Medical use of Cannabinoids in Neurological Diseases
Berner Klinik Montana

Crans-Montana
Neurological rehabilitation clinic in the alps

300 PwMS/year
20 years ago in 1993...

28 y old MS patient:
- can barely stand on his own
- walks a few steps only with aid and
- suffers from severe spasms

Lioresal, Sirdalud + Valium ...
- Did not work, were badly tolerated
- and made him tired

Is there anything that helps you?

“I smoke a joint!”
1998
Request to the FOPH (Federal Office of Public Health) for a special authorisation to prescribe Marinol® (=capsules of synthetic delta-9-THC)
### THC for MS - Studies before 1998

<table>
<thead>
<tr>
<th>Studie</th>
<th>n</th>
<th>Form</th>
<th>Wirkung</th>
</tr>
</thead>
</table>
| Petro 1981      | 10 | Thc oral | Spastik  
| Clifford 1983   | 8  | Thc oral | Tremor +/- |
| Ungerleider 1986 | 13 | Thc oral | Spastik  
| Brenneisen 1996 | 2  | Thc supp | Spastik  
| Meinck 1989     | 1  | Thc joint| Ataxie  

Cannabinoide in der Medizin – Eine Option?

Cannabinoids in Medicine – An Option?

Dienstag 22. Januar 2013, 9:15 – 17:30 h
Tuesday 22. January 2012, 9:15 am – 5:30 pm

Laboratory of Phytopharmacology, Bioanalytics & Pharmacokinetics
Group Prof. R. Brenneisen
Cannabidiol (CBD) minimizes the psychoactive effects of THC and delays their onset...
Pharmacological properties of the 2 main cannabinoids

<table>
<thead>
<tr>
<th>Tetrahydrocannabinol (THC)</th>
<th>Cannabidiol (CBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiemetic</td>
<td>Analgesic</td>
</tr>
<tr>
<td>Muscle relaxant</td>
<td>Anticonvulsant</td>
</tr>
<tr>
<td>Appetitistimulation</td>
<td>Anxiolytic</td>
</tr>
<tr>
<td>Psychoactive</td>
<td>Neuroprotective</td>
</tr>
</tbody>
</table>
Asworth score (0-4) didn’t change more on verum than on placebo

verum = THC

placebo

Not significant
The comparison of the patients spasm protocol is significant.

\[ p = 0.013 \]
Editorial:
The therapeutic value of cannabinoids in MS: real or imaginary?

Killestein J. *Mult Scler* 2004
Chanvre d’hôpital

Le cannabis a-t-il un avenir en tant que médicament?
Intéressante étude en cours à Montana, sous l’égide de l’OFSP.

AVEC CE TRAITEMENT, IL SE SENT PLUS LÉGER!
Sirven JI and Berg AT
Marijuana as a treatment for Epilepsy and MS?

....or is it cruelly hoaxing on vulnerable patients who have lost hope?“
Prescribed for: cholera, tetanos, rheumatism, sleeplessness and pain...

"On the preparation of indian or gunja"  
William B. O‘Shaughnessy, 1839
Reynolds Sir J.R. Therapeutic Uses & Toxic Effects of Cannabis Indica. *(Lancet 1890)*

"One of the most valuable medicines we possess..."
More potent analgesic drugs such as aspirine
Injectable drugs (opioids)

Marijuana tax act 1937:
Hemp seen as danger for the cotton industry...and for the youth!

In 1961 the United Nation single convention on narcotic drugs declares that cannabis has no medical or scientific benefit!
1964, the cannabinoid $\triangle^9$Tetrahydrocannabinol (THC) was identified as the primary psychoactive substance of the hemp plant.
Recent clinical trials point to the prospect of cannabis as a medication in the treatment of multiple sclerosis

Pryce G & Baker D. *Trends Neuroscience* 2005

**Publications on THC & MS**

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>80--90</td>
<td>3</td>
</tr>
<tr>
<td>91--00</td>
<td>18</td>
</tr>
<tr>
<td>01--02</td>
<td>30</td>
</tr>
<tr>
<td>03--04</td>
<td>42</td>
</tr>
<tr>
<td>05--06</td>
<td>58</td>
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<tr>
<td>07--08</td>
<td>80</td>
</tr>
<tr>
<td>09--10</td>
<td>96</td>
</tr>
<tr>
<td>11--12</td>
<td>125</td>
</tr>
</tbody>
</table>
The clinical consequences of demyelination

Impaired electric conduction
The clinic depends on the localisation of the sites of demyelination.

- Pyramidal tracts: weakness/spasticity
- Posterior columns: pain
- Cerebellum: ataxia
- Autonomic system: bladder & sexual problems
- Optic nerve: loss of vision
- Brainstem: diplopia
- Cortex: cognitive & emotional changes

The localisation of "Plaque inflammation" impacts various parts of the nervous system, including muscle and brain regions.
In spite of the disease modifying drugs, MS is a chronic progressive disease (Roxborough RH et al. *Neurology* 2005).
They suffer from being immobile

“I am a burden for my family…”
They have neuropathic pain and suffer from muscle spasms

La columna rota  1944  F.Kahlo
Museo Dolores Olmado - Mexico
Incontinence makes their life miserable and prevents them from going out.
Prevalence of medicinal cannabis use among patients 15%.

Clark AJ et al. *Neurology* 2004
Gebrauch zu medizinischen Zwecken
(Ware MA, Int J Clin Pract 2005)

- Review 1998-2002 in UK
- 3663 Fragebogen (R'lauf: 2669; 73%)

- Hanf Gebrauch:
  - Chronischer Schmerz 25 %
  - Multiple Sclerosis 22 %
  - Depression 22 %
  - Arthritis 21 %
  - Neuropthischer Schmerz 19 %
Properties of an ideal drug for MS?

- Slow down progression
- No serious side effects
- Reasonable costs
- Favorable effect on symptoms
Favorable on what symptoms?

- Lower spasticity
- Reduce pain
- Calm the bladder
- Increase mobility
- Slow down progression?
- No serious side effects
- Low cost
- Favorable effect on symptoms
La fontaine de jouvence  1546
J .Cranach Nationalgalerie - Berlin
Cannabinoids slow down progression...

CB1 deficient mice tolerate inflammatory and exotoxic insult poorly and develop substantial neurodegeneration following immun attack. (Pryce G et al. *Brain* 2003)
Cannabinoids slow down progression...

- In vitro evidence that cannabinoids can reduce glutamate ( = neurotoxin) release. (Hampson AJ et al. Proc Natl Acad Sci USA 1998)
Endogenous cannabinoids participate in retrograde signalling

(Wilson RI, Nicoll RA. Science 2002; 296: 678-82)

By pre-synaptic inhibition endocannabinoids modulate the flow of information from one cell to the other!
## RCT with THC for other neurological diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Author</th>
<th>n</th>
<th>Thc form</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motorneuron disease</td>
<td>Weber M. <em>JNNP</em> 2010</td>
<td>27</td>
<td>Thc oral 2 X 5mg</td>
<td>No effect on cramps</td>
</tr>
<tr>
<td>Idiopathic Parkinson</td>
<td><em>Sieradzan KA Neurology</em> 2001</td>
<td>7</td>
<td>Thc oral</td>
<td>improvement of dyskinesia</td>
</tr>
<tr>
<td>Tourette’s Syndrome</td>
<td>Müller-Vahl KR <em>Pharmacopsy</em> 2002</td>
<td>12</td>
<td>Thc oral (single) 5;7.5,10mg</td>
<td>Less motor tics</td>
</tr>
<tr>
<td>Huntington Disease</td>
<td>Curtis A <em>Mov Disord</em> 2009</td>
<td>44</td>
<td>Nabilone Synthetic THC</td>
<td>Positive on chorea &amp; behaviour</td>
</tr>
</tbody>
</table>
THC reduces the relapse rate!  
CAMS Study- J.Zaijcek, *Lancet* 03

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Cannabis extract (n=12)</th>
<th>Δ9-THC (n=18)</th>
<th>Placebo (n=20)</th>
<th>Total (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis relapse or possible relapse</td>
<td>1</td>
<td>1</td>
<td>7*</td>
<td>9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>2 (1 death)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Blocked/insertion of suprapubic catheter</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td></td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Grand mal seizures</td>
<td>1</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>6†</td>
<td>11‡</td>
<td>2§</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>18</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>
CUPID Study 2008-2011 in the UK with 500 PwMS (2Mio £)

Cannabinoioid use in progressive inflammatory brain disease

Cannabis?
• Slow down progression ✓

• No serious side effects?

• Low cost

• Favorable effect on symptoms
What are the comments concerning side effects?

- Zaijcek et al. Lancet 2003
  “Number of serious events are similar across the treatments, with slightly more events in the placebo group”

- Wade DT et al. Mult Scler 2004
  “Most people achieved benefit without troublesome side effects”
The available clinical trial data suggest that the adverse side effects associated with using CBMEs are generally mild, such as dry mouth, dizziness, somnolence, nausea and intoxication.

There may be reason to be concerned about the use of therapeutic cannabinoids by adolescents, people predisposed to psychosis and pregnant women.
The psychiatric side of Cannabis effects are well known...

...And he who has an empty brain and eats hemp, it will cause him some pain in the head.

But it does not harm the healthy head and the full brain.

Hildegard von Bingen 1098-1179
(In Physica)
Side effects were also found in patients taking placebo...

Vaney et al. Mult Scler 2004
Effect of centrally active drugs on the web building activity of a new species of Indian spider


LSD  Cannabis  Meskaline  coffee
• Slow down progression ✓
• No serious side effects ✓
• Low cost ?
• Favorable effect on symptoms
• Cheaper than DMS...

A,B,C ~ 20 000.- /y
The price of pain relief /day

<table>
<thead>
<tr>
<th>Product</th>
<th>Price (Euro)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mg Marinol®</td>
<td>27</td>
</tr>
<tr>
<td>10 mg Dronabinol</td>
<td>12</td>
</tr>
<tr>
<td>10mg Sativex®</td>
<td>10</td>
</tr>
<tr>
<td>12mg Tizanidine</td>
<td>1.2</td>
</tr>
<tr>
<td>10mg Bedrocan</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Source: F. Grotenhermen, *Hanf Journal* 06/06
• Slow down progression ✓
• Few side effects ✓
• Low cost ✓

• Favorable effect on symptoms?
Favorable effect on symptoms:

• Lower spasticity ?
• Reduce pain
• Calm the bladder
• Increase mobility
What can be done against pain and muscle spasms?
Drugs commonly used to lessen spasticity and spasms

<table>
<thead>
<tr>
<th>Substance</th>
<th>System</th>
<th>Dosage (max. /j)</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>dazepam</td>
<td>GABA</td>
<td>3 x 2mg (40 mg)</td>
<td>sedation +++ cog. problems</td>
</tr>
<tr>
<td>baclofen</td>
<td>GABA</td>
<td>3 x 5mg (120 mg)</td>
<td>sedation +/- weakness</td>
</tr>
<tr>
<td>tizanidine</td>
<td>Nor-adrenergic</td>
<td>2 x 4mg (36 mg)</td>
<td>sedation +/- dry mouth</td>
</tr>
<tr>
<td>dantrolen</td>
<td>Calcium release</td>
<td>3 x 25mg (400mg)</td>
<td>no sedation liver toxicity</td>
</tr>
</tbody>
</table>

Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis (Cochrane Review 2003)
Cannabinoids control spasticity and tremor in a multiple sclerosis model

Cannabinoids control spasticity and tremor in a multiple sclerosis model
Reduced spasticity ...subjectively

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Measure</th>
<th>Spasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ungerleider</td>
<td>13</td>
<td>Subjective rating</td>
<td>improved</td>
</tr>
<tr>
<td>1987</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaney</td>
<td>57</td>
<td>Spasm frequency</td>
<td>improved P=0.013</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zaijcek</td>
<td>667</td>
<td>Category rating scale</td>
<td>Improved P =0.01</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wade</td>
<td>160</td>
<td>VAS</td>
<td>Improved P=0.001</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reduction of spasm frequency
Vaney et al. *Mult Scler* 2004

![Graph showing reduction of spasm frequency over days with different phases: placebo, dose finding, cannabis, washout.](image)
• Lower spasticity ✓
• reduce pain ?
• Calm the bladder
• Increase mobility
Converging evidence supports a role of endocannabinoids in the tonic inhibition of pain responses and the setting of nociceptive thresholds.

Dynamic regulation of the endocannabinoid system: implications for analgesia
Cannabinoids and Pain Pathways

Adapted from Di Marzo 2001

Possible sites of action

Endocannabinoids

Dorsal root ganglion

Dorsal horn of spinal cord

Peripheral terminals of primary afferent neurons

A², A § & C-fibres

Thalamus

Periaqueductal grey

Rostral ventromedial medulla
That takes away neuropathic pain!
Rog DJ et al. Neurology 2005

Visual analog scale (VAS)

2.7 (Cannabis)

1.4 (Placebo)
Cannabis Spray licensed Sativex® in Canada in 2005
Reduced pain ...subjectively

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>time</th>
<th>measure</th>
<th>pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaijcek 2003</td>
<td>667</td>
<td>15 w</td>
<td>Category rating scale</td>
<td>$P = 0.002$</td>
</tr>
<tr>
<td>Svendson 2004</td>
<td>24</td>
<td>3 w</td>
<td>Numerical rating scale (0-10)</td>
<td>$P = 0.02$</td>
</tr>
<tr>
<td>Brady 2004</td>
<td>14</td>
<td>35 w</td>
<td>VAS</td>
<td>$P &lt; 0.05$</td>
</tr>
<tr>
<td>Wade 2004</td>
<td>160</td>
<td>6 w</td>
<td>VAS</td>
<td>0.243</td>
</tr>
</tbody>
</table>
• Lower spasticity ✓
• Reduce pain ✓
• Calm the bladder ?
• Increase mobility
What can be done against incontinence?
Background

- CB1 receptors exist in the mouse bladder (Pertwee and Fernando, 1996) and in regions of the central nervous system associated with bladder control (Glass, 1997).

- Cannabinoids can reduce bladder hyperreflexia induced by inflammation in rats (Jaggar and Rice, 1998; Jagger et al., 1998)
Intraperitoneal administration of THC

ANTAGONIST/ SR 141716A IP
Brady CM et al. *Mult Scler* 2004

- 15 patients
- THC : CBD Spray
- Urinary urgency ↓
- Incontinence episodes ↓
- Nocturia ↓
• Lower spasticity ✓
• reduce pain ✓
• Calm the bladder ✓
• Increase mobility ?
t speeds walking time over 10 m

CAMS Study - J. Zaijcek, Lancet 03

- **Cannabis**
- **Placebo**

<table>
<thead>
<tr>
<th></th>
<th>Initial Value</th>
<th>Treatment</th>
<th>End Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sekunden</td>
<td>30</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Changes in the Rivermead Mobility Index


**Arm A**
- **Cannabis**
- **Placebo**
- **Washout**

**Arm B**
- **Placebo**
- **Cannabis**
- **Washout**
What would happen to our lady if she could take some Cannabis?
By taking cannabinoids she will spend a wonderful afternoon moving around without any pain or episodes of incontinence!
A wonder drug for people with Multiple Sclerosis!
Sorry, I have led you astray...
In the follow up study there was no difference in the relapse rate between THC and Placebo

Zajicek J.P. et al. *JNNP* 2005
CUPID Study 2008-2011 in the UK with 500 PwMS (2Mio £)

Cannabinoid use in progressive inflammatory brain disease

Cannabis?
CUPID Study 2008-2011 in the UK with 500 PwMS (2Mio £)

Disease progression could not be stopped 😞
Spasticity as the primary outcome measure was not significantly reduced.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Ashworth</th>
<th>Spasm/well being</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ungerleider 1987</td>
<td>13</td>
<td>ns</td>
<td>improved</td>
</tr>
<tr>
<td>Killestein 2002</td>
<td>16</td>
<td>ns</td>
<td>worse with THC</td>
</tr>
<tr>
<td>Zaijcek 2003</td>
<td>667</td>
<td>ns</td>
<td>improved</td>
</tr>
<tr>
<td>Vaney 2004</td>
<td>57</td>
<td>ns</td>
<td>Only trends in favour of THC</td>
</tr>
</tbody>
</table>
Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial

Jody Corey-Bloom MD PhD, Tanya Wolfson MA, Anthony Gamst PhD, Shelia Jin MD MPH, Thomas D. Marcotte PhD, Heather Bentley BA, Ben Gouaux BA

- *CMAJ* July 2012
- 30 PwMS
- 3 times daily
- 1 cigarette
- Placebo vs. cannabis
- Ashworth spasticity score (0-5)
Side effects were more pronounced in the cannabis group!

Drop out rate = 12% (7/57)
Reduced the dose = 26% (13/50)
There seems to be a tendency that the more disabled persons are more motivated to continue the treatment.

<table>
<thead>
<tr>
<th></th>
<th>continue</th>
<th>stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>66</td>
<td>44</td>
</tr>
<tr>
<td>age</td>
<td>54.1</td>
<td>55.4</td>
</tr>
<tr>
<td>women</td>
<td>54%</td>
<td>57%</td>
</tr>
<tr>
<td>EDSS</td>
<td>$6.8 \pm 1.6$</td>
<td>$6.1 \pm 1.9$</td>
</tr>
</tbody>
</table>
Reasons for stopping Cannabis intake (44 patients)

- Dizziness: 10
- Did not help: 9
- Tired: 7
- Difficult supply: 6
- Not necessary anymore: 5
- Bad taste of the milk: 4
- Low blood pressure: 2
- Doctor against: 1
« Gut schweizerischer Kompromiss..”
Throwing the baby with the bath water
... In the meantime, when other treatment inadequately controls spasticity, oral cannabinoids should be considered... (L.Metz, *Lancet* 2003)
While 2-3 years ago there was little consensus in the literature, now the majority of studies are beginning to suggest that cannabinoids are useful in the treatment of MS in at least a subset of individuals...

Smith PF *Expert Rev Neurother* 2007
Double blind placebo controlled study with 279 patients with MS (PwMS)

- 2 week dosefinding
- 10 weeks treatment with THC / CBD caps.
- CRS (Category Rating Scale) 0-10
- Muscle spasm, sleep, pain and mobility
Sativex third pivotal clinical trial: Patients’ disposition

- Screened = 670
- Entered phase A = 573
  - Responders (≥20%) = 271 (47%)
  - Non-responders = 53%
Sativex third pivotal clinical trial results:
Patients improving ≥30% from baseline at the 4 + 12th week

Novotna et al, European Journal of Neurology 2011
Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis.

Wade DT, Collin C, Stott C, Duncombe P.
Oxford Centre for Enablement, Windmill Road, Oxford, OX3 7LD, UK. derick.wade@noc.nhs.uk

Abstract

OBJECTIVE: To determine the efficacy of Sativex (USAN: nabiximols) in the alleviation of spasticity in people with multiple sclerosis.

METHODS: The results from three randomized, placebo-controlled, double-blind parallel group studies were combined for analysis.

PATIENTS: 666 patients with multiple sclerosis and spasticity.

MEASURES: A 0-100 mm Visual Analogue Scale (VAS, transformed to a 0-10 scale) or a 0-10 Numerical Rating Scale (0-10 NRS) was used to measure spasticity. Patients achieving a > or =30% improvement from baseline in their spasticity score were defined as 'responders'. Global impression of change (GIC) at the end of treatment was also recorded.

RESULTS: The patient populations were similar. The adjusted mean change of the numerical rating scale from baseline in the treated group was -1.30 compared with -0.97 for placebo. Using a linear model, the treatment difference was -0.32 (95% CI -0.61, -0.04, p = 0.026). A statistically significant greater proportion of treated patients were responders (odds ratio (OR) = 1.62, 95% CI 1.15, 2.28; p = 0.0073) and treated patients also reported greater improvement: odds ratio 1.67 (95% CI 1.05, 2.65; p = 0.030). High numbers of subjects experienced at least one adverse event, but most were mild to moderate in severity and all drug-related serious adverse events resolved.

CONCLUSION: The meta-analysis demonstrates that nabiximols is well tolerated and reduces spasticity.
<table>
<thead>
<tr>
<th>Country</th>
<th>Indication</th>
<th>Approval status*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Cancer, pain, spasticity</td>
<td>x</td>
</tr>
<tr>
<td>Austria</td>
<td>spasticity</td>
<td>x</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>spasticity</td>
<td>x</td>
</tr>
<tr>
<td>Denmark</td>
<td>spasticity</td>
<td>x</td>
</tr>
<tr>
<td>Germany</td>
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<td>x</td>
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<tr>
<td>New Zealand</td>
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<td>x</td>
</tr>
<tr>
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Le cannabis bientôt vendu en pharmacie?
Checkliste: Ausnahmebewilligung Marinol® (& Dronabinol)

- Arzt trägt volle Verantwortung für alle Folgen
- Name, Geburtsdatum und Adresse des Patienten
- Schriftliche Einverständniserklärung des Patienten
- Liste der bisher eingesetzten Medikamente
- Beabsichtigte Dosierung & Behandlungsdauer
- Zwischenberichte & Schlussbericht verfassen
- Art der Überwachung und Betreuung des Patienten
- Logistik für die Abgabe des Medikaments (Arzt, öffentliche Apotheke oder durch ein Spital?)
- Art der Finanzierung der Therapie

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The therapeutic value of cannabinoids in MS: real or imaginary?
Thanks for your attention