of the Health Insurance

- Life-threatening disease?
- Serious threat of the quality of life?
- Are others prior to this indication authorized medicines available???
- Qualified study situation???
- Exists in the off-label-use at least an on circumstantial evidence based prospect of successful treatment??
- Is this medicine mandatory for medical reasons necessary and economically?
- Cost coverage socio-medical recommended?

Current Status

- Withdrawal of opioids
- THC 2 x 5 mg in the morning and the evening
- weight 51 kg
- Significant more agile and powerful
- Again in training
- Insurance rejects the application after three medical reports of the medical service of the insurances
- Lawsuit in front of the social court

Rediscovery of Cannabis

- Discovery of the endocannabinoid-system: 1992
- Relegalisation of Cannabis for medical use in California: 1996
- THC („Dronabinol“) is allowed for prescription: 1998
- Cannabis for medical use in the Netherlands: 2003
- First special permits for the acquisition of cannabis herbs in Germany: 2007
- German government „legalised“ cannabis for medical use: 2010

Cannabis Products in Germany

- **Dronabinol (THC)**
 - in capsules or oily solution by prescription drugs (BtM= narcotics law)
- **„Sativex“ (Nabiximols)**
 - permitted for treatment of spastic in patients with multiple sclerosis, spray (BtM)
- **CBD**
 - in capsules by prescription drugs (not under narcotics law!)
 - Oily solution
- **Imported Cannabis plants**
 - §3 BtMG (narcotics law)

Use of Cannabis in Germany

- about 5000 persons use medical cannabis officially
- Reimbursement only for Sativex in patients with multiple sclerosis for spastic treatment, Sativex and Dronabinol in palliative care
- Cannabis-herbs
 - Certificate of exemption §3 Abs. 2 BtMG
 - Essential prerequisite: „treated-out patients“
 - costs: 15-25€ per gramm, no reimbursement
 - One provider: Bedrocan (Netherlands)

Certificate of Exemption

- **TOP 5 Diagnoses**

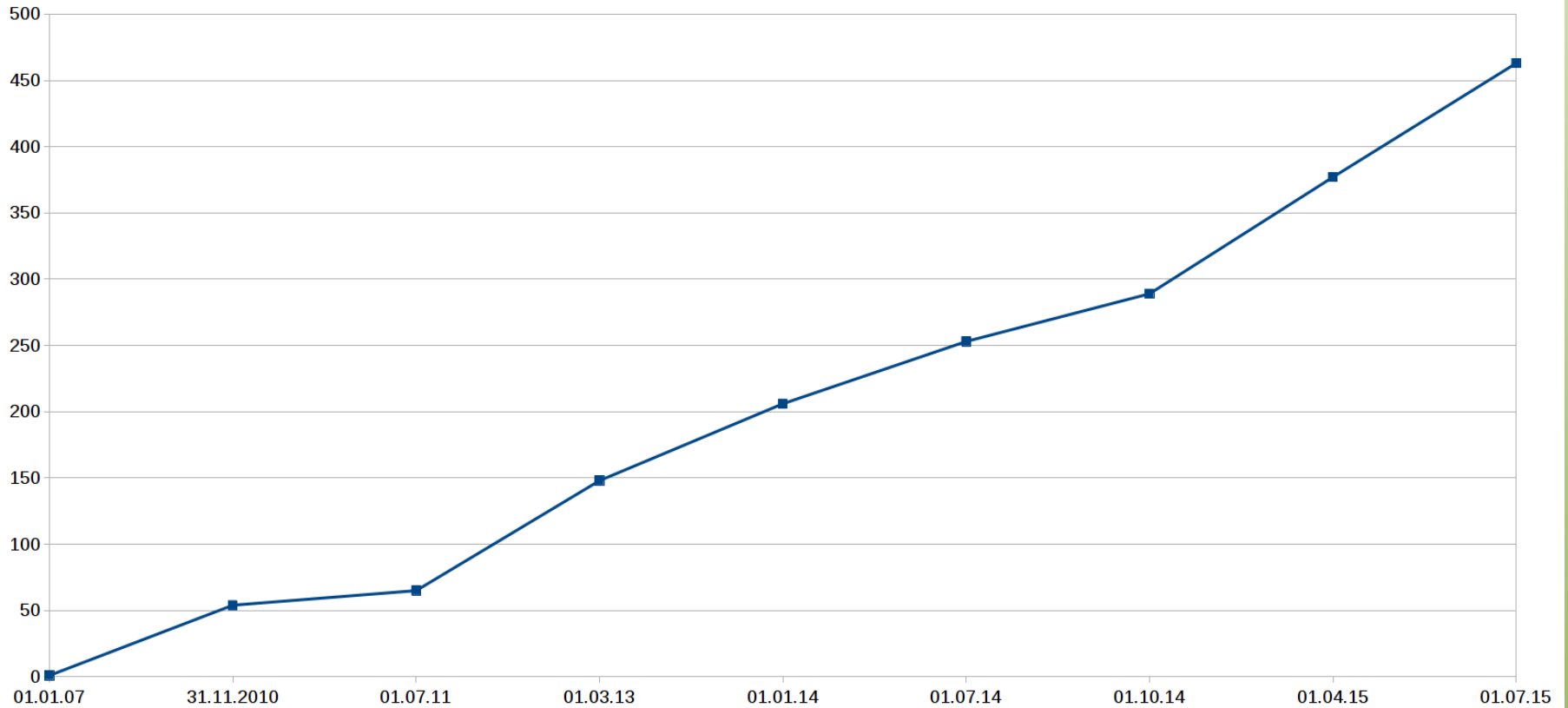
- Chronic Pain
- Multiple Sclerosis
- Tourette-Syndrome
- Depression
- Attention deficit hyperactivity disorder (ADHD)

- Open register

- approximate 40 further diagnoses known

Entwicklung bei Cannabis als Medizin

Zahl der Erlaubnisinhaber



Current Patients Problems

- High costs
- Law enforcement if illegal supply
- Imposing disproportionate bureaucracy
- Only a few doctors prescribe cannabis due to prejudices and knowledge gaps
- Supply gaps of a number of months with cannabis herbs
- Residence obligation if treatment with cannabis herbs
- Driving license law
- Police violence
 - „Cannabis-Patient is not allowed to smell of cannabis“
 - Confiscation of legal herbs...

Current Situation – World Wide

- often only medicines like Sativex, Dronabinol etc.
- Natural Cannabis
 - Canada (now 90000 Patients)
 - Israel (25000 Patients)
 - 23 (+ x) states of the USA including Washington D.C. (over one million)
 - Netherlands
- California is not representative for the USA
- 16% of the US-population have access without limitation of the diagnoses
- 31% with special diagnoses (positive list) receive cannabis, mostly only tumor pain, chronic pain, glaucoma, HIV/AIDS and nausea/emaciation

Politics

- Progresses in medical cannabis use were claimed by patients against the will of the politicians
 - Oberlandesgericht Karlsruhe 2004: justifying state of emergency with self grown products
 - Bundesverfassungsgericht 2000: Gesundheit ist im öffentlichen Interesse
 - Bundesverwaltungsgericht 2005: BfArM muss Anträge genehmigen
 - Oberverwaltungsgericht Münster 2014, VG Köln: Ablehnung von Anbauanträgen rechtswidrig
 - Bundesverfassungsgericht 2015: Unverletzlichkeit der Wohnung gilt auch bei Eigenanbau von Cannabis durch Patienten
 - Bundesverwaltungsgericht 2015/2016: BfArM muss Anbau genehmigen ?

Politics

- Bill of the German Government 26.06.2016
- Draft law amending the law for drugs and other regulations
- This law shall serve to coordinate the prescription of further indications and further cannabis medication

Article 1

- Cannabis cultivation for medical use shall be subject for inspection of the Federal Institute of drugs and medical devices

Article 4

- Insured persons with a severe disease are entitled to supply with cannabis in terms of dried herbs or essences and to the supply with the active ingredient of Dronabinol or Nabilon if

Article 4

- A generally accepted according to the medical standard therapy is not available in the individual case
- A not so far away being chance to succeed the history of the disease or to serious symptoms
- The insured person commits oneself to take part in a not interventional accompanying investigation over a certain time in application to this medication.

Article 4

The first prescription requires the approval of the health insurance!

Patients must have reached the end of their options with conventional therapy!



Cannabinoids and Evidence?

MEDIZIN

ÜBERSICHTSARBEIT

Das therapeutische Potenzial von Cannabis und Cannabinoiden

Franjo Grotenhermen, Kirsten Müller-Vahl

Ärzteblatt 2012 Heft 29



Cannabinoids for fibromyalgia (Review)

Walitt B, Klose P, Fitzcharles MA, Phillips T, Häuser W

CURRENT ORIGINAL ARTICLE

Integrating cannabis into clinical cancer care

D.I. Abrams MD*

ABSTRACT

Cannabis species have been used as medicine for thousands of years; only since the 1940s has the plant not been widely available for medical use. However, an increasing number of jurisdictions are making it possible for patients to obtain the botanical for medicinal use.

For the cancer patient, cannabis has a number of potential benefits, especially in the management of symptoms. Cannabis is useful in combatting anorexia, chemotherapy-induced nausea and vomiting, pain, insomnia, and depression. Cannabis might be less potent than other available antiemetics, but for some patients, it is the only agent that works, and it is the only antiemetic that also increases appetite. Inhaled cannabis is more effective than placebo in ameliorating peripheral neuropathy in a number of conditions, and it could prove useful in chemotherapy-induced neuropathy. A pharmacokinetic interaction study of vaporized cannabis in patients with chronic pain on stable doses of sustained-release opioids demonstrated no clinically significant change in plasma opiates, while suggesting the possibility of synergistic analgesia.

Aside from symptom management, an increasing body of *in vitro* and animal-model studies supports a possible direct anticancer effect of cannabinoids by way of a number of different mechanisms involving apoptosis, angiogenesis, and inhibition of metastasis. Despite an absence of clinical trials, abundant anecdotal reports that describe patients having remarkable responses to cannabis as an anticancer agent, especially when taken as a high-potency orally ingested concentrate, are circulating. Human studies should be conducted to address critical questions related to the foregoing effects.

Key Words Cannabis, cannabinoids, symptom management, nausea, anorexia, pain

Curr Oncol. 2016 Mar;23(S2):S8-S14 www.current-oncology.com

Schmerz
DOI 10.1007/s00482-015-0085-2

© Deutsche Schmerzgesellschaft e.V. Published by Springer-Verlag Berlin Heidelberg - all rights reserved 2015



M. Mücke^{1,2,3} · C. Carter¹ · H. Cuhls¹ · M. Prüß⁴ · L. Radbruch^{1,5} · W. Häuser^{6,7}

¹ Klinik für Palliativmedizin, Universitätsklinikum Bonn, Bonn, Deutschland

² Institut für Hausarztmedizin, Medizinische Fakultät, Universität Bonn, Bonn, Deutschland

³ Zentrum für Seltene Erkrankungen (ZSEB), Universitätsklinikum Bonn, Bonn, Deutschland

⁴ Charité Centrum Innere Medizin mit Gastroenterologie und Nephrologie, Universitätsmedizin Berlin, Berlin, Deutschland

⁵ Zentrum für Palliativmedizin, Malteser Krankenhaus Seliger Gerhard Bonn/Rhein-Sieg, Bonn, Deutschland

⁶ Innere Medizin I, Klinikum Saarbrücken gGmbH, Saarbrücken, Deutschland

⁷ Klinik für Psychosomatische Medizin und Psychotherapie, Technische Universität München, München, Deutschland

Cannabinoide in der palliativen Versorgung

Systematische Übersicht und Metaanalyse der Wirksamkeit, Verträglichkeit und Sicherheit

Research

Original Investigation

Cannabinoids for Medical Use A Systematic Review and Meta-analysis

Penny F. Whiting, PhD, Robert F. Wolff, MD, Sohan Deshpande, MSc, Marcello Di Nisio, PhD, Steven Duffy, PgD, Adrian V. Hernandez, MD, PhD, J. Christiaan Keurentjes, MD, PhD, Shona Lang, PhD, Kata Misso, MSc, Steve Ryder, MSc, Simone Schmidtkofer, MSc, Marie Westwood, PhD, Jos Kleijnen, MD, PhD

IMPORTANCE Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

OBJECTIVE To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.

DATA SOURCES Twenty-eight databases from inception to April 2015.

Editorial page 2431

Related article page 2474

Supplemental content at jama.com

Evidence in Pain Therapy?

- Neuropathic pain – pain relief of 30%! But NNT 14!!
- In comparison: compliant to guidelines drugs have a NNT of 2 or 3
- Rheumatic pain: in four studies pain reduction of 0.5 to 1 on a scale of ten
- Visceral pain: Moderate pain reduction and minor improvement of appetite
- Ineffective in acute pain

Moderate Evidence

Cannabinoids and Cachexia?

- In cancer patients no significant improvement of the weight
- In patients with HIV significant improvement of the weight with minor influence to nausea and vomiting, the effect of Megestrol was better
- In patients with Alzheimer-Disease significant weight increase (only one study)

Weak to moderate Evidence

Cannabinoids and Nausea?

- 28 studies including 1772 patients show an advantage of cannabinoids in comparison to placebo, but not significantly
- Elder studies from the 70th and 80th show equal or better results in comparison to metoclopramide or prochlorperazine
- But advantages through additive application with modern antiemetics like Ondansetron

Weak Evidence

Cannabinoids and Spasticity?

- 14 randomized clinical studies with 2280 patients: improvement of the MS related spasticity but not significant
- Novotna et al. 2011: 572 patients with multiple sclerosis! In 47.6% of the patients significant reduction of spasticity during a four week therapy with cannabinoids. This study is responsible for the admission of Sativex for treatment of MS related spasticity (reimbursement)
- In comparison to placebo improved Cannabis spasticity, spasm frequency and quality of sleep significantly

Moderate Evidence

Metaanalysis of side effects

	No. of Studies (No. of Patients)	Summary OR (95% CI)	P, %	Individual AEs			
General AE categories							
Any	29 (3714)	3.03 (2.42-3.80)	31	Dizziness	41 (4243)	5.09 (4.10-6.32)	18
Serious	34 (3248)	1.41 (1.04-1.92)	0	Dry mouth	36 (4181)	3.50 (2.58-4.75)	28
Withdrawal due to AE	23 (2755)	2.94 (2.18-3.96)	2	Nausea	30 (3579)	2.08 (1.63-2.65)	0
MedDRA high-level grouping¹⁶⁴				Fatigue	20 (2717)	2.00 (1.54-2.62)	0
Gastrointestinal disorders	10 (1960)	1.78 (1.43-2.22)	0	Somnolence	26 (3168)	2.83 (2.05-3.91)	27
Infections and infestations	7 (1681)	1.13 (0.87-1.46)	0	Euphoria	27 (2420)	4.08 (2.18-7.64)	49
Psychiatric disorders	8 (1672)	3.10 (1.81-5.29)	55	Depression	15 (2353)	1.32 (0.87-2.01)	0
Nervous system disorders	10 (1521)	3.17 (2.20-4.58)	46	Vomiting	17 (2191)	1.67 (1.13-2.47)	0
Musculoskeletal and connective tissues disorders	7 (1310)	1.32 (0.75-2.32)	34	Diarrhea	17 (2077)	1.65 (1.04-2.62)	15
General disorders and administration site conditions	6 (1208)	1.78 (1.34-2.36)	0	Disorientation	12 (1736)	5.41 (2.61-11.19)	0
Death	5 (929)	1.01 (0.51-2.00)	0	Asthenia	15 (1717)	2.03 (1.35-3.06)	0
Ear and labyrinth disorders	3 (922)	2.72 (1.55-4.75)	0	Drowsiness	18 (1272)	3.68 (2.24-6.01)	44
Respiratory, thoracic, and mediastinal disorders	5 (851)	0.80 (0.46-1.39)	0	Anxiety	12 (1242)	1.98 (0.73-5.35)	54
Cardiac disorders	7 (833)	1.42 (0.58-3.48)	0	Confusion	13 (1160)	4.03 (2.05-7.97)	0
Blood disorders	3 (543)	1.42 (0.20-10.25)	18	Balance	6 (920)	2.62 (1.12-6.13)	0
Injury, poisoning and procedural complications	3 (543)	1.18 (0.48-2.93)	0	Hallucination	10 (898)	2.19 (1.02-4.68)	0
Renal and urinary disorders	3 (470)	2.45 (2.27-2.65)	0	Dyspnea	4 (375)	0.83 (0.26-2.63)	0
Investigations	2 (427)	1.55 (0.36-6.71)	0	Paranoia	4 (492)	2.05 (0.42-10.10)	0
Metabolism and nutrition	2 (427)	2.37 (1.00-5.61)	0	Psychosis	2 (37)	1.09 (0.07-16.35)	25
Neoplasms, benign, malignant, and unspecified	2 (427)	0.99 (0.47-2.08)	0	Seizures	2 (42)	0.91 (0.05-15.66)	0
Skin and subcutaneous	3 (405)	0.85 (0.34-2.13)	0				
Eye disorders	1 (339)	1.42 (0.46-4.33)	NA				
Reproductive system	1 (246)	1.55 (0.20-11.92)	NA				
Hepatobiliary disorders	1 (181)	3.07 (0.12-76.29)	NA				
Mental status change	3 (106)	2.49 (0.49-12.64)	0				
Other body systems	1 (42)	2.59 (0.34-19.47)	NA				
Injection site pain	1 (32)	2.49 (0.92-6.68)	NA				

Unsolved Issues

- Examination of the initial application – how and in what time?
 - Normal reimbursement?
 - Security of supply?
 - Access barriers?
 - Driving license regulations?
 - Freedom of travel?
 - Specialized medical training?
 - Research?
-
- **Cannabinoids for medical use – a landmark??**

Conclusion

- »Cannabis seems to be an alternative treatment for a special group of patients«
- Only weak to moderate evidence but individualized treatment in patients with nausea, loss of appetite, weakness, spasticity, depression, pain useful
- There is no evidence that cannabis herbs are more effective in comparison to THC, THC/CBD or synthetic THC
- A greater benefit in patients with chronic pain possible

