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?

Integrating cannabis into clinical cancer care

**ABSTRACT**

Cannabinoids 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 plant for medicinal use.

For the cancer patient, cannabis has a number of potential benefits, especially in the management of symptoms. Cannabis is useful in combating 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 a synthetic cannabinoid in patients with chronic pain and on the doses of opioids did not show a clinically significant change in plasma opioids, 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 antitumor 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 describe patients having remarkable responses to cannabis as an anti-cancer agent, especially when taken as a high-potency orally ingested concentrate. Ongoing clinical trial and human studies should be conducted to address critical questions related to the foregoing effects.

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

Cannabinoide in der palliativen Versorgung

Systematische Übersicht und Metaanalyse der Wirksamkeit, Verträglichkeit und Sicherheit
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
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)
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.
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.
<table>
<thead>
<tr>
<th>General AE categories</th>
<th>No. of Studies (No. of Patients)</th>
<th>Summary OR (95% CI)</th>
<th>P², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>29 (3714)</td>
<td>3.03 (2.42-3.80)</td>
<td>61</td>
</tr>
<tr>
<td>Serious</td>
<td>34 (3248)</td>
<td>1.41 (1.04-1.92)</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal due to AE</td>
<td>23 (2755)</td>
<td>2.94 (2.18-3.96)</td>
<td>2</td>
</tr>
<tr>
<td>MedDRA high-level grouping¹⁶⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10 (1960)</td>
<td>1.78 (1.43-2.22)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>7 (1681)</td>
<td>1.13 (0.87-1.46)</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>8 (1672)</td>
<td>3.10 (1.81-5.29)</td>
<td>55</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>10 (1521)</td>
<td>3.17 (2.20-4.58)</td>
<td>46</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>7 (1310)</td>
<td>1.32 (0.75-2.32)</td>
<td>34</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>6 (1208)</td>
<td>1.78 (1.34-2.36)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>5 (929)</td>
<td>1.01 (0.51-2.00)</td>
<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>3 (892)</td>
<td>2.72 (1.55-4.75)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>5 (851)</td>
<td>0.80 (0.46-1.39)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>7 (833)</td>
<td>1.42 (0.58-3.48)</td>
<td>0</td>
</tr>
<tr>
<td>Blood disorders</td>
<td>3 (543)</td>
<td>1.42 (0.20-10.25)</td>
<td>18</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>3 (543)</td>
<td>1.18 (0.48-2.93)</td>
<td>0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3 (470)</td>
<td>2.45 (2.27-2.65)</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td>2 (427)</td>
<td>1.55 (0.36-6.71)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>2 (427)</td>
<td>2.37 (1.00-5.61)</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasms, benign, malignant, and unspecified</td>
<td>2 (427)</td>
<td>0.99 (0.47-2.08)</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous</td>
<td>3 (405)</td>
<td>0.85 (0.34-2.13)</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1 (239)</td>
<td>1.42 (0.46-4.33)</td>
<td>NA</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>1 (246)</td>
<td>1.55 (0.20-11.92)</td>
<td>NA</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>1 (181)</td>
<td>3.07 (0.12-76.29)</td>
<td>NA</td>
</tr>
<tr>
<td>Mental status change</td>
<td>3 (106)</td>
<td>2.49 (0.49-12.64)</td>
<td>0</td>
</tr>
<tr>
<td>Other body systems</td>
<td>1 (42)</td>
<td>2.59 (0.34-19.47)</td>
<td>NA</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1 (32)</td>
<td>2.49 (0.92-6.68)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Individual AEs

<table>
<thead>
<tr>
<th>AE</th>
<th>No. of Studies (No. of Patients)</th>
<th>Summary OR (95% CI)</th>
<th>P², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>41 (4243)</td>
<td>5.09 (4.10-6.32)</td>
<td>18</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>36 (4181)</td>
<td>3.50 (2.58-4.75)</td>
<td>28</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (3579)</td>
<td>2.08 (1.63-2.65)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (2717)</td>
<td>2.00 (1.54-2.62)</td>
<td>0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>26 (3168)</td>
<td>2.83 (2.05-3.91)</td>
<td>27</td>
</tr>
<tr>
<td>Euphoria</td>
<td>27 (2420)</td>
<td>4.08 (2.18-7.64)</td>
<td>49</td>
</tr>
<tr>
<td>Depression</td>
<td>15 (2353)</td>
<td>1.32 (0.87-2.01)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (2191)</td>
<td>1.67 (1.13-2.47)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (2077)</td>
<td>1.65 (1.04-2.62)</td>
<td>15</td>
</tr>
<tr>
<td>Disorientation</td>
<td>12 (1736)</td>
<td>5.41 (2.61-11.19)</td>
<td>0</td>
</tr>
<tr>
<td>Asasthenia</td>
<td>15 (1717)</td>
<td>2.03 (1.35-3.06)</td>
<td>0</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>18 (1272)</td>
<td>3.68 (2.24-6.01)</td>
<td>44</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12 (1242)</td>
<td>1.98 (0.73-5.35)</td>
<td>54</td>
</tr>
<tr>
<td>Confusion</td>
<td>13 (1160)</td>
<td>4.03 (2.05-7.97)</td>
<td>0</td>
</tr>
<tr>
<td>Balance</td>
<td>6 (920)</td>
<td>2.62 (1.12-6.13)</td>
<td>0</td>
</tr>
<tr>
<td>Hallucination</td>
<td>10 (898)</td>
<td>2.19 (1.02-4.68)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (375)</td>
<td>0.83 (0.26-2.63)</td>
<td>0</td>
</tr>
<tr>
<td>Paranola</td>
<td>4 (492)</td>
<td>2.05 (0.42-10.10)</td>
<td>0</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2 (37)</td>
<td>1.09 (0.07-16.35)</td>
<td>25</td>
</tr>
<tr>
<td>Seizures</td>
<td>2 (42)</td>
<td>0.91 (0.05-15.66)</td>
<td>0</td>
</tr>
</tbody>
</table>
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 chronical pain possible