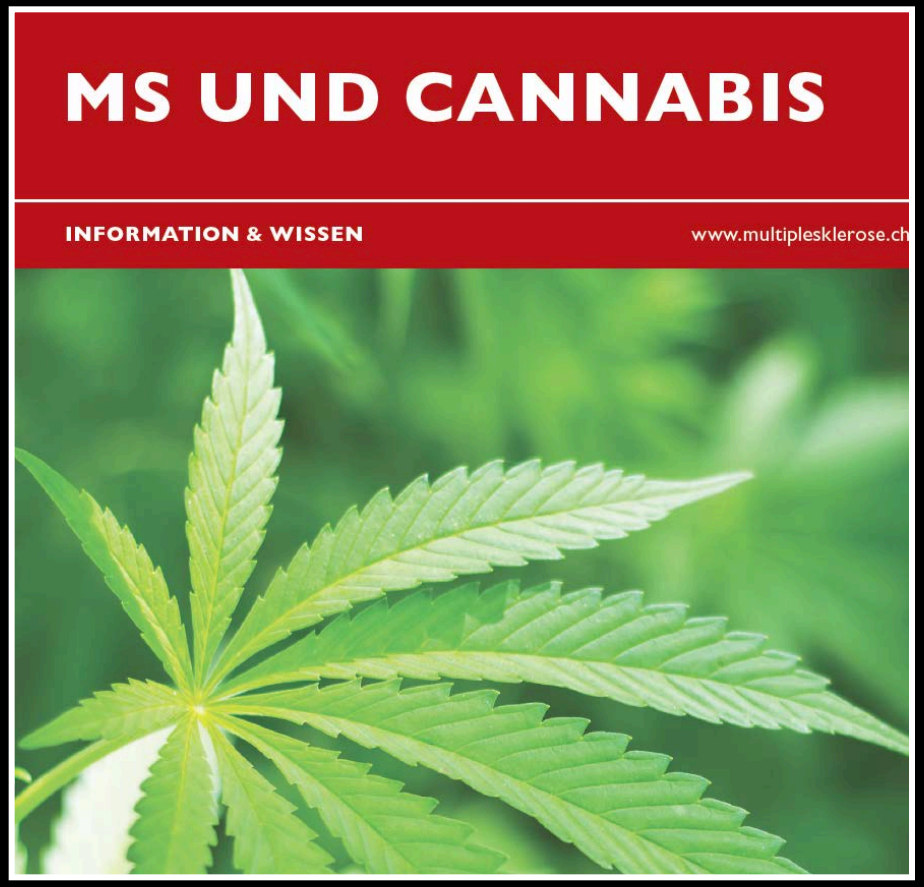
Seminar der SMSG
Brig 13.August 2016



Sir Russel Reynolds;

Therapeutic Uses &
Toxic Effects
of Cannabis Indica.

Lancet 1890

"...wenn sorgfältig verabreicht, das kostbarste Heilmittel, das wir haben! "

Sirven JI and Berg AT

Marijuana as a treatment for Epilepsy and MS ?

***Neurology* 2004;62:1924-25.**

„...an der Nase herumführen von hoffnungslosen Patienten!“

Berner Klinik Montana

über 250 MS-Betrofffene werden hier jährlich betreut

1960

KARTE DER SCHWEIZ

der Kantons- und der Bezirksgrenzen.

Bing et al.
1930

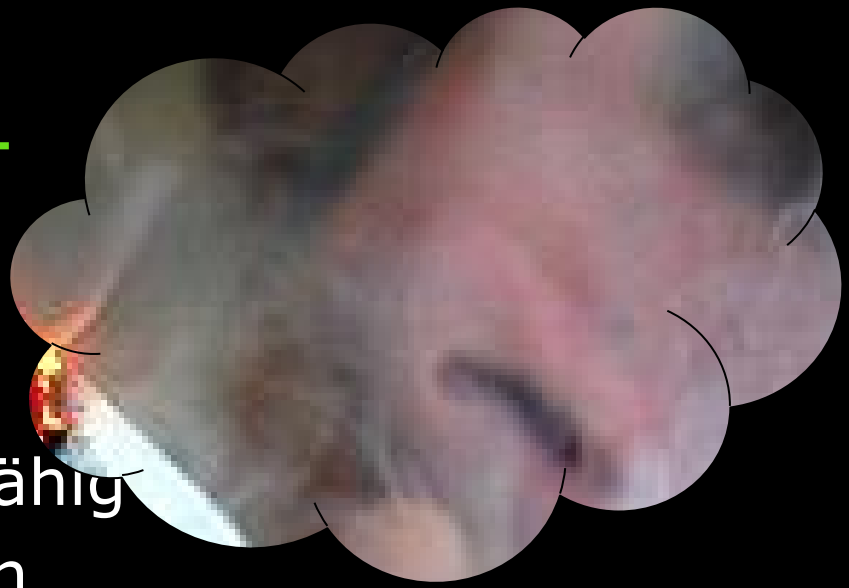
Fälle von multip
ler Sklerose pro
10 000 Einwohne

bis 1,0
" 2,0
" 3,0
" 4,0
" 5,0
über 5,0

Karte mit Angabe der Morbidität nach Bezirken.

Robert Bing
1878-1956

1991



28 j. Patient mit MS

knapp stehfähig, kaum gehfähig

über schmerzhafte Spasmen

Lioresal, Sirdalud +Valium ... wirken

ungenügend und machen müde

Was hilft Ihnen ?

"Ich drehe mir einen Joint !"

1998

Gesuch um eine Sonderbewilligung für die Abgabe von Marinol® für einen MS Betroffenen....

Antwort des BAG Dr. Dietschi:

THC bei MS - Studien vor 1998

Studie	n	Form	Wirkung
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 ↓

Consroe et al. 1997

- Umfrage bei 255 MS Betroffenen
- „Returnrate“ 57%
- Spasmen beim Einschlafen:
  - 75% “deutlich besser”
  - 21% “wenig besseer”
- Weniger Muskelschmerzen > 90%
- Balance verschlechtert 13,5%

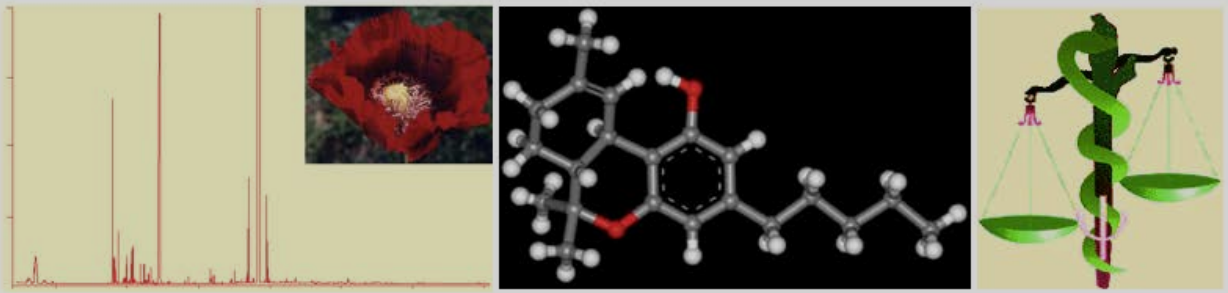
THC bei MS - Studien vor 1998

Studie	n	Form	Wirkung
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 ↓

UNIVERSITÄT
BERN

University of Bern

Department of Clinical Research



Laboratory of Phytopharmacology, Bioanalytics & Pharmacokinetics

Group Prof. R. Brenneisen

Infotagung zu Cannabis am 12.11 in Bern

Themenblöcke

(I) Grundlagenforschung, Pharmazeutische Perspektiven

- Endocannabinoidsystem als therapeutisches Target
- R&D innerhalb holländischer Medizinalcannabis-Programme
- Sativex, Epidiolex
- Indikationsspezifische Cannabis-Chemovarietäten

(II) Medizinische Anwendungsbereiche

- Schmerz
- Krebs – Pharmakologische Perspektiven
- Krebs – Erfahrungen aus der ärztlichen Praxis
- Palliativmedizin
- Neurologische Krankheiten
- Psychosen
- Cannabinoide in der österreichischen Hausarztpraxis

(III) Verschreibungsmodelle, Internationale Erfahrungen

- Das USA-Modell: Unkontrollierte Experimente im Wilden Westen
- Medizinal-Cannabis in Israel: Fortschritte und Tücken

(IV) Rechtliche und regulatorische Aspekte, Rückblick - Ausblick

- Das BetmG als Schranke der medizinischen Anwendung von Cannabis
- Swissmedic-Zulassung – Optionen und Limiten
- Meine Reise mit Cannabis: Vergangenheit, Gegenwart und Zukunft

(V) Diskussionsrunde – Von der Pflanze zum Patienten

Referierende

Jürg Gertsch (CH), Arno Hazekamp (NL), Stephen Wright (UK), Ethan Russo (USA), Joachim Nadstawek (D), Guillermo Velasco (E), Eva Milz (D), Daniel Büche (CH), Markus Weber (CH), Markus Leweke (D), Kurt Blaas (A), Ilya Reznik (IL), Peter Albrecht (CH), Uwe Koetter (CH), Mahmoud ElSohly (USA).

Tagungssprachen

Deutsch und Englisch; Simultanübersetzung in Deutsch, Englisch und Französisch.

Teilnahmegebühr

CHF 100.00, Studierende 50.00.

Schweizer Arbeitsgruppe für Cannabinoide in der Medizin
SACM
Schweizer Akademie der Pharmazeutischen Wissenschften
SAPhW

Tagung 2016

Cannabinoide in der Medizin - Neue Trends

Samstag 12. November 2016
Inselspital-Universitätsspital Bern

Programm

Registrierung
www.saphw.ch

Multiple Sclerosis 2004; 10: 417–424
www.multiplesclerosisjournal.com

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

C Vaney[,1], M Heinzel-Gutenbrunner[2], P Jobin[1], F Tschopp[1], B Gattlen[1], U Hagen[1], M Schnelle[2] and M Reif[2]*
[1]Neurologische Rehabilitations- & MS-Abteilung, Berner Klinik, Montana, Switzerland; [2]Institute for Oncological and Immunological Research, Berlin, Germany

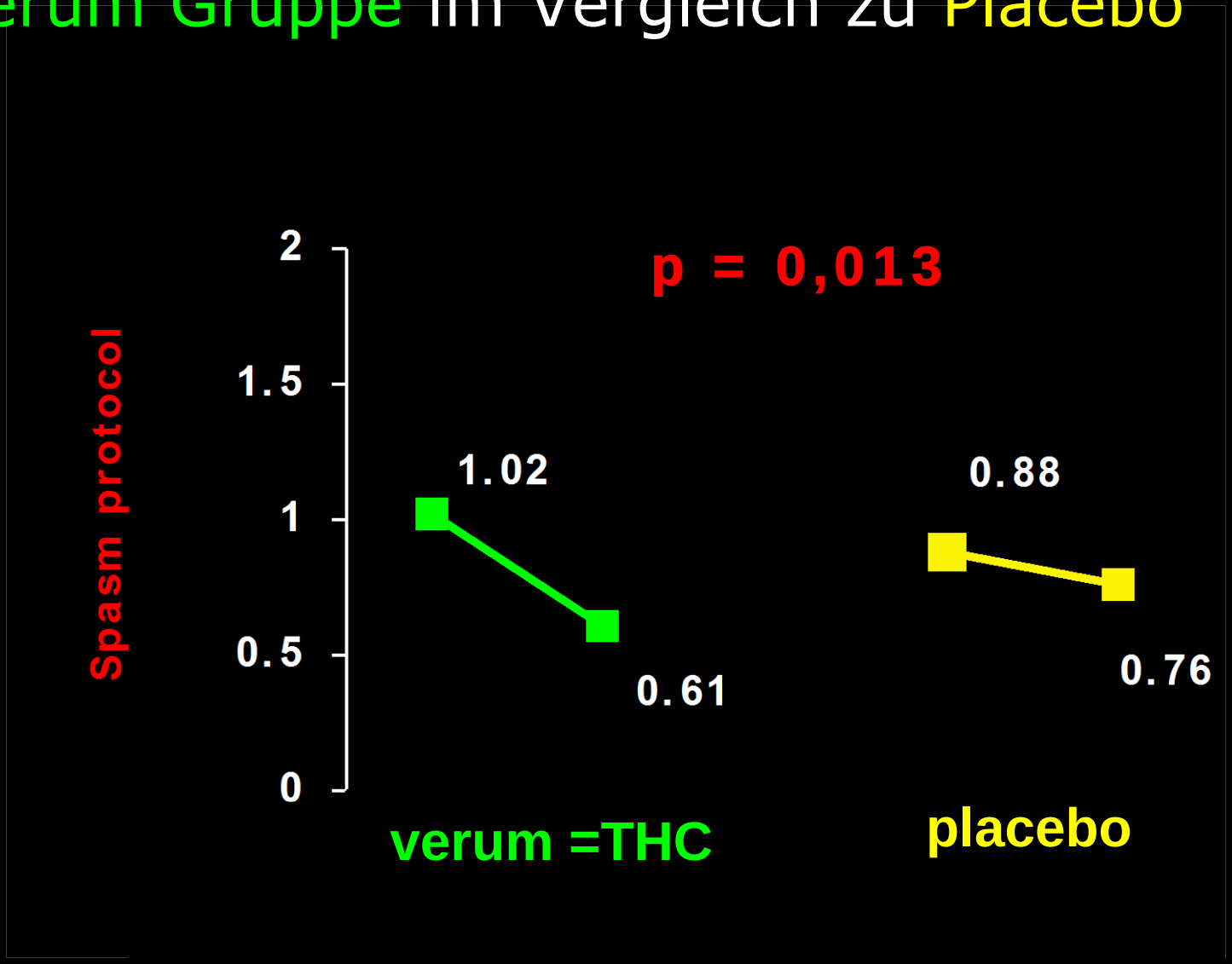
Hanfkapseln

= Cannador ®

Pharmakologische Eigenschaften der 2 wichtigsten Cannabinoide

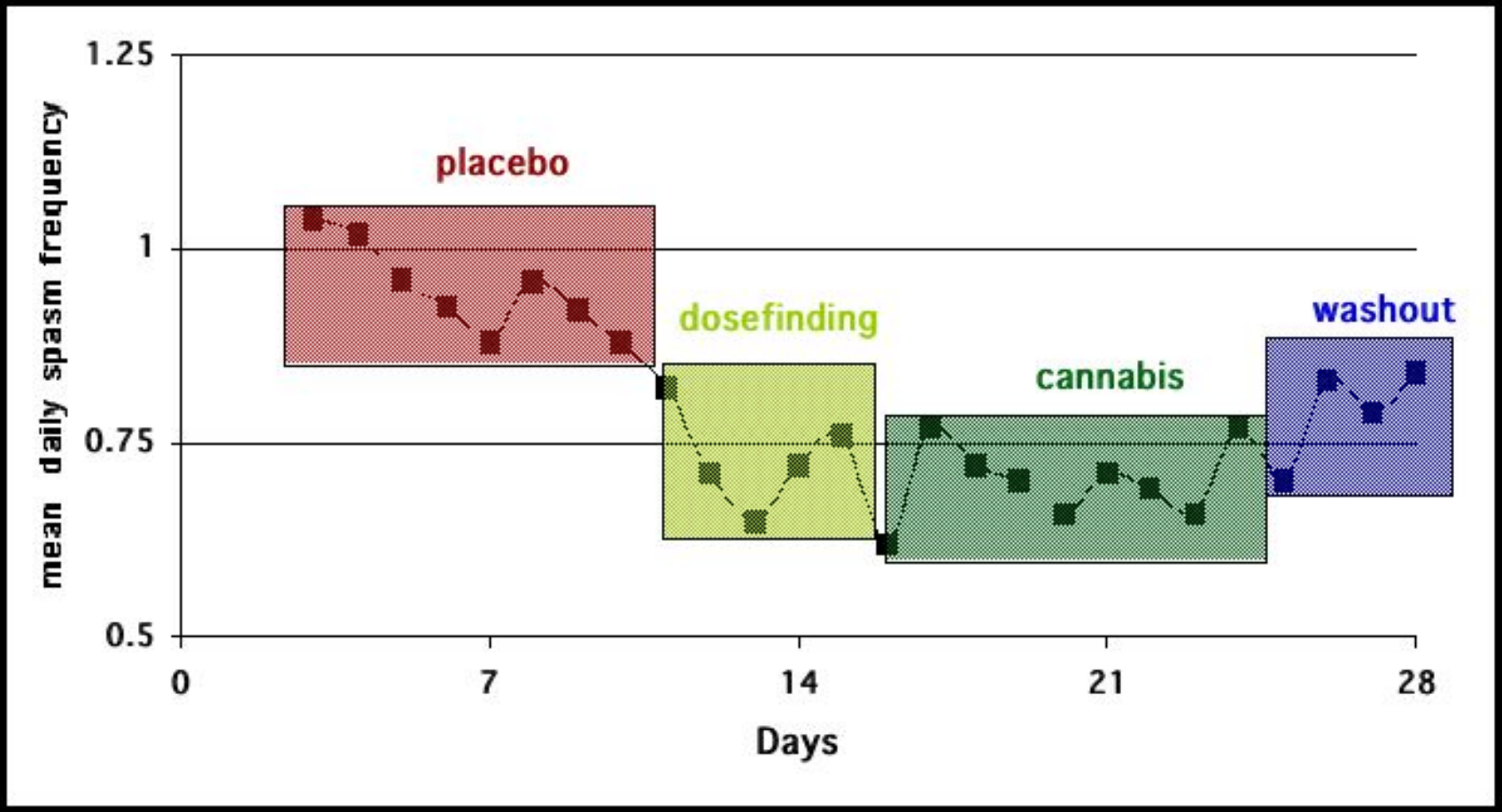
Tetrahydrocannabinol (THC)	Cannabidiol (CBD)
Antiemetisch	Analgetisch
Muskelentspannend	Antiepileptisch
Appetitstimulation	Anxiolytisch
Psychoactiv	Neuroprotectiv

Significant weniger Muskelspasmen in der Verum Gruppe im Vergleich zu Placebo

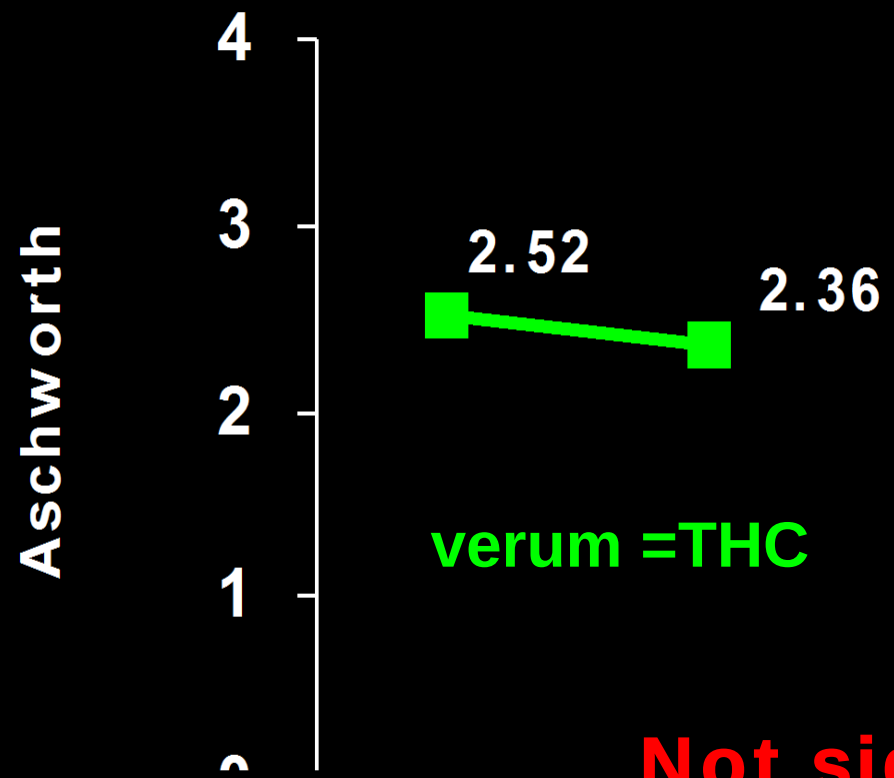


Reduction of spasm frequency

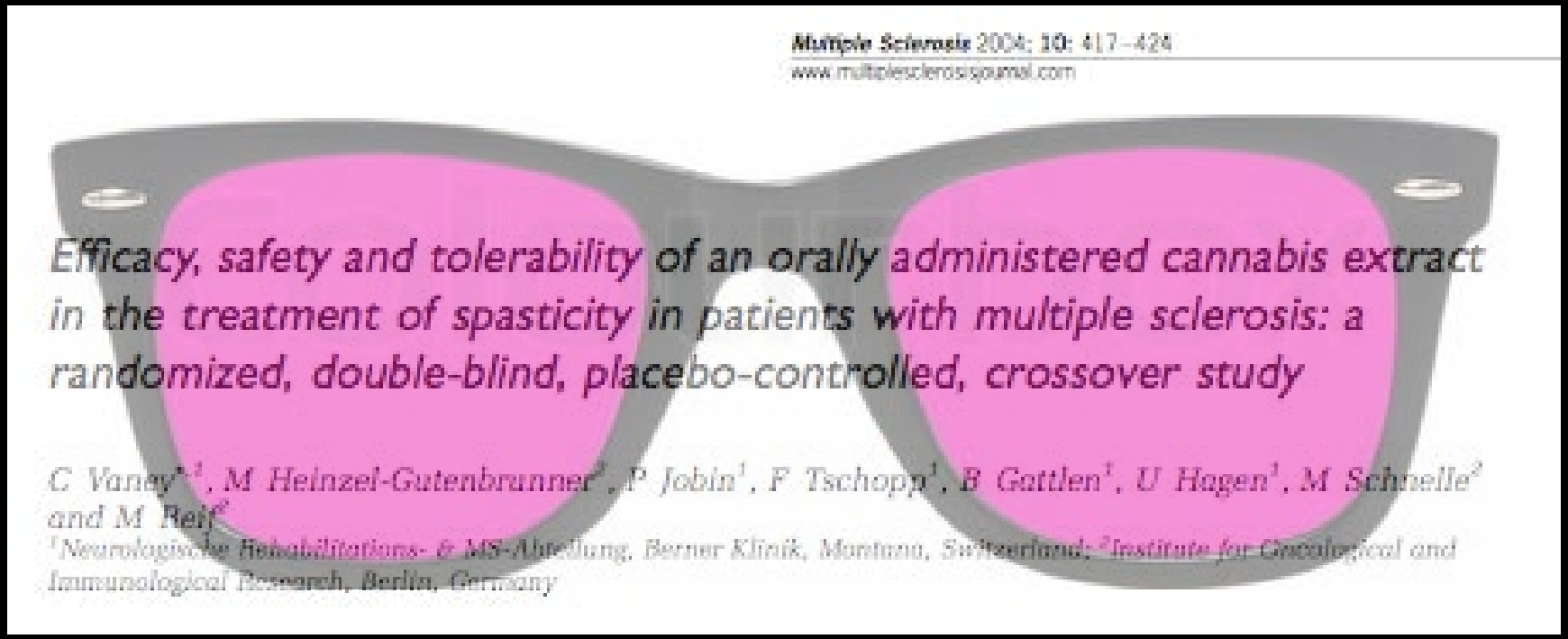
Vaney et al. *Mult Scler* 2004



..Keine Aenderung der Spastizität gemessen an der Asworth score (0-4)



Not significant



Editorial:

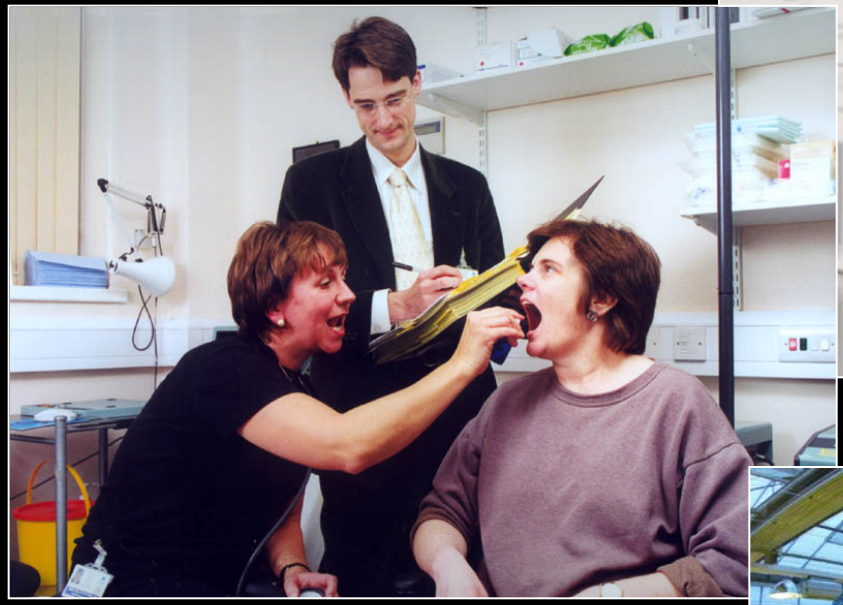
The therapeutic value of cannabinoids in MS: real or imaginary ?

Killestein J. *Mult Scler 2004*

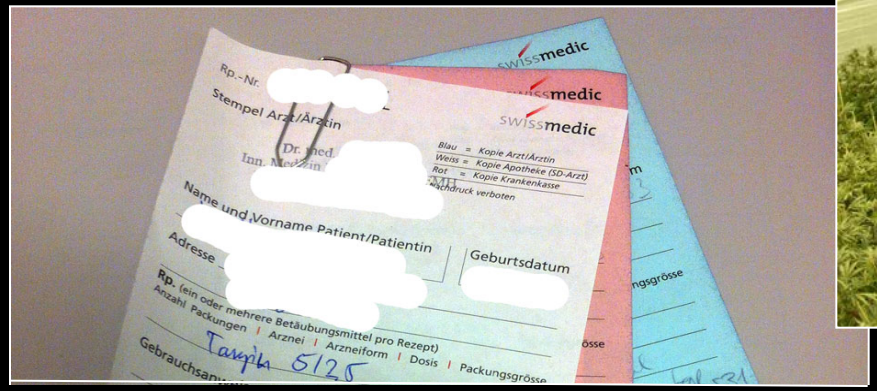
Chanvre d'hôpital

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

Sativex® im Handel in der CH seit 2014



Mit einem BetmG Rezept



Bundesgesetz
über die Betäubungsmittel und die psychotropen Stoffe
(Betäubungsmittelgesetz, BetmG)[1]

812.121

vom 3. Oktober 1951 (Stand am 1. Oktober 2013)

Art. 8 Verbotene Betäubungsmittel[34]

[1] Die folgenden Betäubungsmittel dürfen weder angebaut, eingeführt, hergestellt noch in Verkehr gebracht werden:[35]

a. Rauchopium und die bei seiner Herstellung oder seinem Gebrauch entstehenden Rückstände;

b. Diacetylmorphin und seine Salze;

c. Halluzinogene wie Lysergid (LSD 25);

d.[36] Betäubungsmittel des Wirkungstyps Cannabis.[37]

[5] Das Bundesamt für Gesundheit kann für die Betäubungsmittel nach den Absätzen 1 und 3 Ausnahmebewilligungen für den Anbau, die Einfuhr, die Herstellung und das Inverkehrbringen erteilen, wenn kein internationales Abkommen entgegensteht und diese Betäubungsmittel der wissenschaftlichen Forschung, der Arzneimittelentwicklung oder der beschränkten medizinischen Anwendung dienen.[40]

Cannabis verschreiben in 2016...

	MS	andere Indikationen	E /2.5mg THC	Prix/j (≈10mg)
Sativex® CBD /THC 1:1	**BetmG Rp**	**Bw. BAG + BetmG Rp**	1 Spray= 2.5mg	**10.-**

Legende:

Bw.BAG : Ausnahme Bewilligung durch das BAG

BetmG Rp: Betäubunsmittelrezept

Checkliste: Ausnahmebewilligung für Dronabinol

- Arzt trägt volle Verantwortung für alle Folgen
- Name, Geburtsdatum und Adresse des Patienten
- Schriftliche Einverständniserklärung des Patienten
- Angaben über die bisher für diese spezifische Krankheit 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

Bundesamt für Gesundheit Nationale Präventionsprogramme
Schwarztorstrasse 96 CH-3003 Bern Telefon:+41 (0)31 323 87 93

Prevalence of medicinal cannabis use among patients with MS

Clark AJ et al. *Neurology* 2004;62:2098-2100

15 %

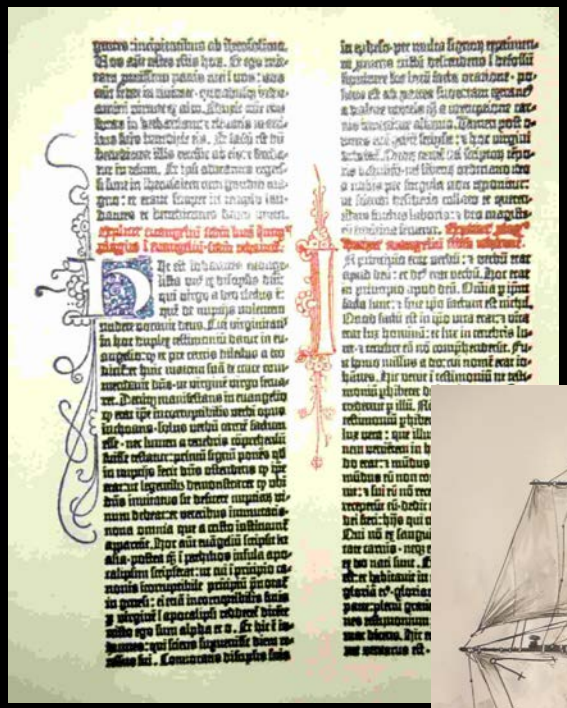
UK survey

return rate 61%=2969;illegal consumation n=969

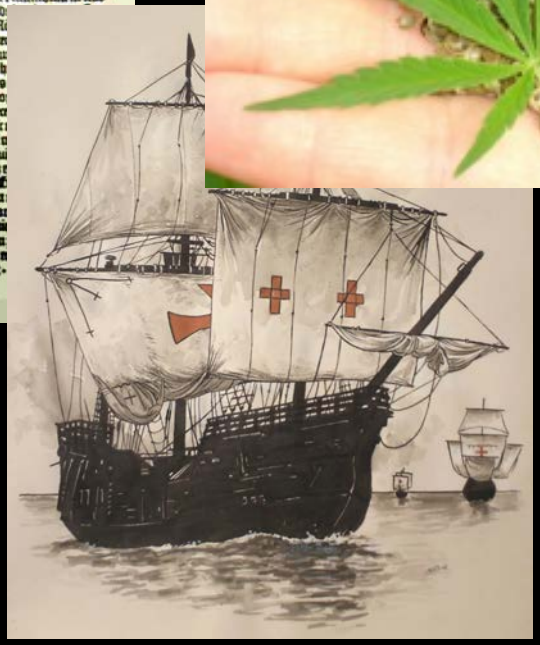
Used for:	%	n
Chronic pain	25	242
Multiple sclerosis	**22**	**213**
Depression	22	213
neuropathic pain	19	184
Arthritis	16	155

Ware MA et al. The medicinal use of cannabis in the UK: results of a nationwide survey.
Int J Clin Pract 2005;3:291-295.

Seit Jahrtausenden vom Menschen genutzte Pflanze aus dem Himalaya stammend...



Fasern



Samen

Ethymologie des Wortes „Hanf“ ?

kunubu (assyrien) = wohlriechende Pfl.

kannab (arabisch)

cannabis (latein)

Hanf (deutsch)

Hemp (englisch)

„...dann werfen sie mitgebrachte Hanfsamen zwischen die Steine. Sofort beginnt es zu rauchen und zu dampfen, mehr noch als in einem griechischen Schwitzbad.
Begeistert heulten die Skythen auf !“

(Herodot ,*Historien* IV, 73-75)

Hanfinhalationsgarnitur aus dem skythischen Grabhügel in Pazyryk.
(*Altai Gebirge-Mongolei*)

Medizinische Hanf-Verwendung in allen Kulturen

- **2000 v.Ch. China**
  Rheumatismus, Durchfall
- **1000 v. Ch. Indien (Ayurveda)**
  langes Leben..*heilige Pflanze*
- **150 n. Ch. Galen**

Gegen Blähungen, als Aphrodiakum

- 1000 n. Ch Avicenna
  Hinweis auf Cannabisabusus

Hanf in den Kräuterbücher des Mittelalters

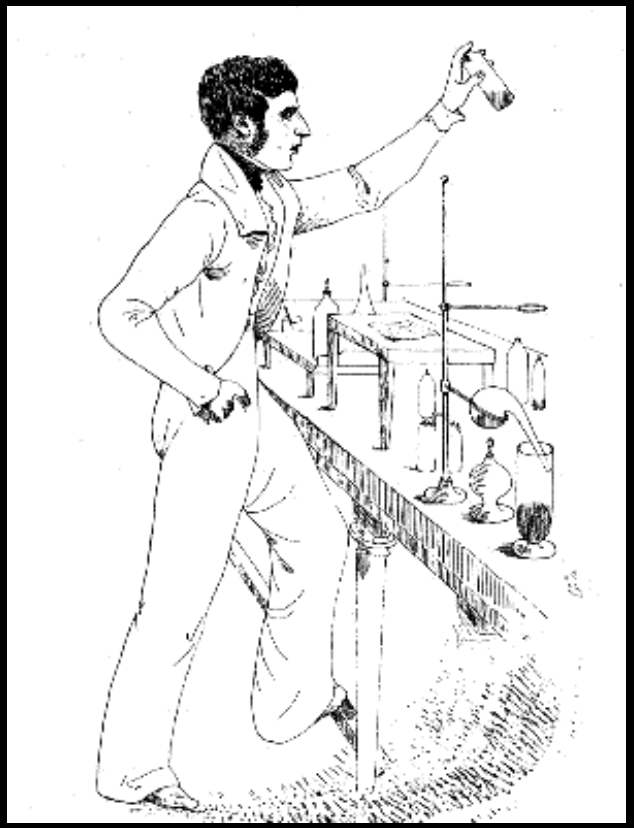
„...Sein Same bringt Gesundheit und ist dem gesunden Menschen *heilsame Kost*..“

„..Im Magen die *schlechten Säfte mindert* und die guten stärkt...“

„..Wer ein *leeres Hirn* dem verursacht der Hanf ein Schmerz im Kopf...“

Hildegard von Bingen
1098-1179
(In *Physica)*

2.Hälfte 19Jh. : „Blütezeit"



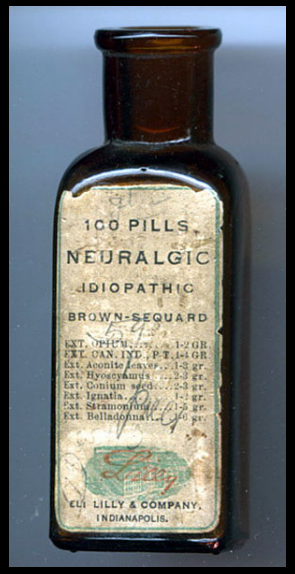
Alkoholische Tinkturen:

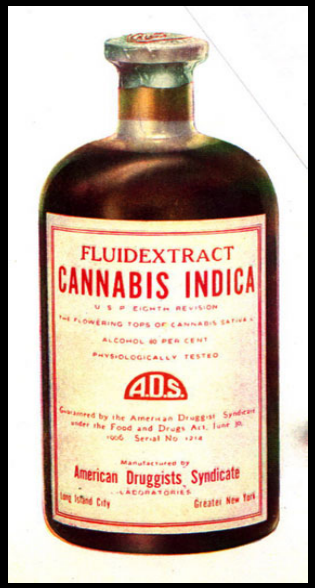
- Spasmolytikum

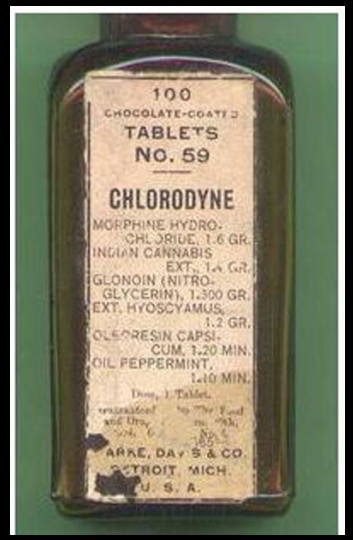
  (*Tetanos, Tollwut, Krämpfe bei Kinder..)*
- Hypnotikum
- Analgetikum (Dysmenorrhoe, Neuralgie,Migräne)

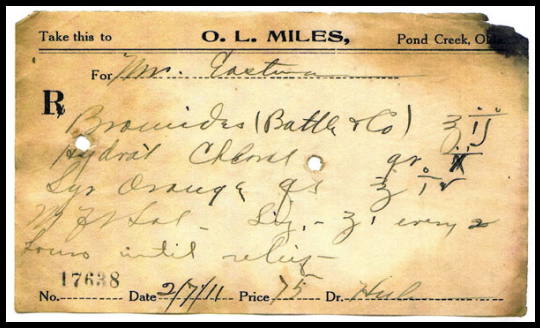
„On the preparation of indian or gunja"
William B. O'Shaughnessy, 1839

Cannabis haltige Präparate um 1900

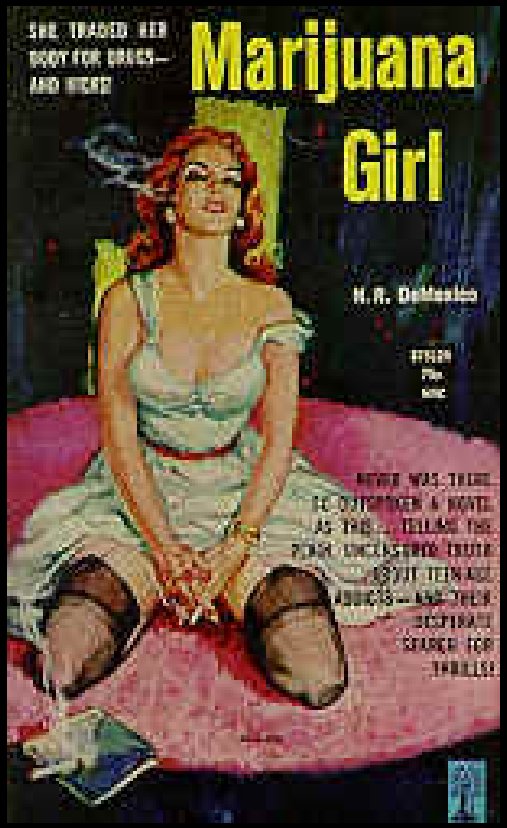






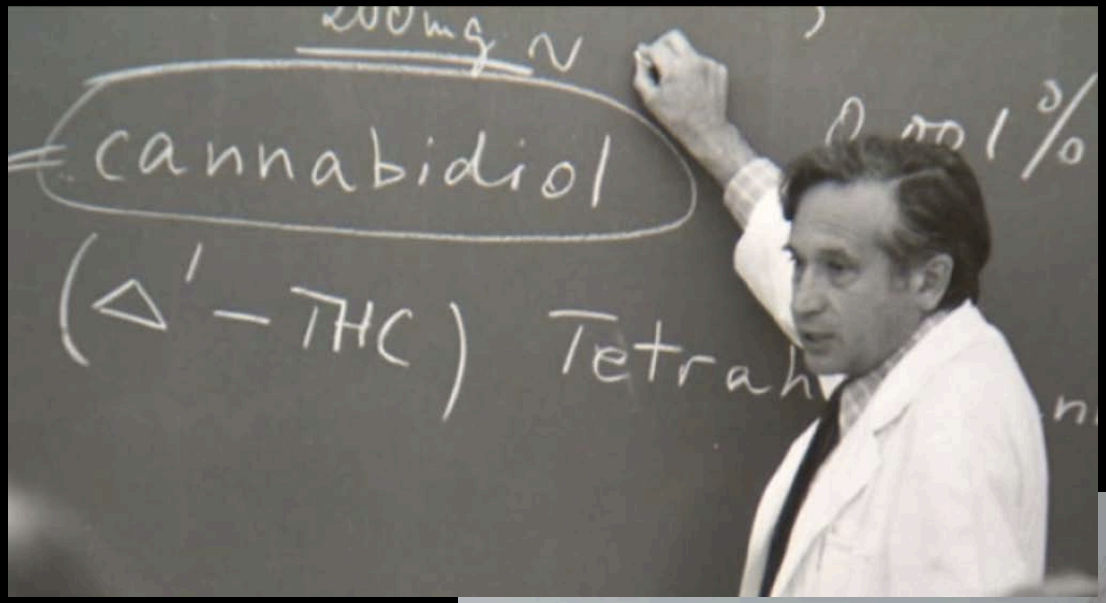


20 Jh. : „Diskreditierung“



- Andere Substanzen:
  - *Asprin, Chloralhydrat, Barbiturate,Opiate...*
  - iv verabreichbar
  - Zuverlässigere Pharmakokinetik

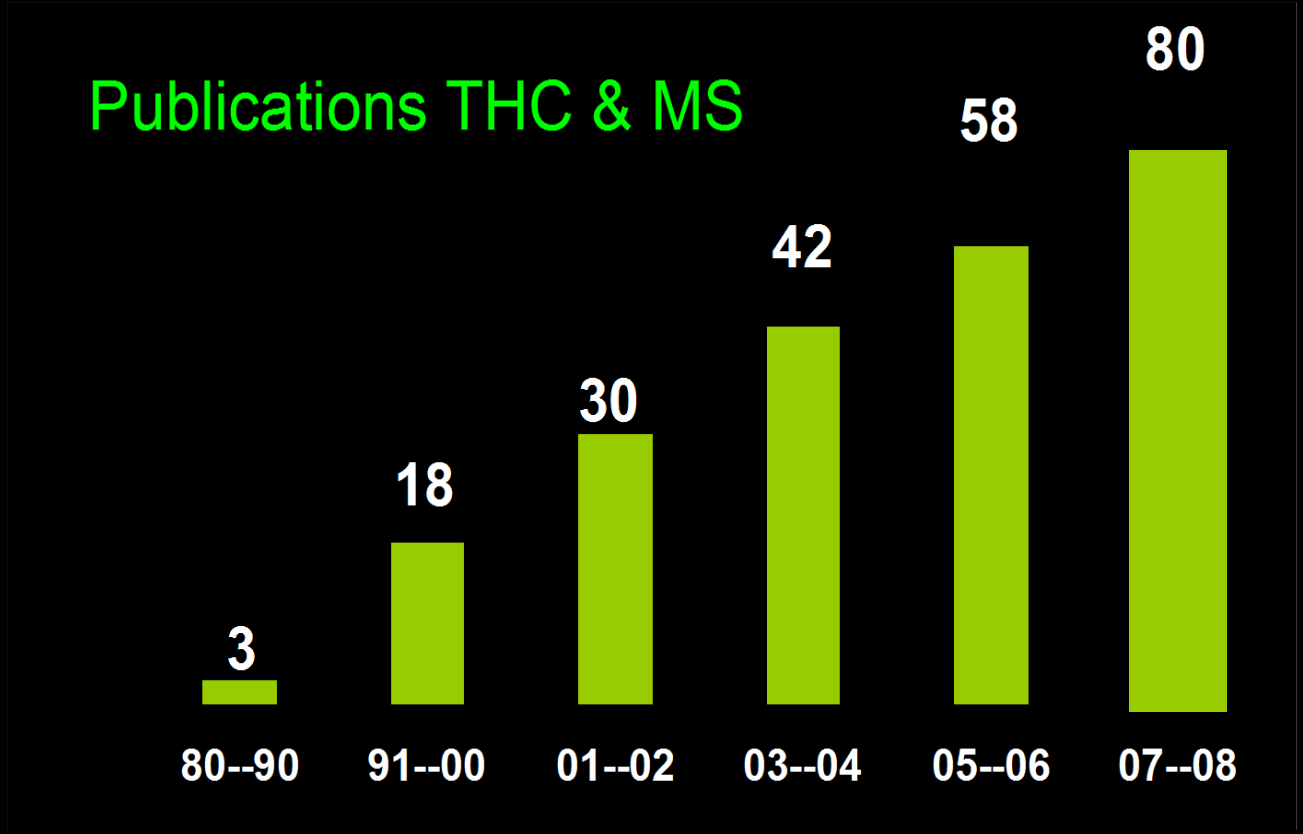
- Marihuana tax act 1937
- „Marihuana : Mörder der Jugend“ „Reefer madness“
- BETäUBUNGSMITTELGESETZ


cannabidiol
(Δ'-THC)


Prof. Raphaël Mechoulam
Chimiste, Hebrew University, Jérusalem

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



Botanik: Cannabis sativa

Zum THC- Gehalt (abh.Temperatur,Licht & Feuchtigkeit)

- Harziges Sekret der weibl.Cannabisblüten: (Haschisch / Charas : 7 - 14 % THC)
- Getrocknete Spitzen weiblicher Blüten: (Ganja/ Sinsemilla : 4 - 7 % THC)
- Getrocknete Blätter und Blüten: (Bhang / Marihuana : 2 - 5 % THC)
- Faser Hanf (CH):< 1.0 %, dafür viele UFA!

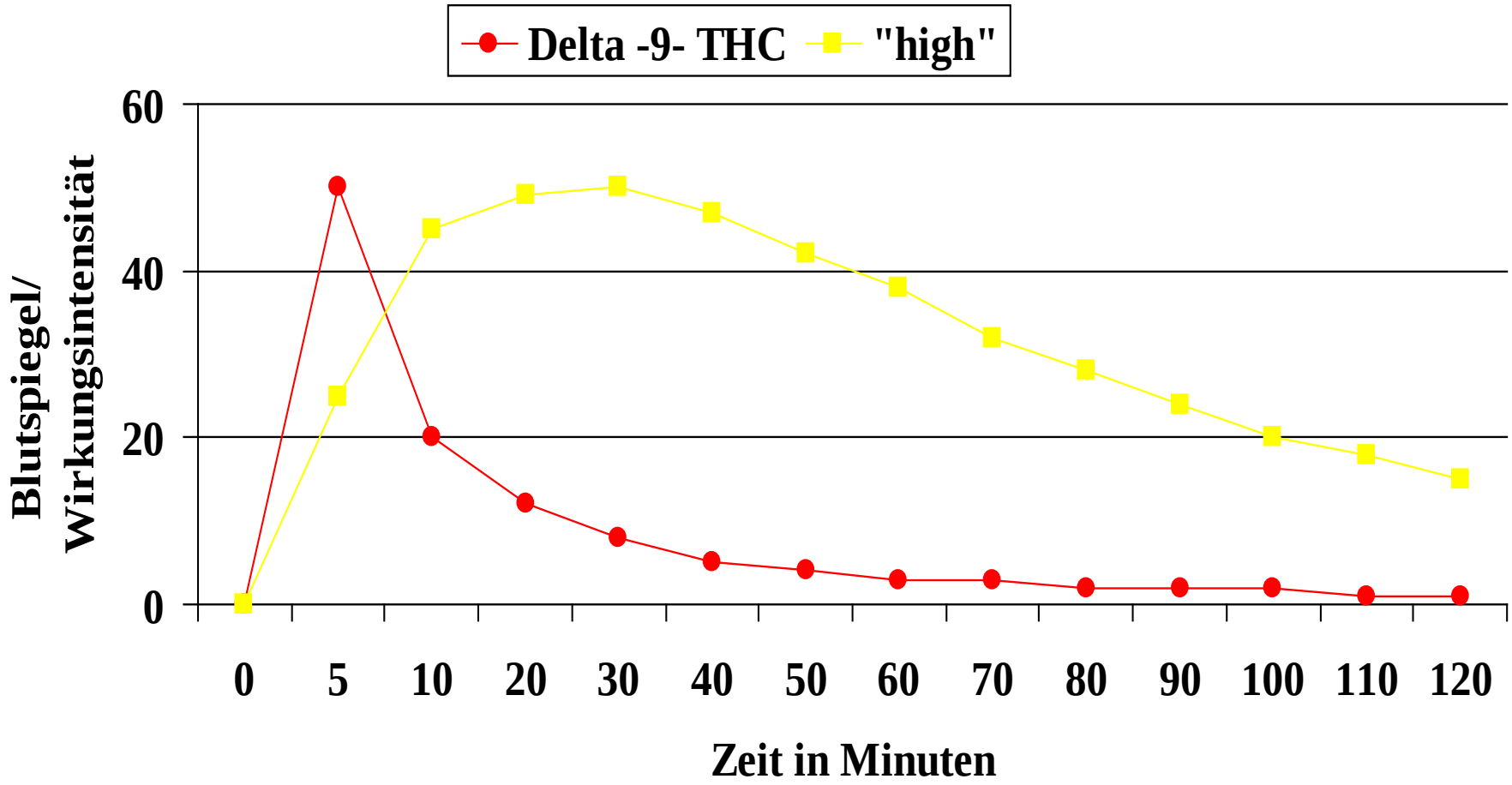
"joint"-Pharmakokinetik

- **1g Marihuana (5%) 50 mg THC**
  ("Marihuana" mex. Dialekt = Hanf)
- **Nur 5 - 10 mg THC in Kreislauf**
  (Inhaliertechnik / Z Mitraucher)
- **Umwandlung ~ T° (5 Min. bei 100°)**
  (Kuchen oder Tee mit Milch)
- **Wirkung dauert 3-4 Stunden an**
  (Urinnachweis nach Tagen möglich)

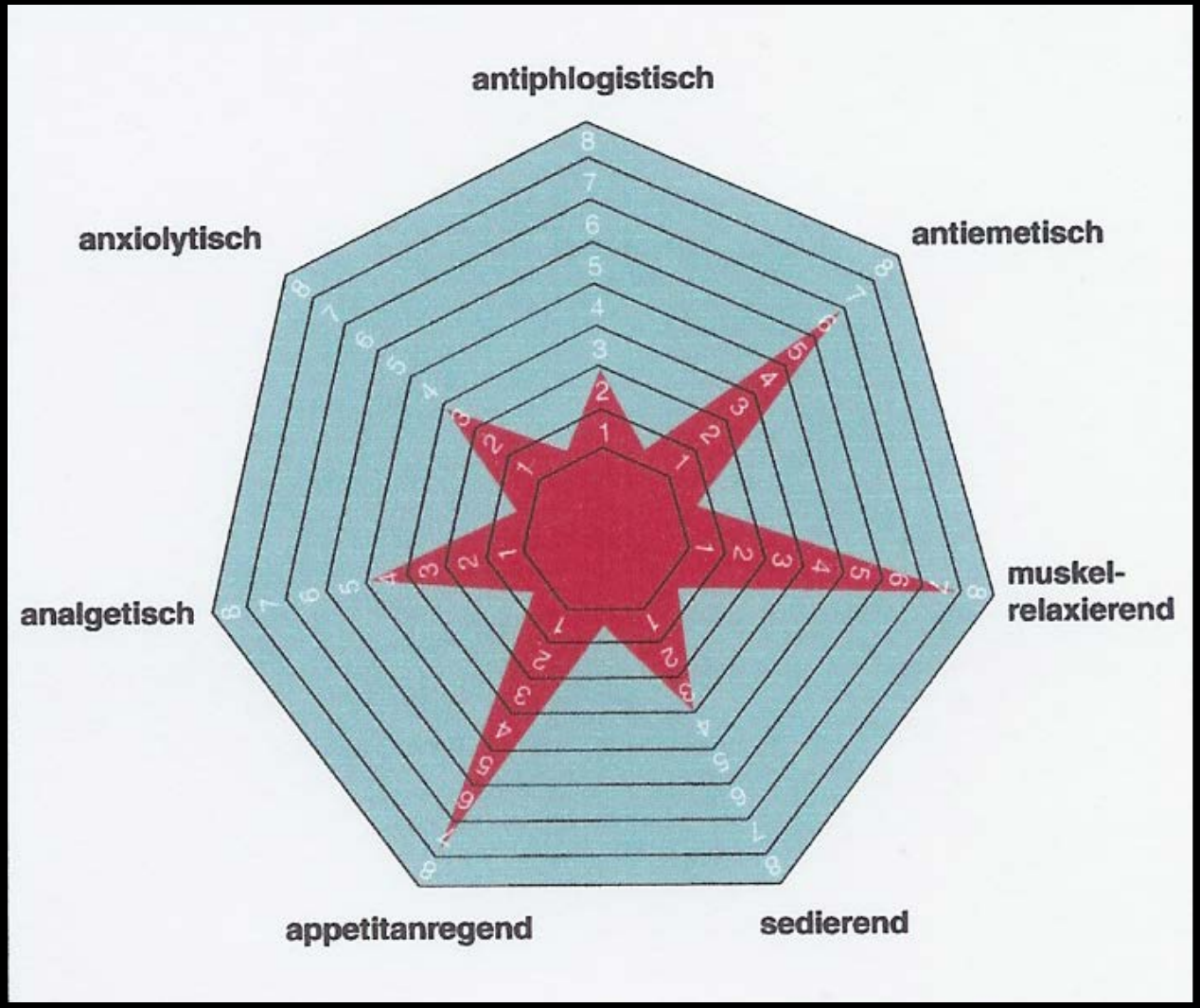
Unterschiede von THC bei oraler oder inhalativer Anwendung

	Rauchen/Inhalieren	Essen/Trinken
Systemische Bioverfügbarkeit	10-30 %	5-10 %
Grenze für Psychische Wirkungen	1-3 mg	5-15 mg
Dosis für ausgeprägten Vollrausch	10-20 mg	30-40 mg
Wirkungsbeginn	2-8 Minuten	30-90 Minuten
Maximale Wirkung	20-30 Minuten	2-4 Stunden
Dauer der psychischen Wirkung	2-3 Stunden	4-8 -? Stunden

Zeit-Effekt Beziehung nach Rauchen von Marihuana



Dronabinol-Wirkstern



Unter Cannabinoid Kontrolle stehende N‘Transmittersysteme

Neurotransmitter	Störungen
Glutamate	Epilepsie, Zelltod
GABA	Spastik, Angst
Serotonine	Depression
Dopamine	Parkinson, Psychose
Neuropeptide	Schmerzen
Acetylcholine	Autonomes NS

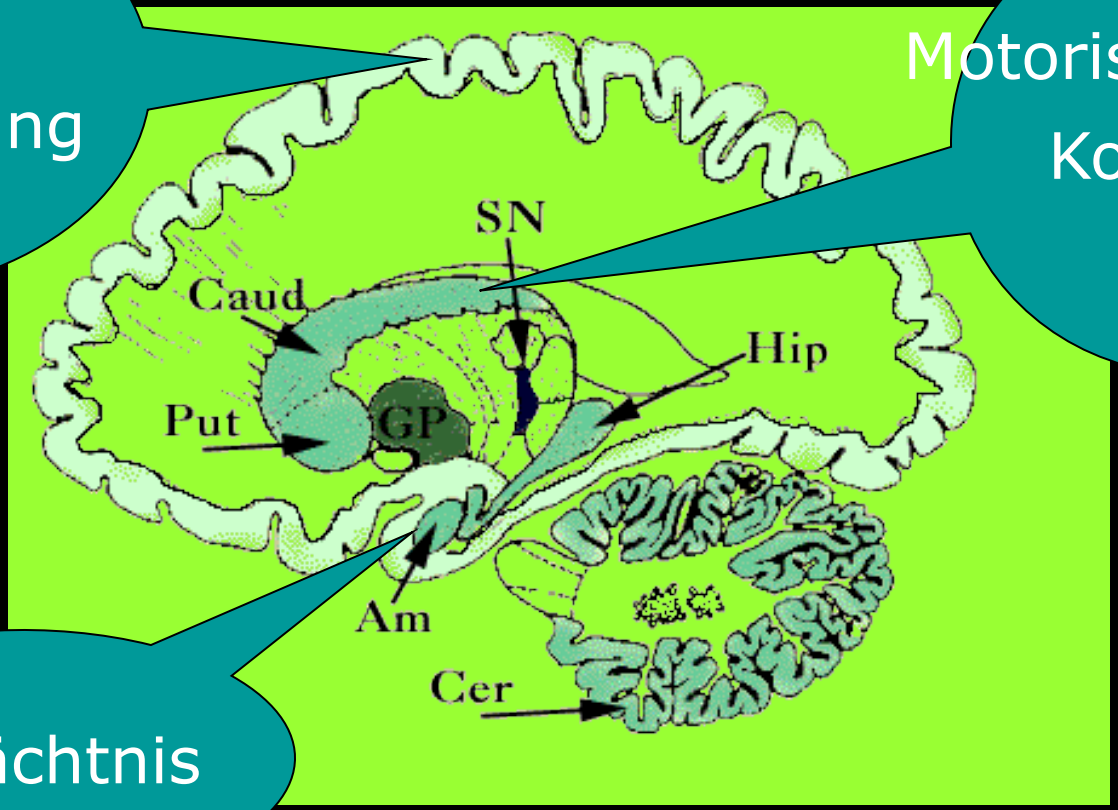
Vegetative (Neben)Wirkungen

- Tachycardie...vorübergehend
- (Selten) Blutdruckabfall beim Stehen
- Rötung der Augen
- Muntrockenheit- wegen verminderter Speichelproduktion
- Keine Atemdepression, wie bei Opiaten

Angriffspunkte von THC gemäss Lokalisation der CB1 Rezeptoren

Sinnes-
wahrnehmung

Motorische
Kontrolle



Gedächtnis

legal

THC 1%

illegal

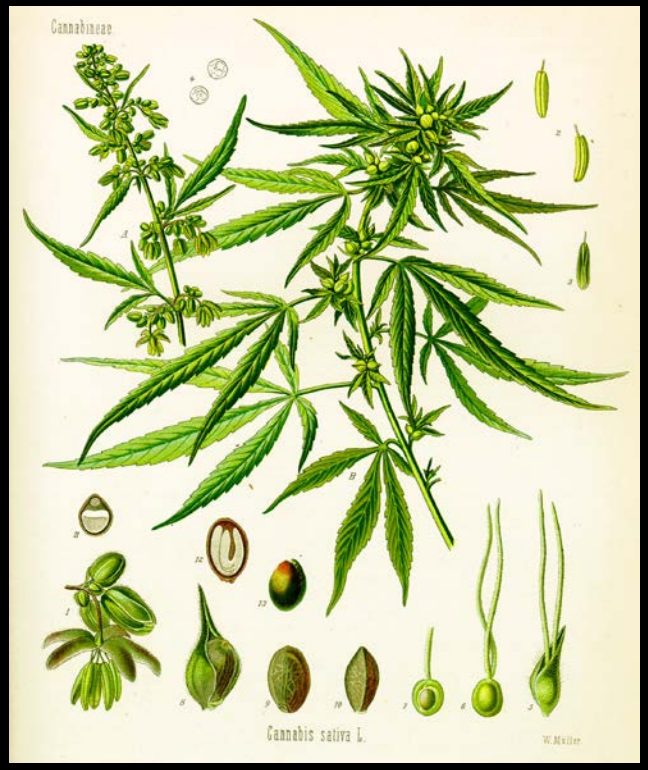
THC > 20%

die Teilrevision des Betäubungsmittelgesetz wurde gutgeheissen (68 % Ja)

Mit der neuen Regelung wird es möglich sein mit einer Ausnahmebewilligung Arzneimittel, die Cannabis auf pflanzlicher Basis enthalten, medizinisch anzuwenden !

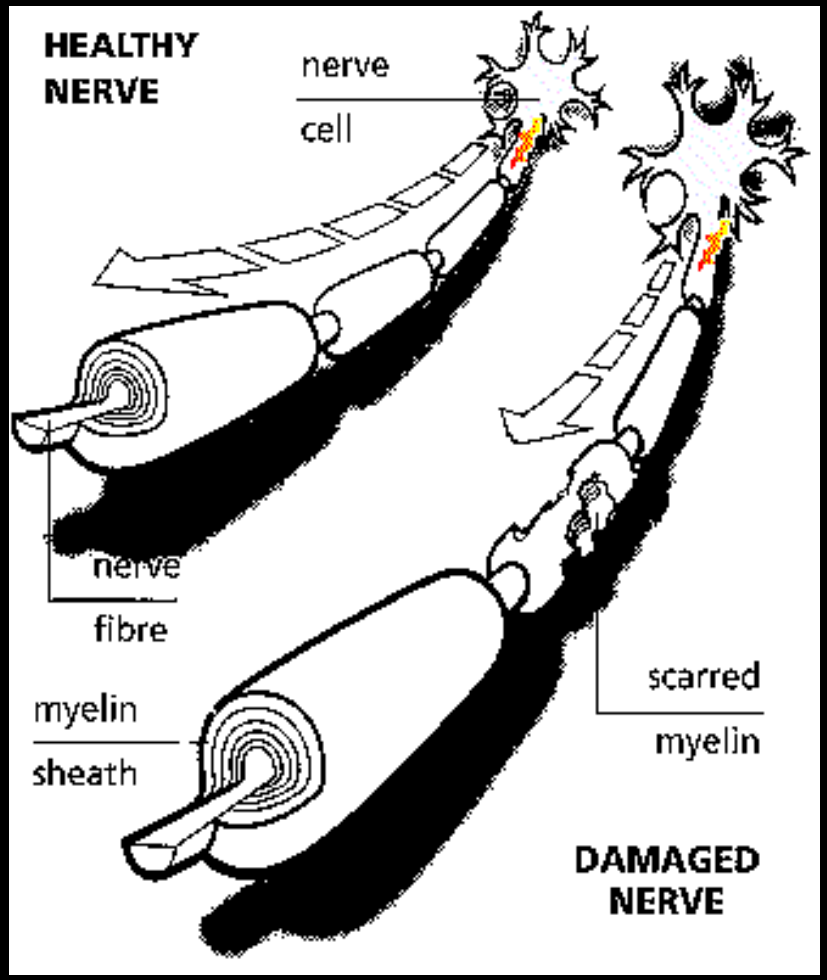
Revision tritt 2011 in Kraft !

Hanf hilft bei MS – Mythos oder Realität ?



vaney.claude@bernerklinik.ch

The clinical consequences of demyelinisation



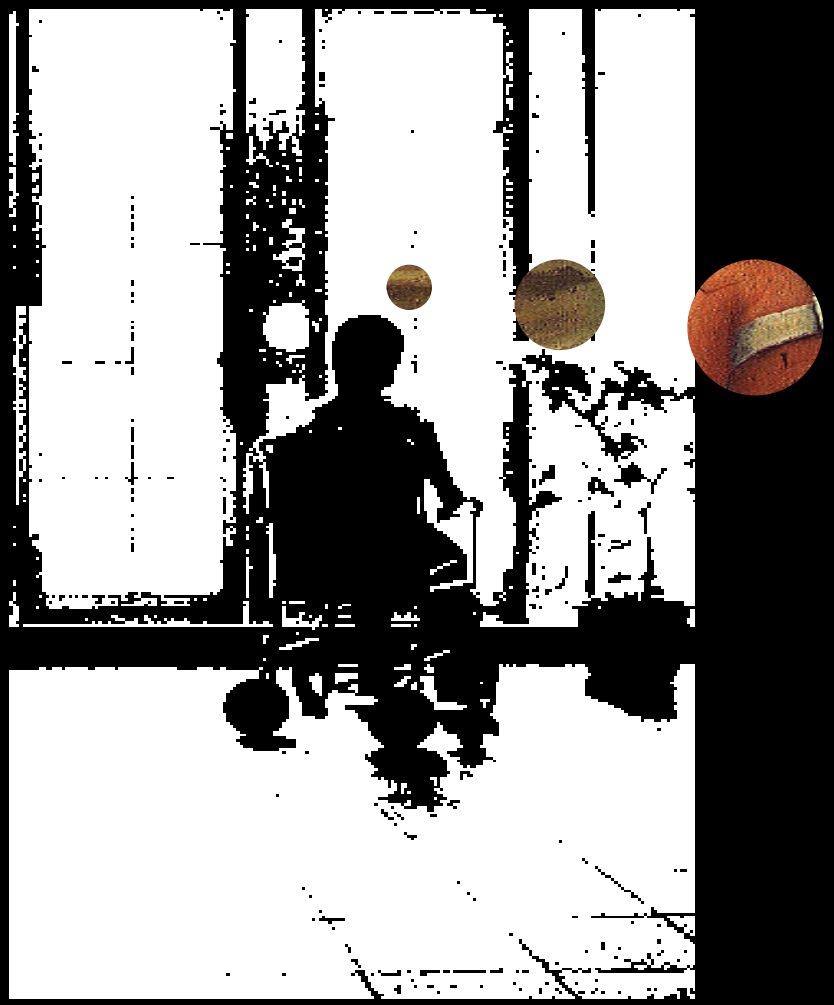
Impaired electric conduction

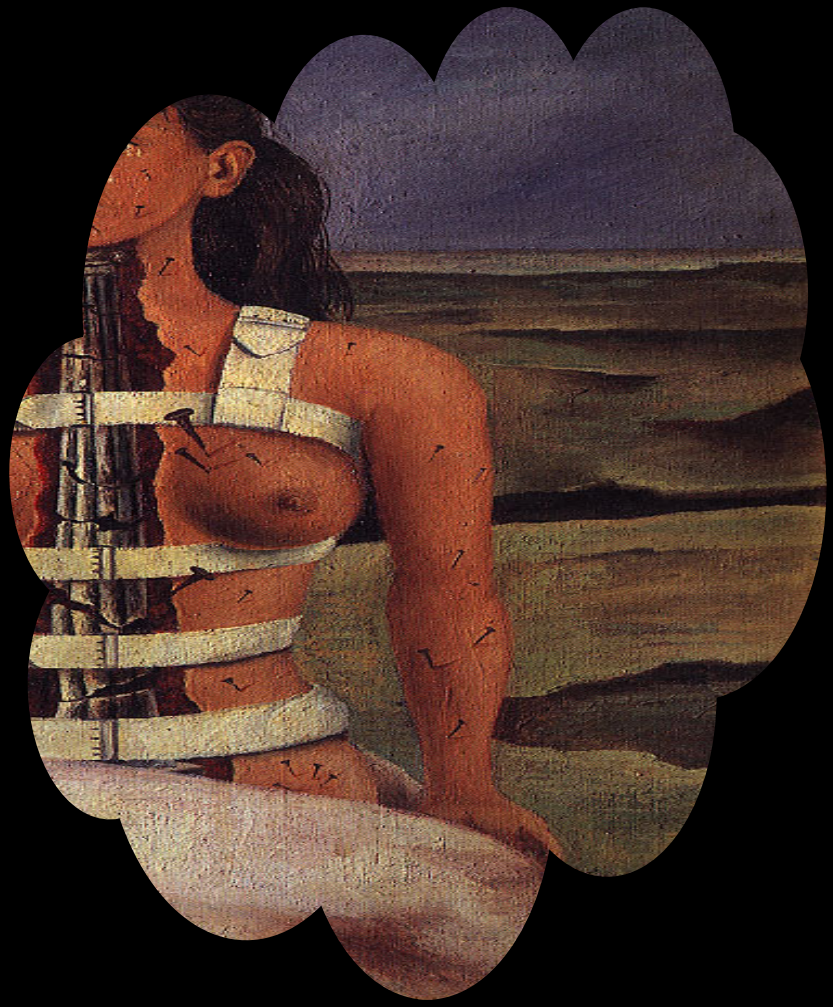
MS …trotz Medis eine fortschreitende Krankheit (Roxborough RH et al. *Neurology* 2005)

immobilité

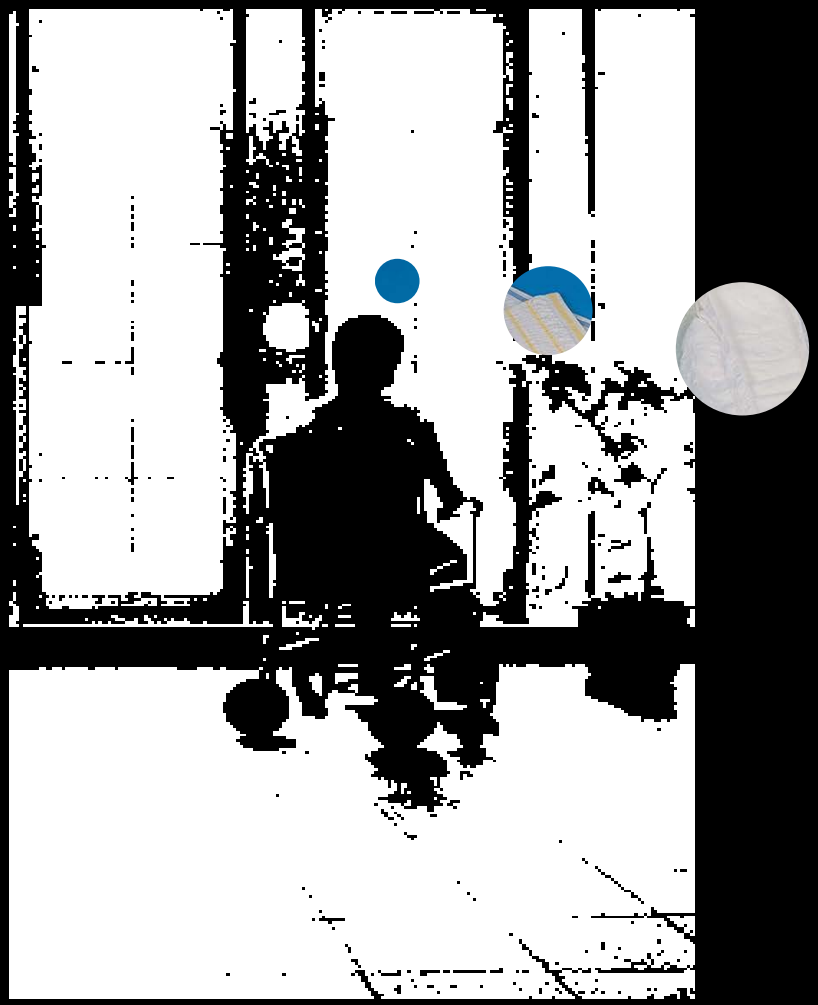
"I am a burden for my family…"

Douleurs neuropathiques & spasmes musculaires





Incontinence



A wonder drug for people with Multiple Sclerosis !

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
- Encrease 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...

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

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)

inhibitors of **CB**-1 receptors
Acomplia® (Rimonabant)

Tableau 3. Après 16 semaines de traitement la perte pondérale moyenne est plus importante pour les groupes ayant les traitements actifs que pour le groupe placebo

La réduction de la circonférence de la taille n'est statistiquement significative que dans le groupe recevant 20 mg de Rimonabant.

		Rimonabant		
	Placebo	5 mg	10 mg	20 mg
Poids (kg) T test (p)	0,9	2,5 < 0,009	2,7 < 0,003	3,8 < 0,00001
Circonf. taille (cm) T test (p)	1,1	2,6 n.s.	2,5 n.s.	3,9 < 0,0005

Cannabinoids slow down progression...

- Case report of women developing MS after recvieving a CB1 antagonist for obesity (Van Oosten BW *Multiple Sclerosis* 2004)

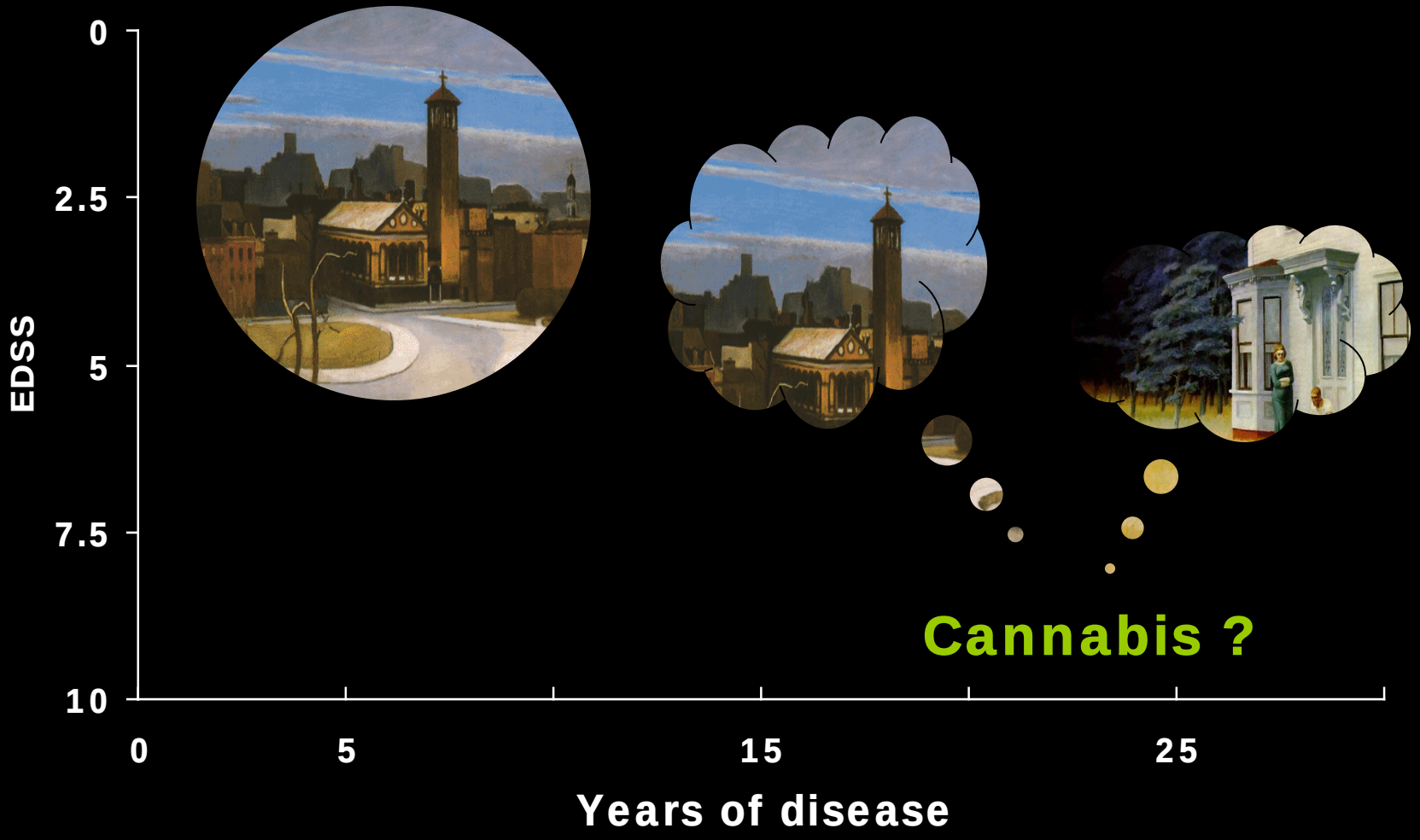
THC reduces the relapse rate !

CAMS Study- J.Zaijcek , *Lancet* 03

	Treatment group			
	Cannabis extract (n=12)	Δ⁹-THC (n=18)	Placebo (n=20)	Total (n=50)
Adverse event				
Multiple sclerosis relapse or possible relapse	1	1	7*	9
Urinary tract infection	1	3	4	8
Pneumonia	1	2 (1 death)	1	4
Blocked/insertion of suprapubic catheter	1	1	2	4
Constipation	1		3	4
Grand mal seizures	1		1	2
Other	6†	11‡	2§	19
Total	12	18	20	50

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

Cannabinoid use in progressive inflammatory brain disease



- Slow down progression
- No serious side effects ?
- Low cost
- Favorable effect on symptoms

Annual death

TOBACCO	400,000
ALCOHOL	100,000
ALL LEGAL DRUGS	20,000
ALL ILLEGAL DRUGS	15,000
CAFFEINE	2,000
ASPIRIN	500
MARIJUANA	0

Source:

United States government, National Institute on Drug Abuse, Bureau of Mortality Statistics.

What are the comments concerning side effects ?

- **Killestein et al. *Neurology* 2002:**

  „Both THC and placebo capsules were well tolerated and no AE emerged"

- **Vaney et al. *Mult Scler* 2004:**

  „ In general cannabis was well tolerated and no serious AE emerged during the trial "

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“

Zentrale (Neben) Wirkungen

- **Antiemetisch**
  (gegen Übelkeit bei Krebstherapie)
- **Appetitsteigernd**
  (bei Kachexie AIDS - 27 %- oder Krebs)
- **Analgetisch = schmerzstillend**
  (eher schwach,wie etwa Codein
- **Augeninnendruck senkend**
  (Glaucom)

Psychodelische (Neben)Wirkungen

- **„High“:**

  leichte Euphorie & gesteigertes Wohlbefinden

- **Veränderte Sinneseindrücke:**

  auditiv, visuell, verzerrtes Zeitgefühl (Dt↑)

- **Kognition beeinträchtigt:**

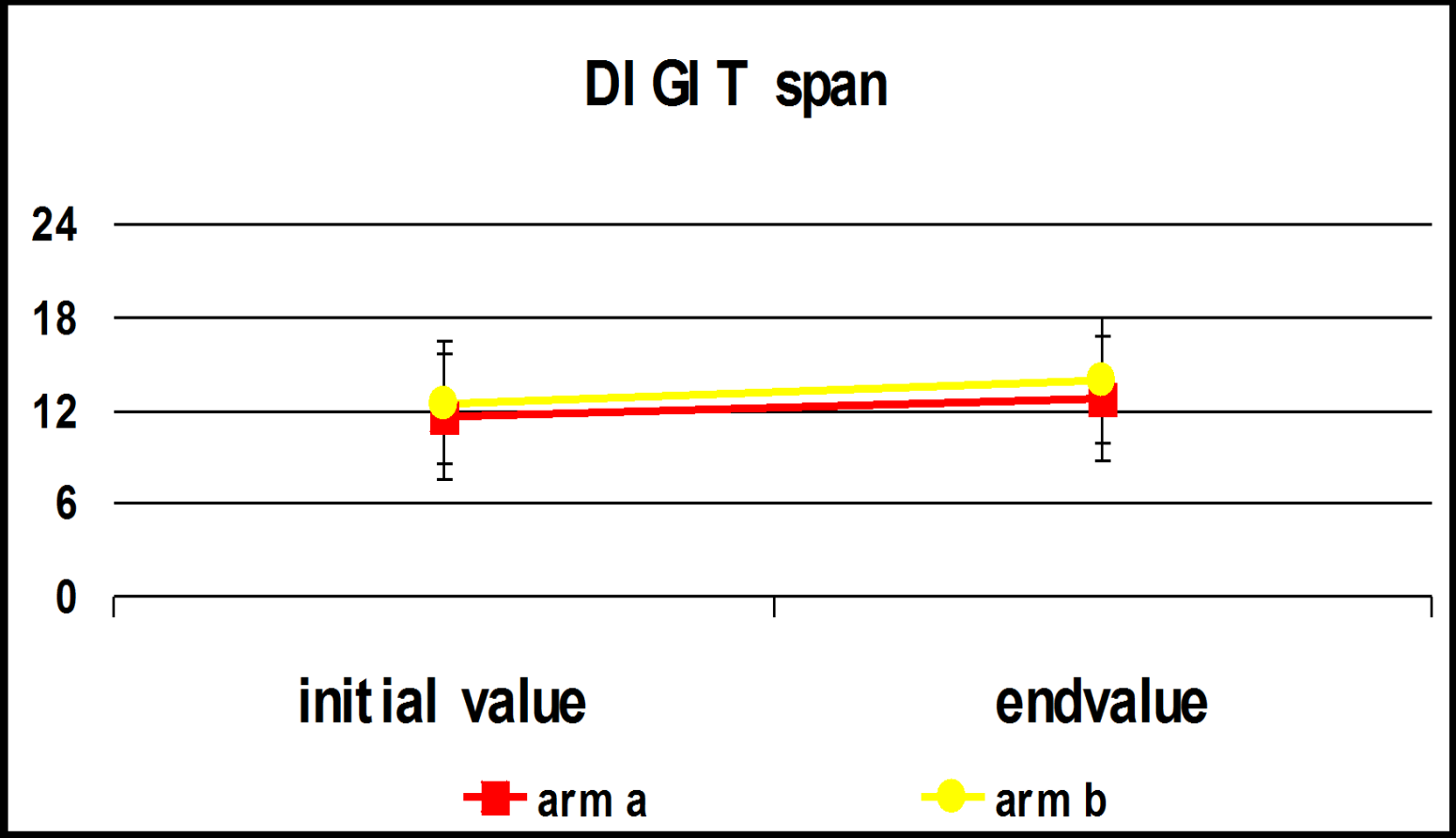
  Aufmerksamkeit ↓: cave Autofahren

  Logik ↓: komplexe Aufgaben erschwert

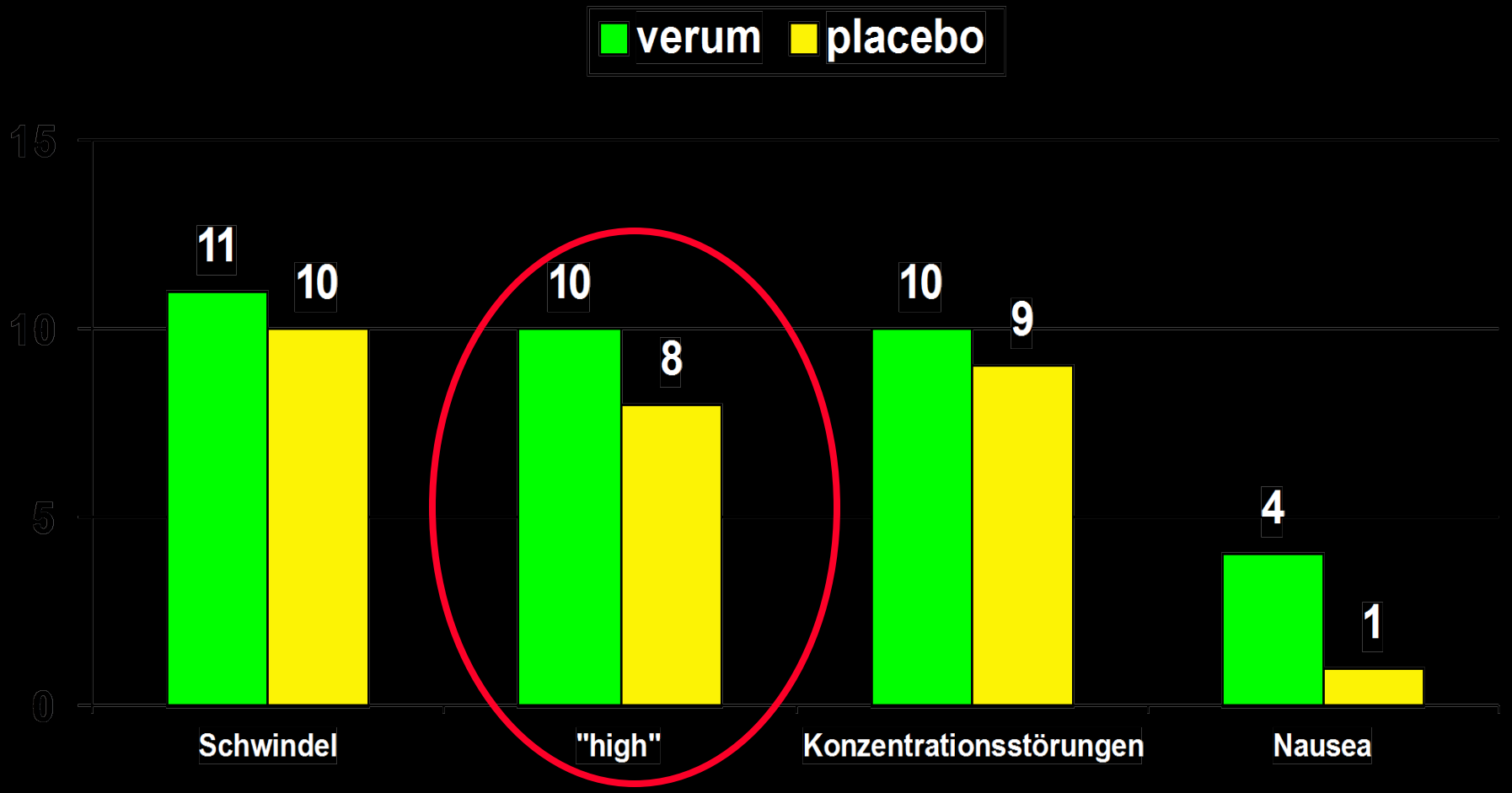
- **Wahnvorstellungen und Paranoia:**

  Psychose : provoziert 5% - demaskiert 24%

No signs of cognitive deterioration

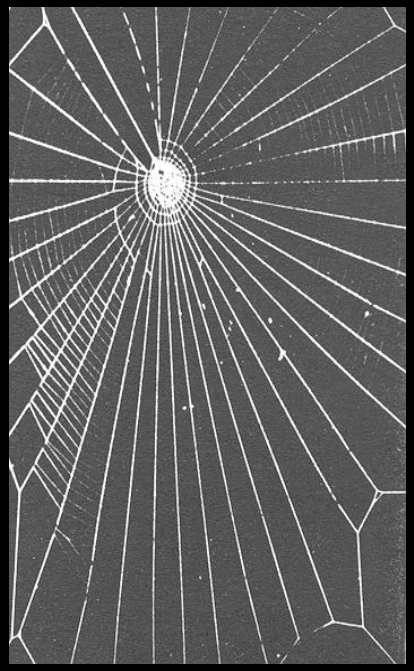


Side effects were also found in he patients taking placebo...

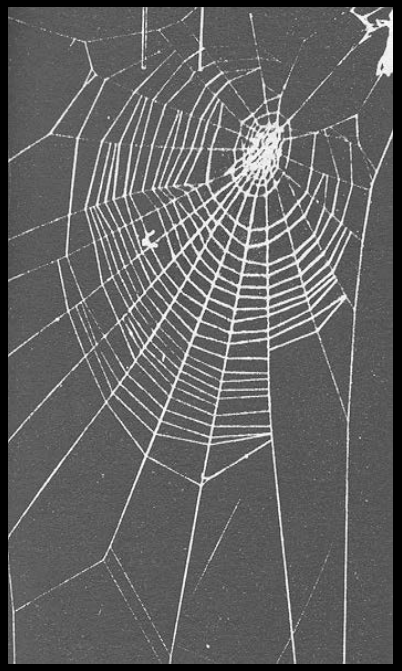


Effect of centraly active drugs on the web building activity of a new species of indian spider

Mardikar BR et al. *Indian Med Sci* 1969; 10:550-8

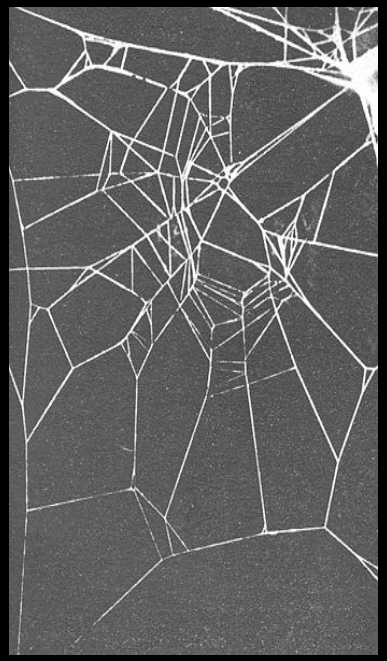


LSD



Cannabis

Meskaline



coffee

legal

THC 1%

illegal

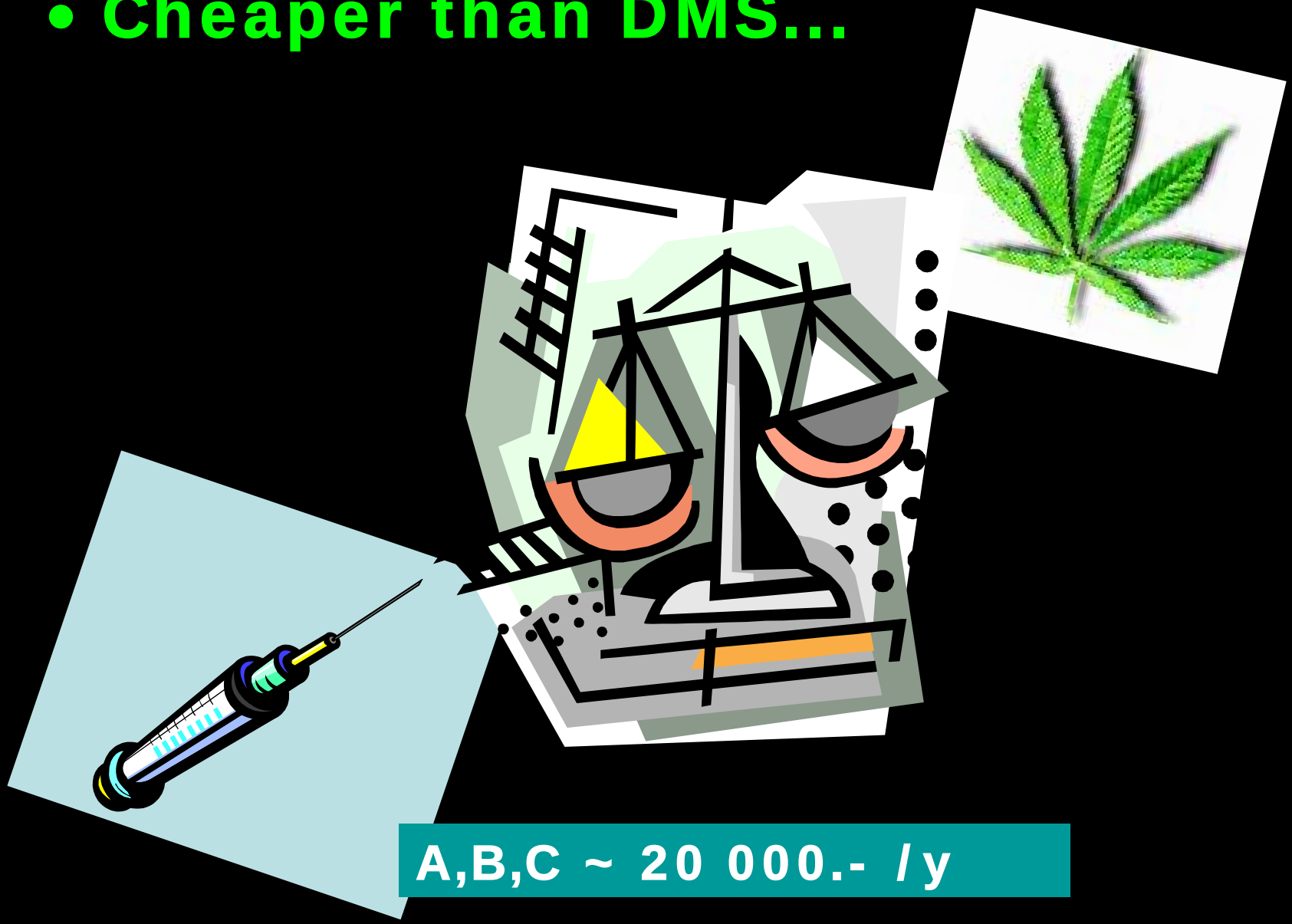
THC > 20%

Unterschiede von THC bei oraler oder inhalativer Anwendung

	Rauchen/Inhalieren	Essen/Trinken
Systemische Bioverfügbarkeit	10-30 %	5-10 %
Grenze für Psychische Wirkungen	1-3 mg	5-15 mg
Dosis für ausgeprägten Vollrausch	10-20 mg	30-40 mg
Wirkungsbeginn	2-8 Minuten	30-90 Minuten
Maximale Wirkung	20-30 Minuten	2-4 Stunden
Dauer der psychischen Wirkung	2-3 Stunden	4-8 -? Stunden

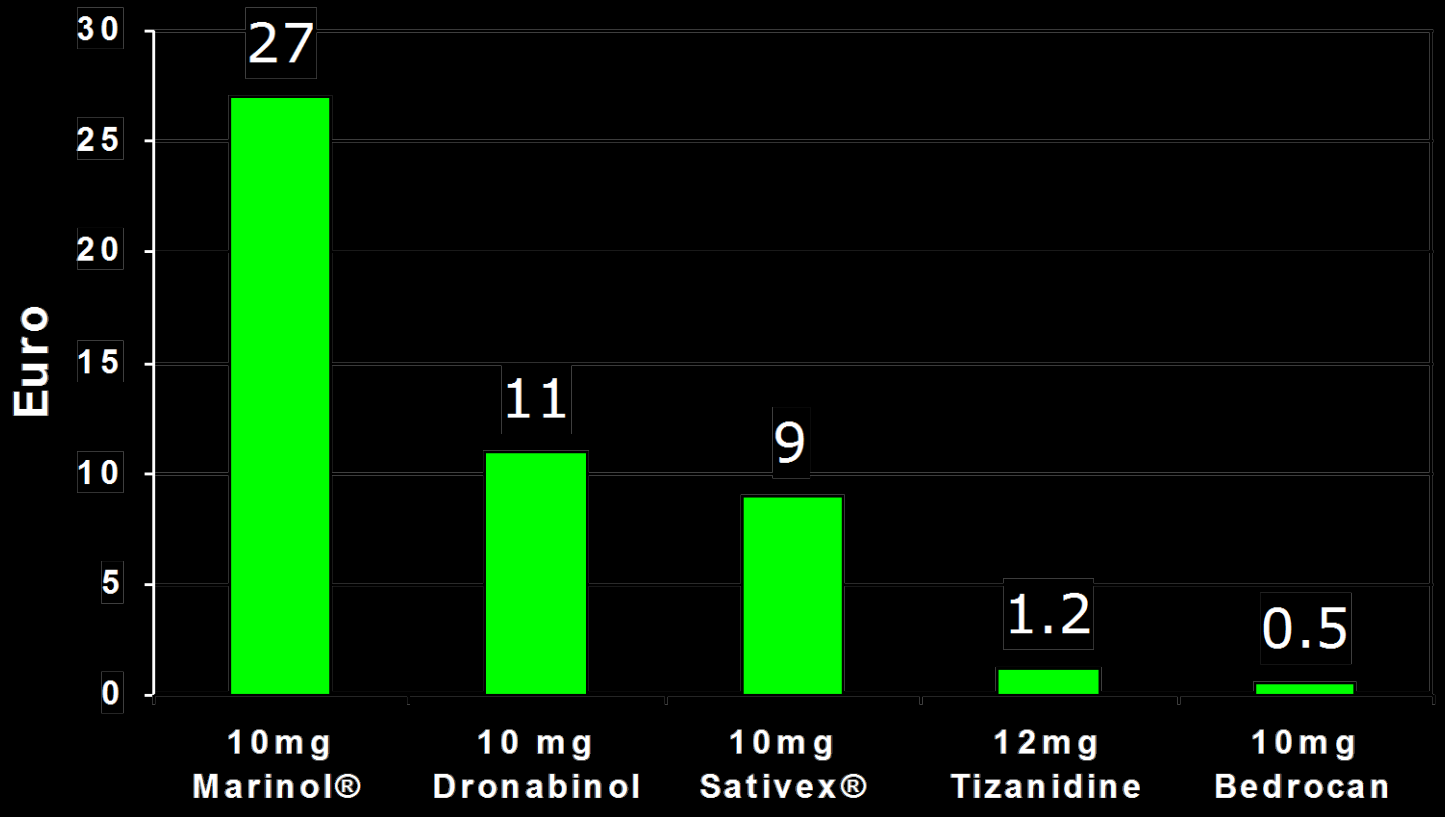
- Slow down progression
- No serious side effects
- Low cost ?
- Favorable effect on symptoms

- **Cheaper than DMS...**

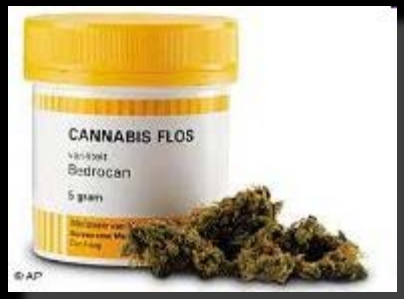


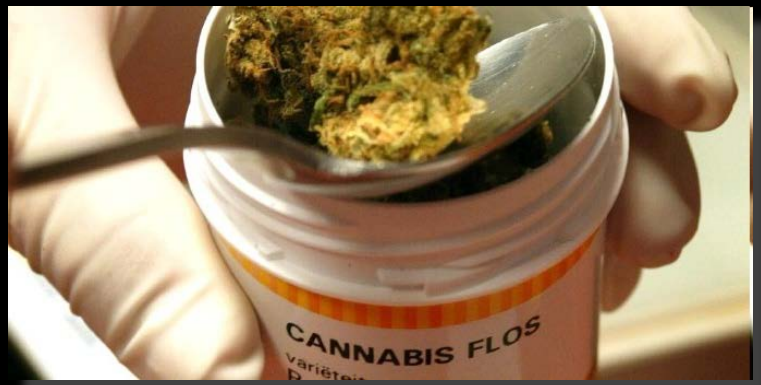
A,B,C ~ 20 000.- /y

The price of pain relief /day



Cannabis flos





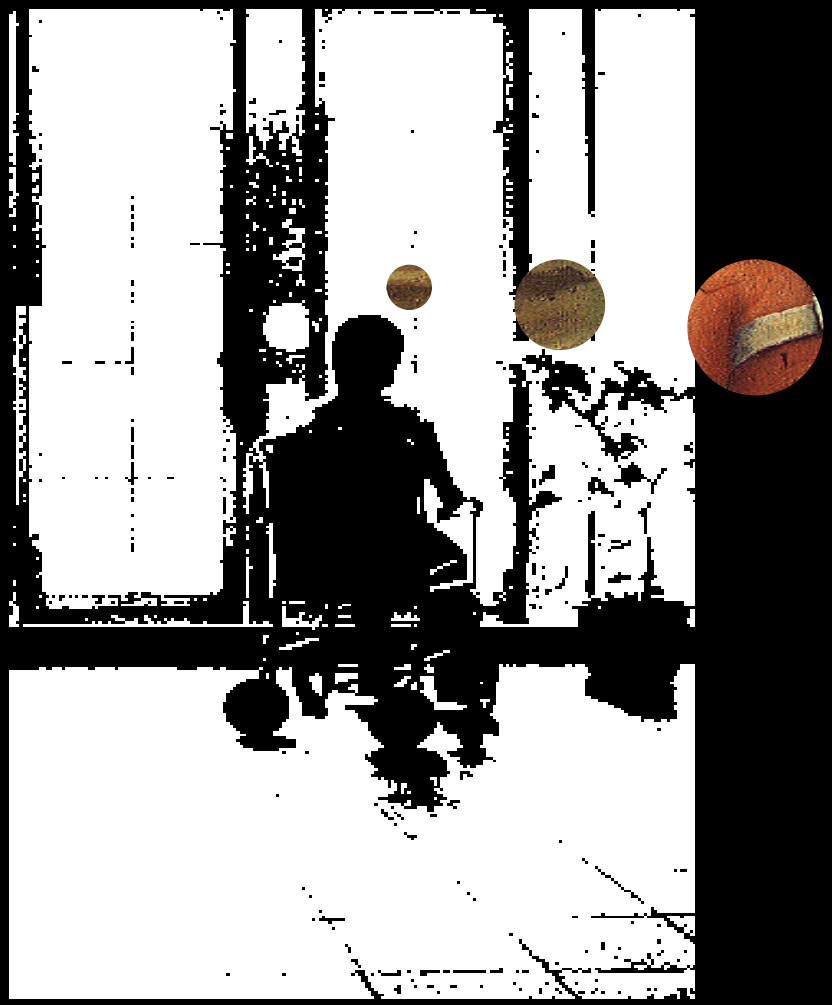
- Hanfblüten sind in Holland rezeptierbar (seit 2003)
- Varietät „Bedrocan“ enthält 18 % THC

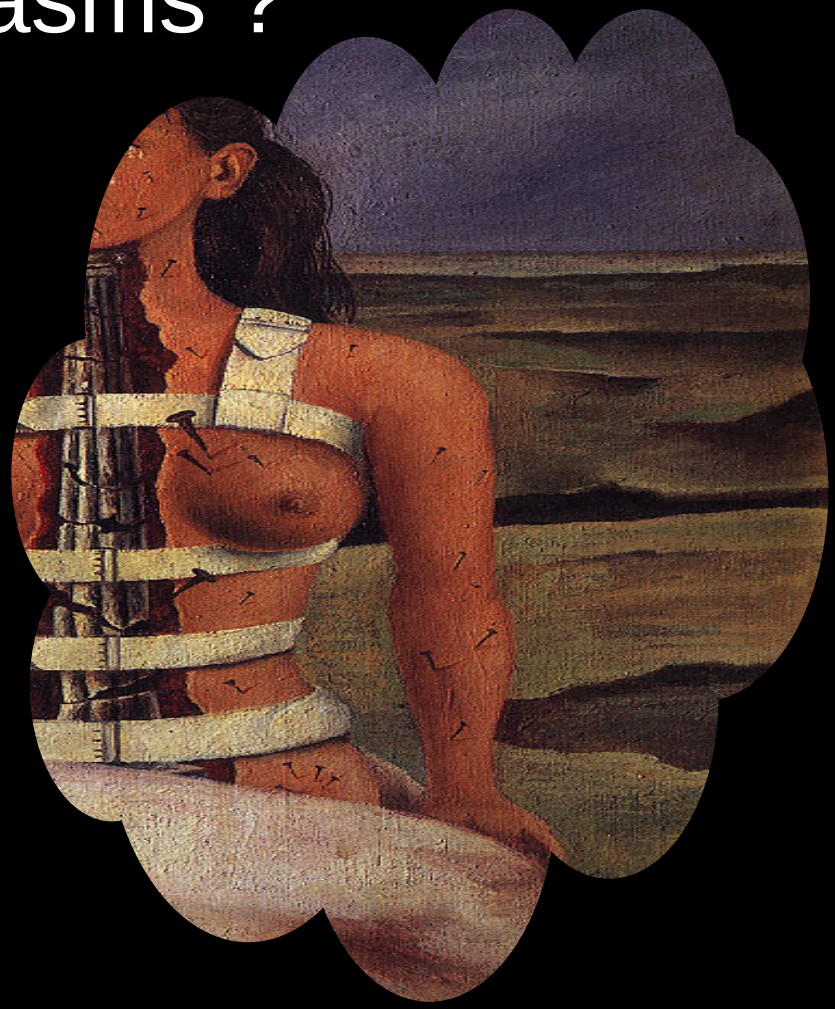
- Slow down progression
- Few side effects
- Low cost
- Favorable effect on symptoms ?

Favorable effect on symptoms:

- Lower spasticity ?
- reduce pain
- Calm the bladder
- Encrease mobility

What can be done against pain and muscle spasms ?





Drugs commonly used to lessen spasticity and spasms

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

Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis (Cochrane Review 2003)

Baker D et al. *Nature* 2000; 404: 84-87

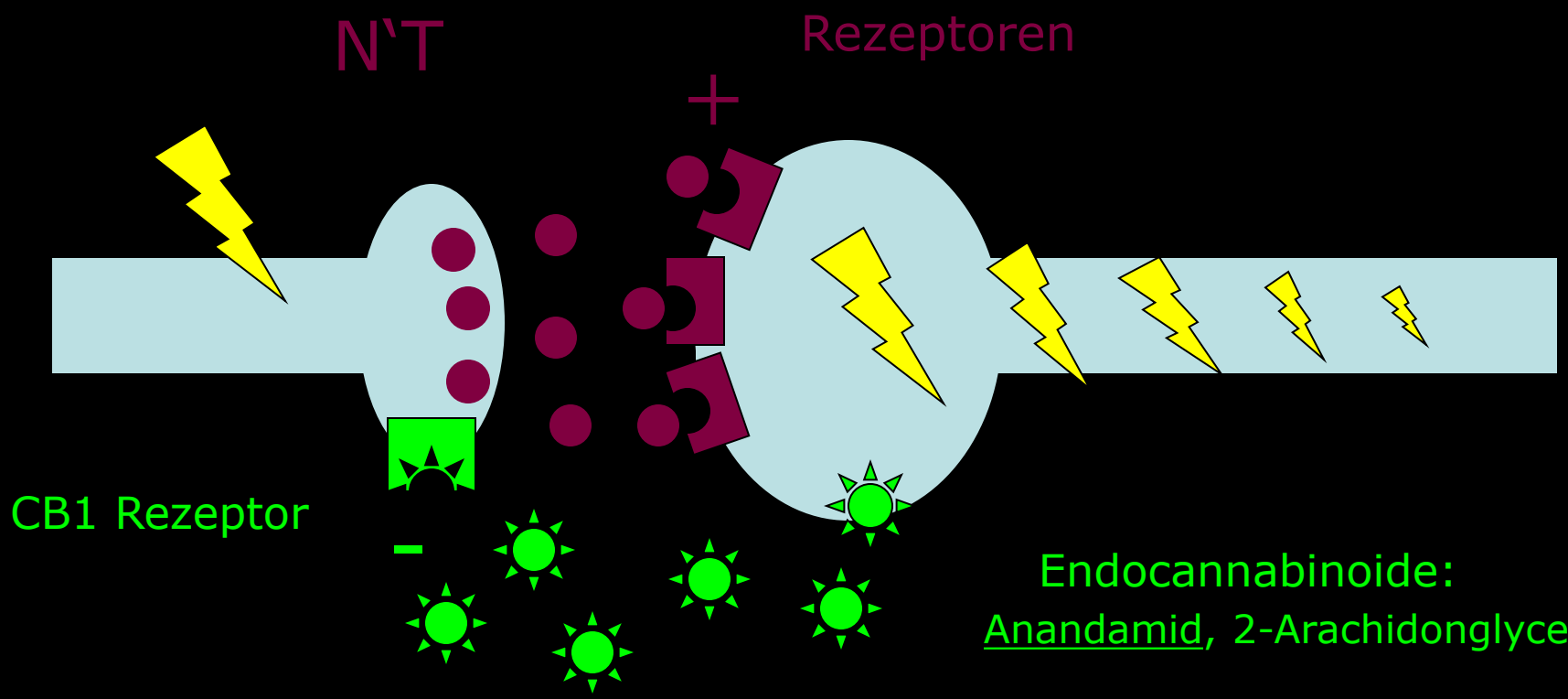
Cannabinoids control spasticity and tremor in a multiple sclerosis model

Baker D et al. *Nature* 2000; 404: 84-87

Cannabinoids control spasticity and tremor in a multiple sclerosis model

Regulation der Signalübertragung durch das Cannabinoidsystem

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



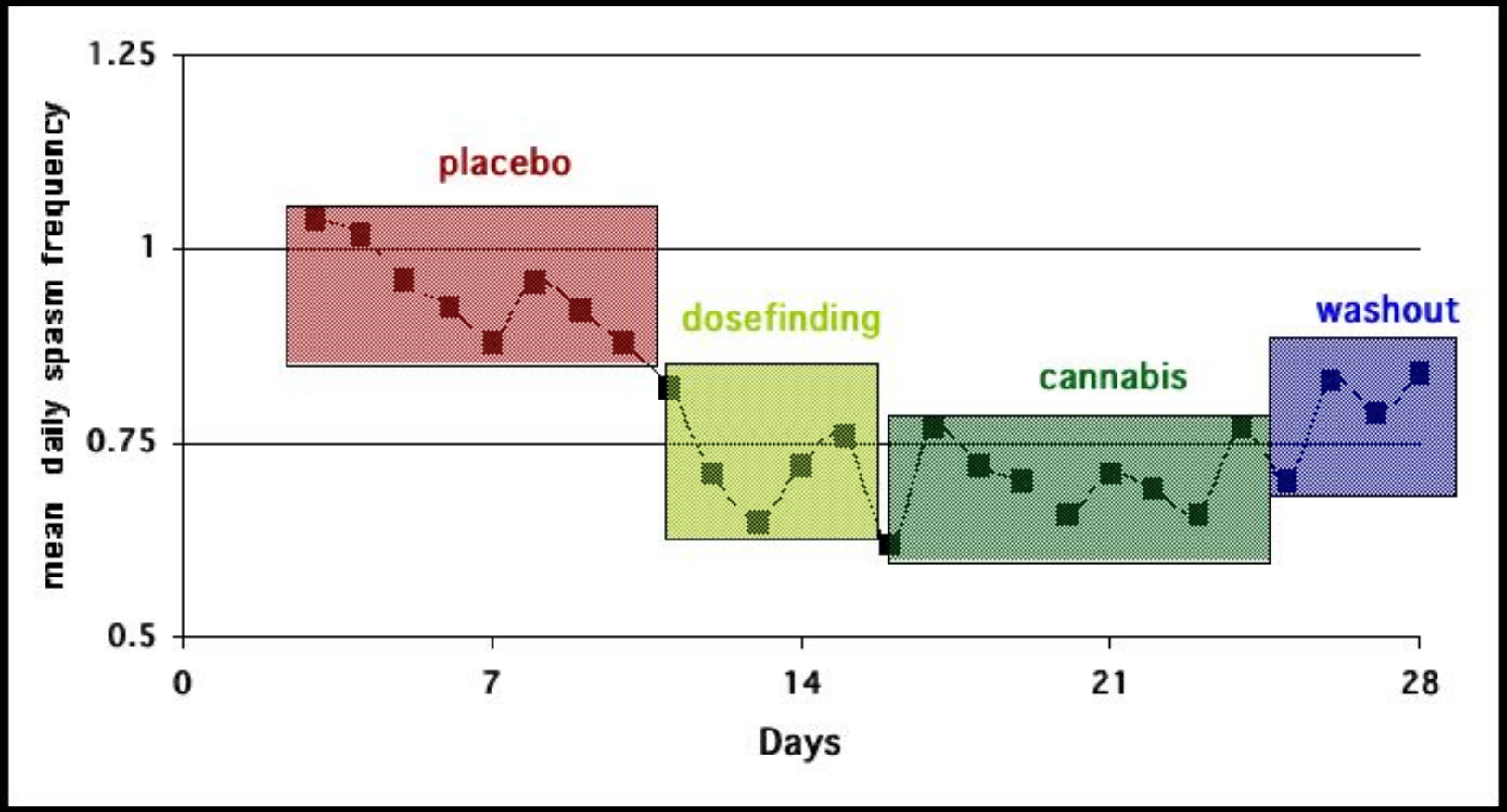
Durch diese retrograde pre-synaptische Hemmung üben die Cannabinoide eine modulierende Wirkung aus !

Reduced spasticity ...subjectively

Study	n	Measure	Spasms
Ungerleider 1987	13	Subjective rating	improved
Vaney 2004	57	Spasm frequency	improved P=0.013
Zaijcek 2003	667	Category rating scale	Improved P =0.01
Wade 2004	160	VAS	Improved P=0.001

Reduction of spasm frequency

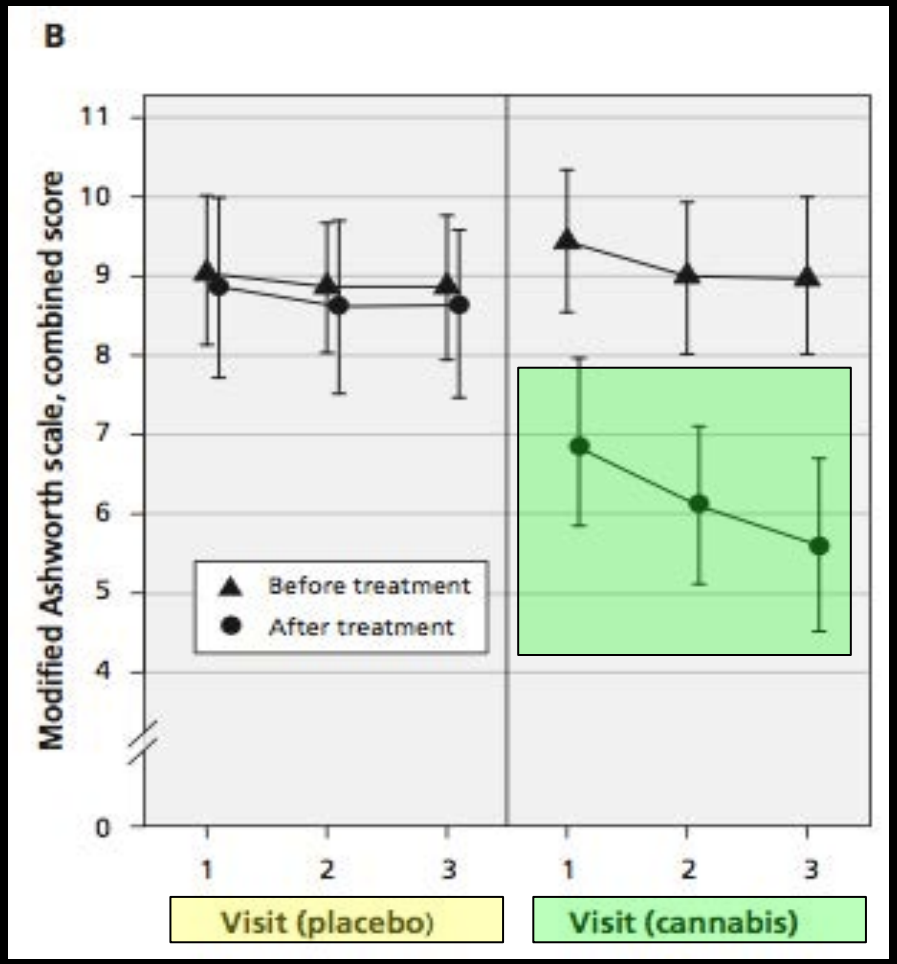
Vaney et al. *Mult Scler* 2004



Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial

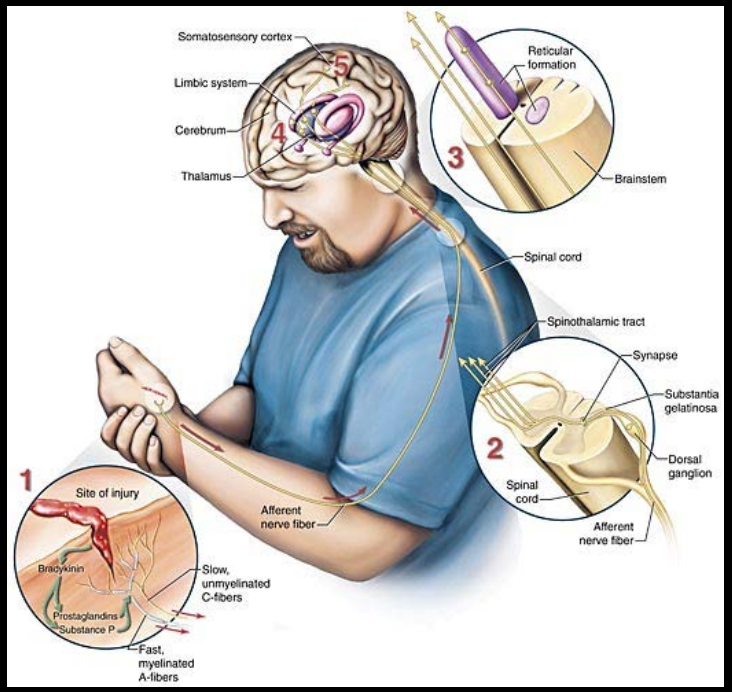
Jody Corey-Bloom MD PhD, Tanya Wolfson MA, Anthony Gamst PhD, Shelia Jin MD MPH, Thomas D. Marcotte PhD, Heather Bentley BA, Ben Gouaux BA

- *CMAJ* july 2012
- 30 PwMS
- 3 times daily
  1 cigarette
  placebo vs.
  cannabis
- Ashworth spasticity score (0-5)



- Lower spasticity
- reduce pain ?
- Calm the bladder
- Encrease mobility

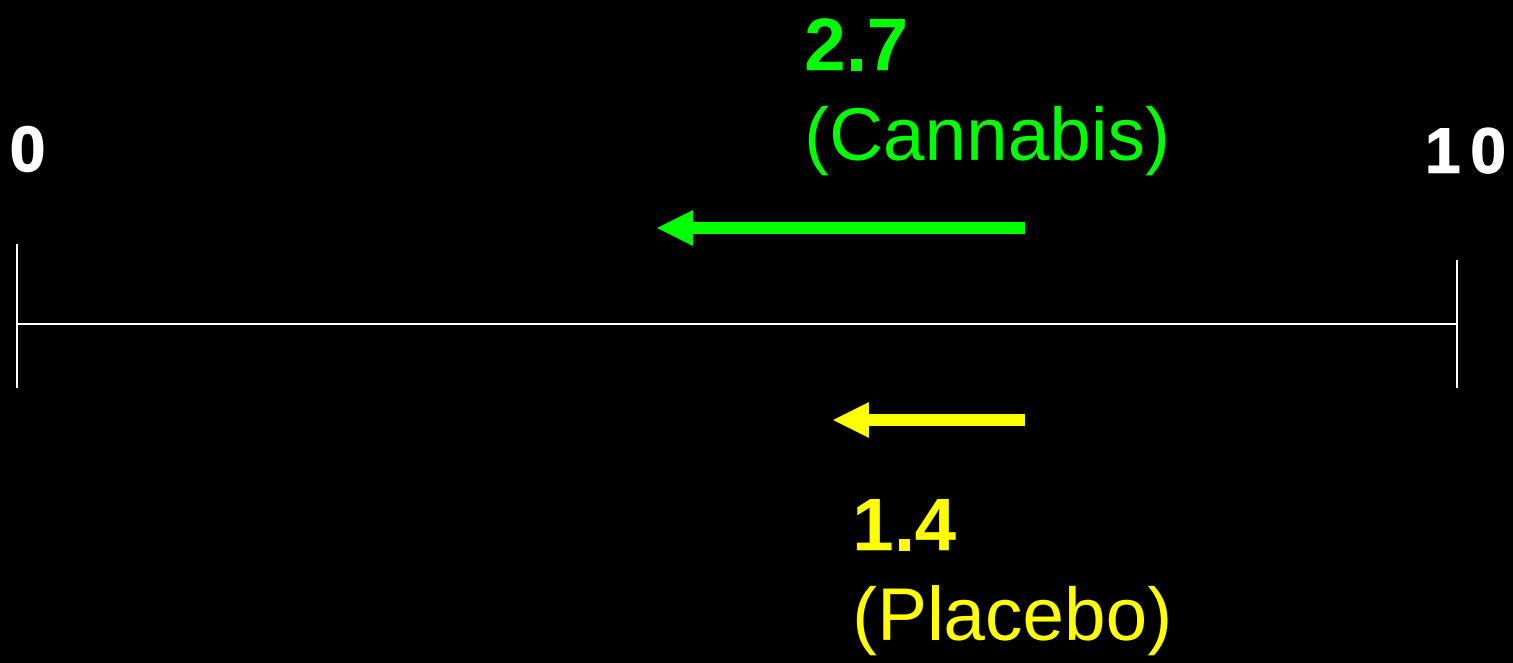
Converging evidence supports a role of endocannabinoids in the tonic inhibition of pain responses and the setting of nociceptive thresholds..



Dynamic regulation of the endocannabinoid system: implications for analgesia
Sagar D et al. *Mol Pain* 2009; 5: 59.

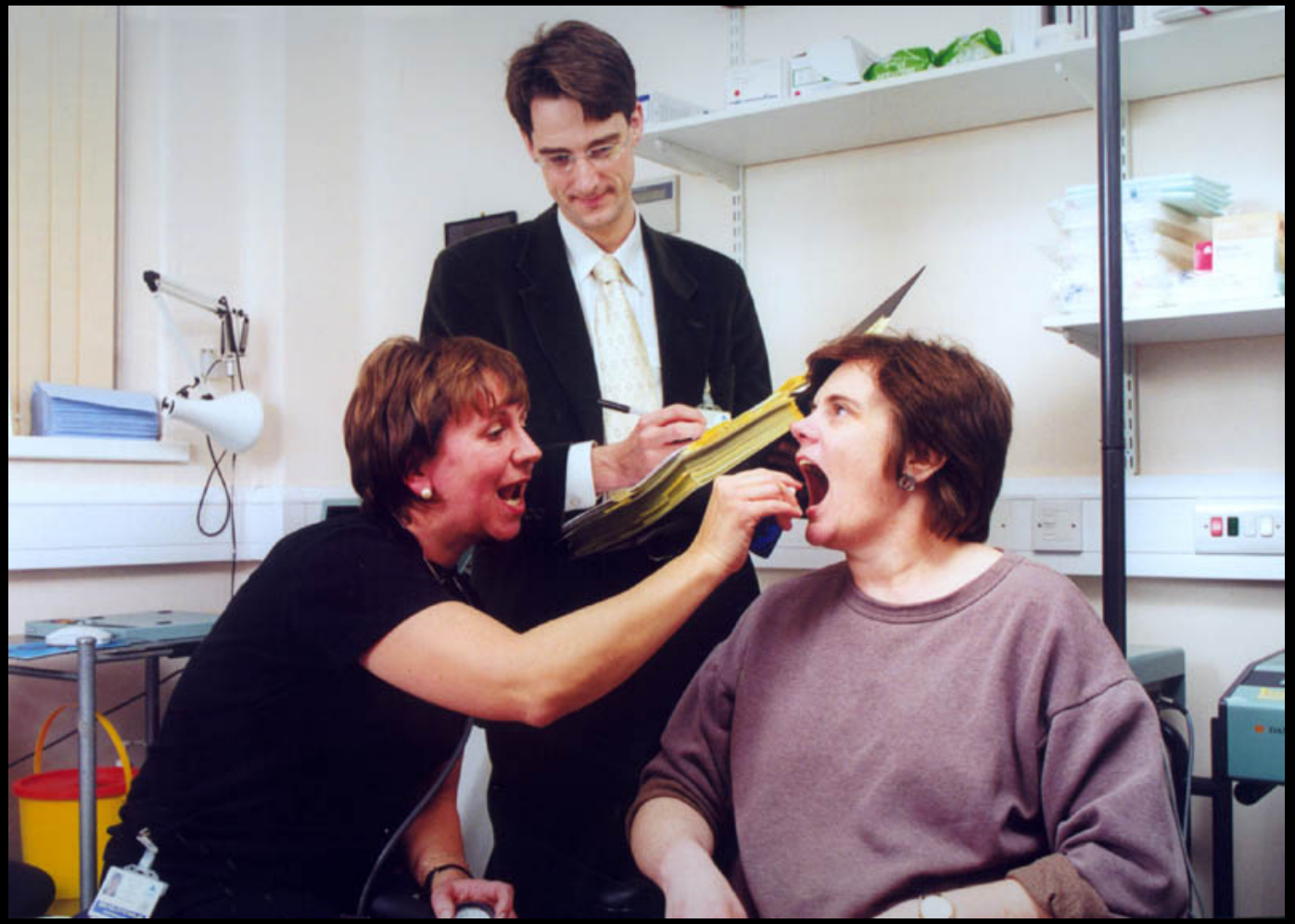
That takes away neuropathic pain !

Rog DJ et al. *Neurology* 2005



?

Visual analog scale (VAS)



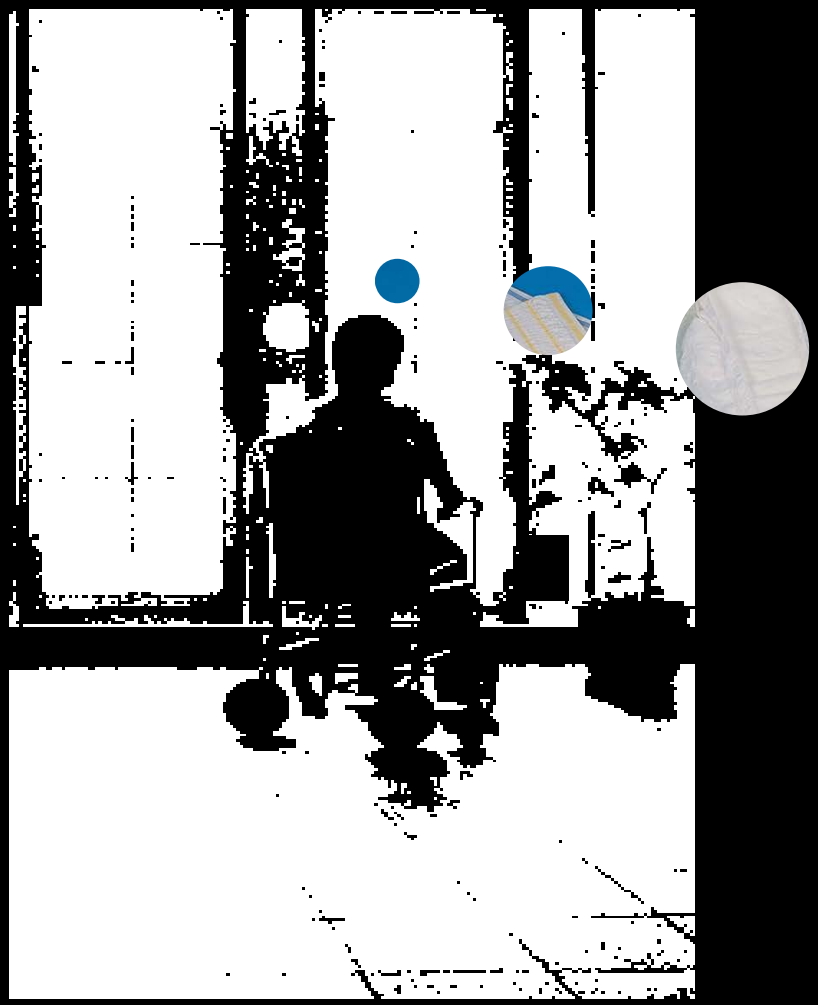
Cannabis Spray licensed Sativex® in Canada

Reduced pain ...subjectively

Study	n	time	measure	pain
Zaijcek 2003	667	15 w	Category rating scale	P =0.002
Svendson 2004	24	3 w	Numerical rating scale (0-10)	P=0.02
Brady 2004	14	35 w	VAS	P <0.05
Wade 2004	160	6w	VAS	0.243

- Lower spasticity
- reduce pain
- Calm the bladder ?
- Encrease mobility

What can be done against incontinence ?



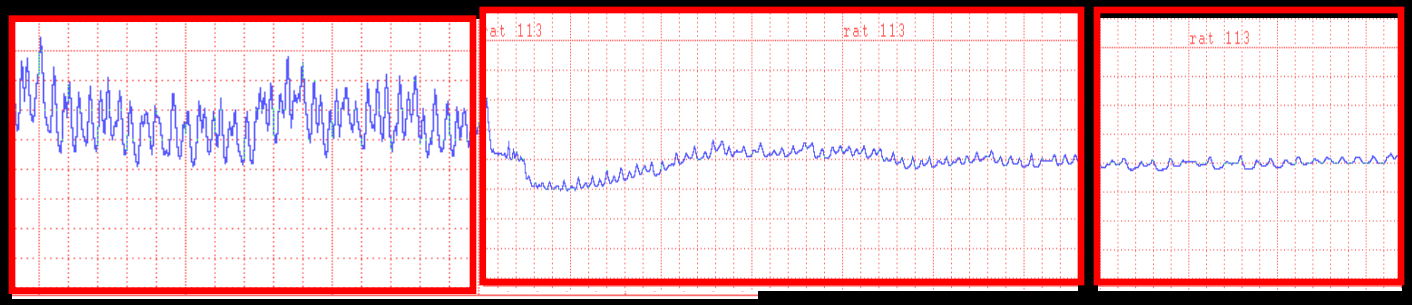
Intraperitoneal administration

AGONIST/ WIN 55,212-2 IP

Before

During

After

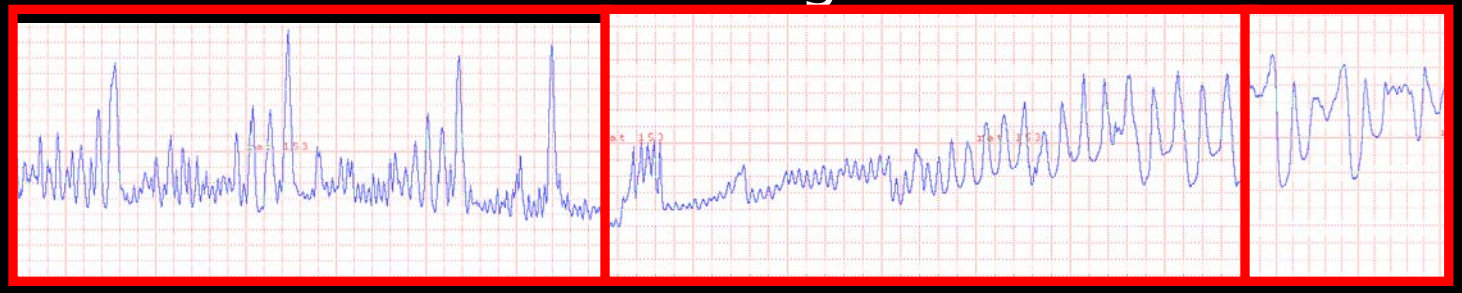


ANTAGONIST/ SR 141716A IP

Before

During

After



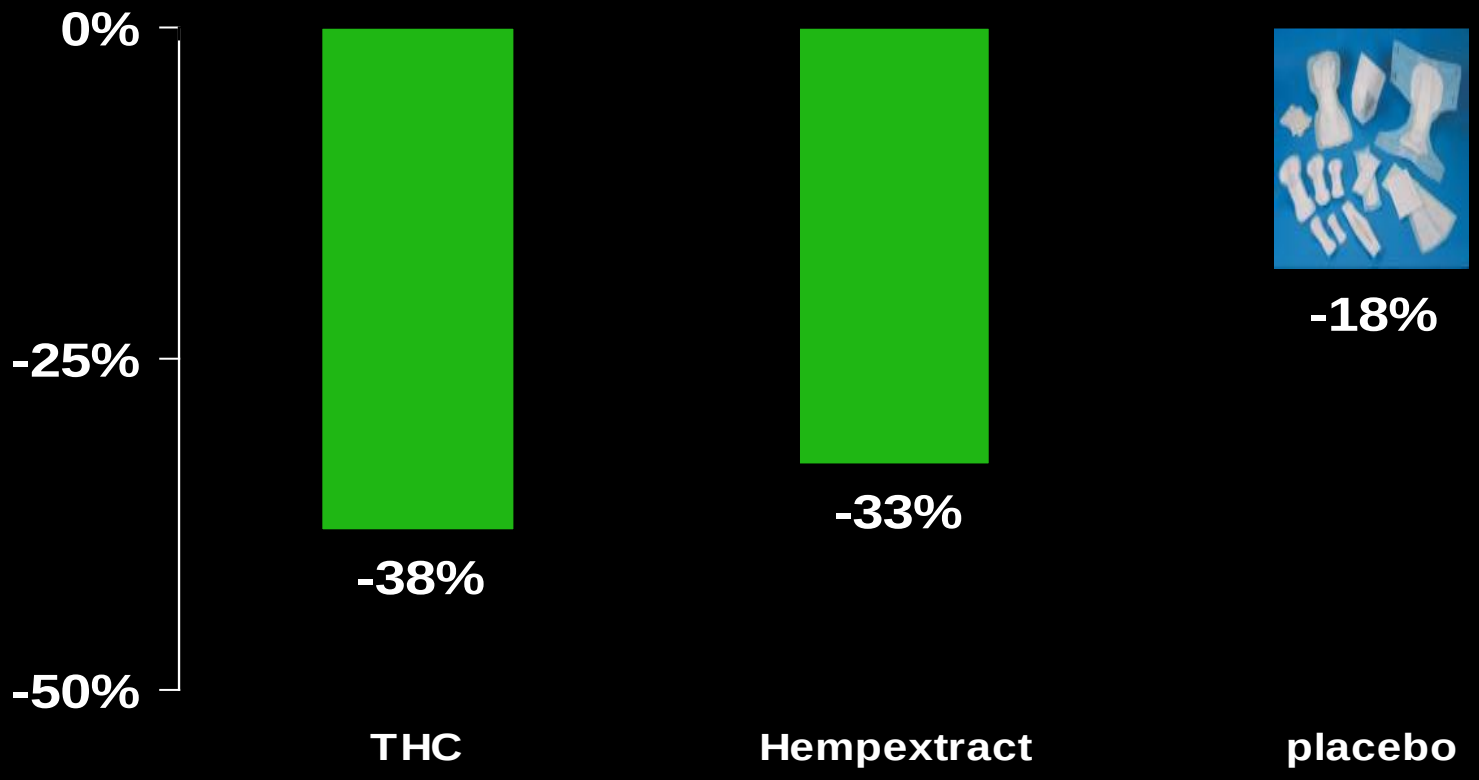
Brady CM et al. *Mult Scler 2004*

- 15 patients
- THC : CBD Spray
- Urinary urgency ↓
- Incontinence episodes ↓
- Nocturia ↓

THC reduces the episodes of incontinence

Freeman RM et al.

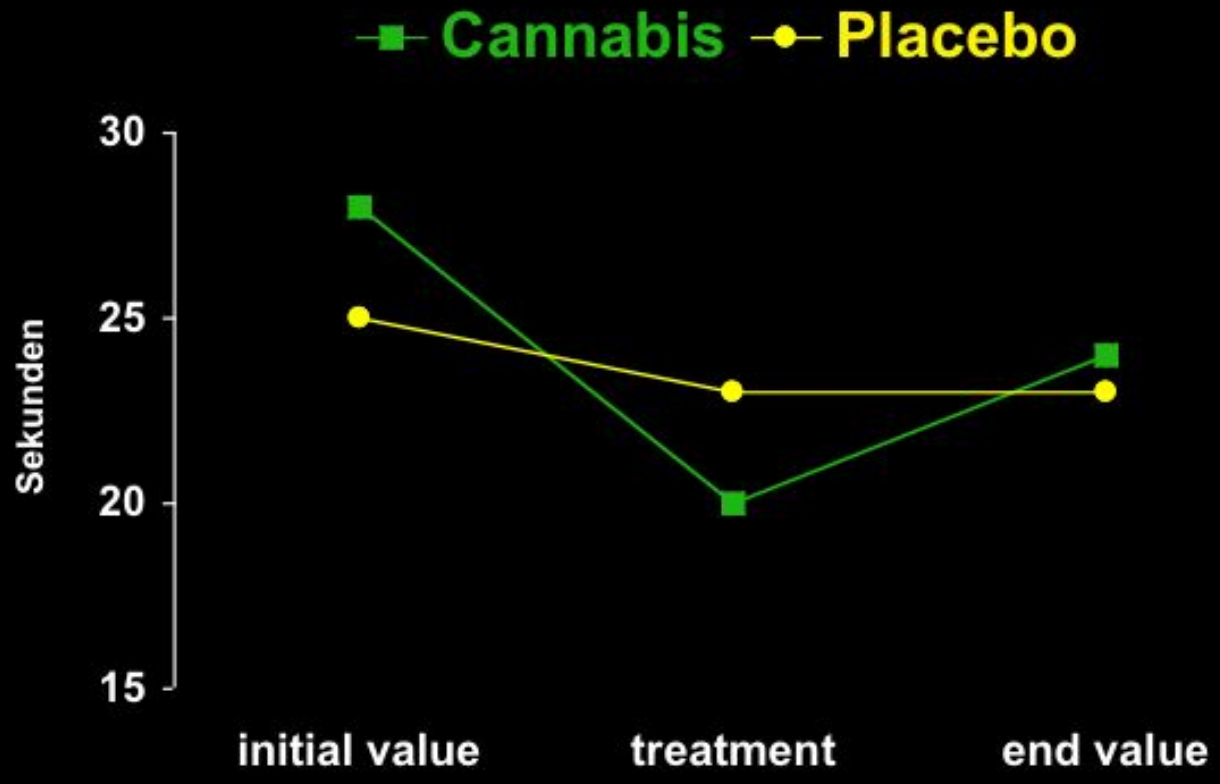
Int.Urogyneacol.J Pelvic floor dysfunction 2006



- Lower spasticity ✓
- reduce pain ✓
- Calm the bladder ✓
- Encrease mobility ?

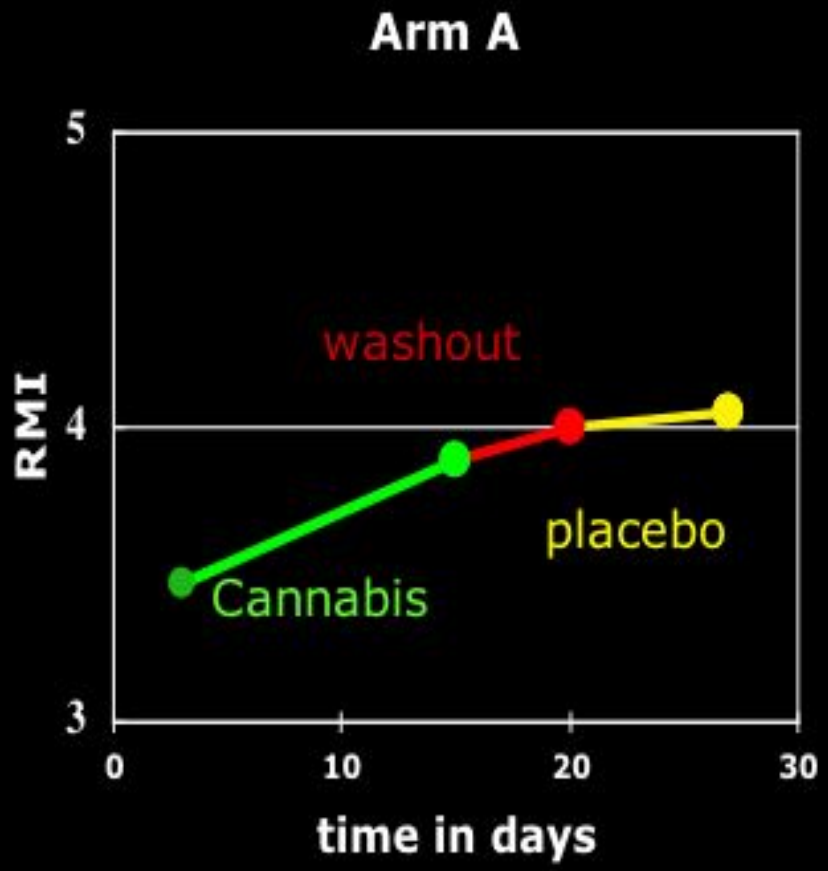
That speeds walking time over 10 m

CAMS Study- J.Zaijcek , *Lancet* 03



Changes in the Rivermead Mobility Index

(Vaney et al. *Mult Scler* 2004)



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 !

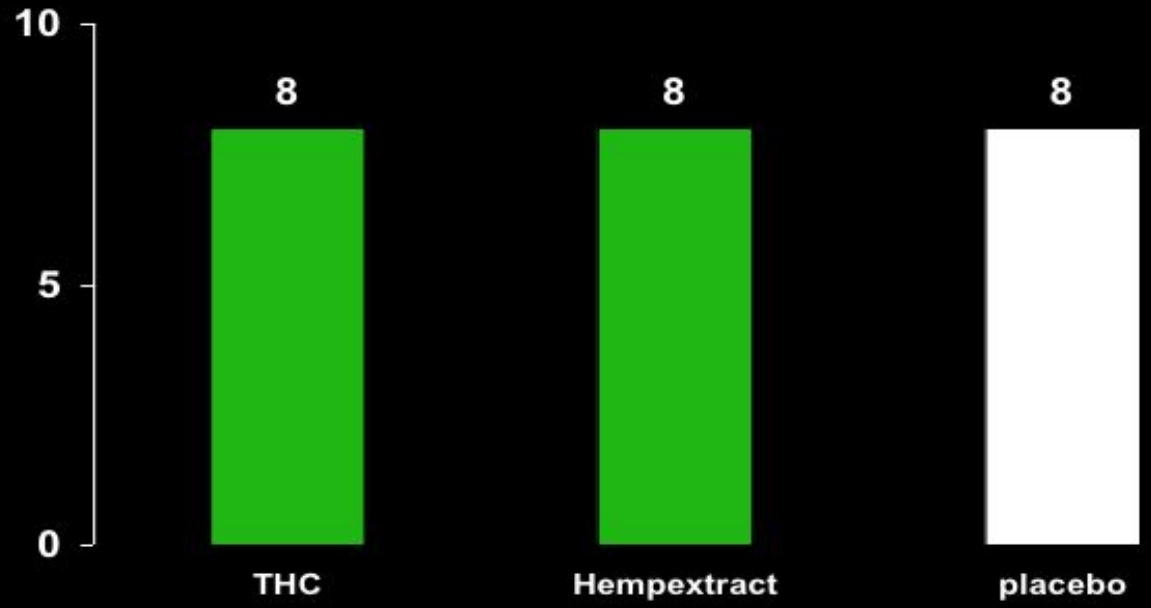
a panacea !?

Sorry , I led you astray !

Pieter Breughel 1568*; la parabole de aveugles.*

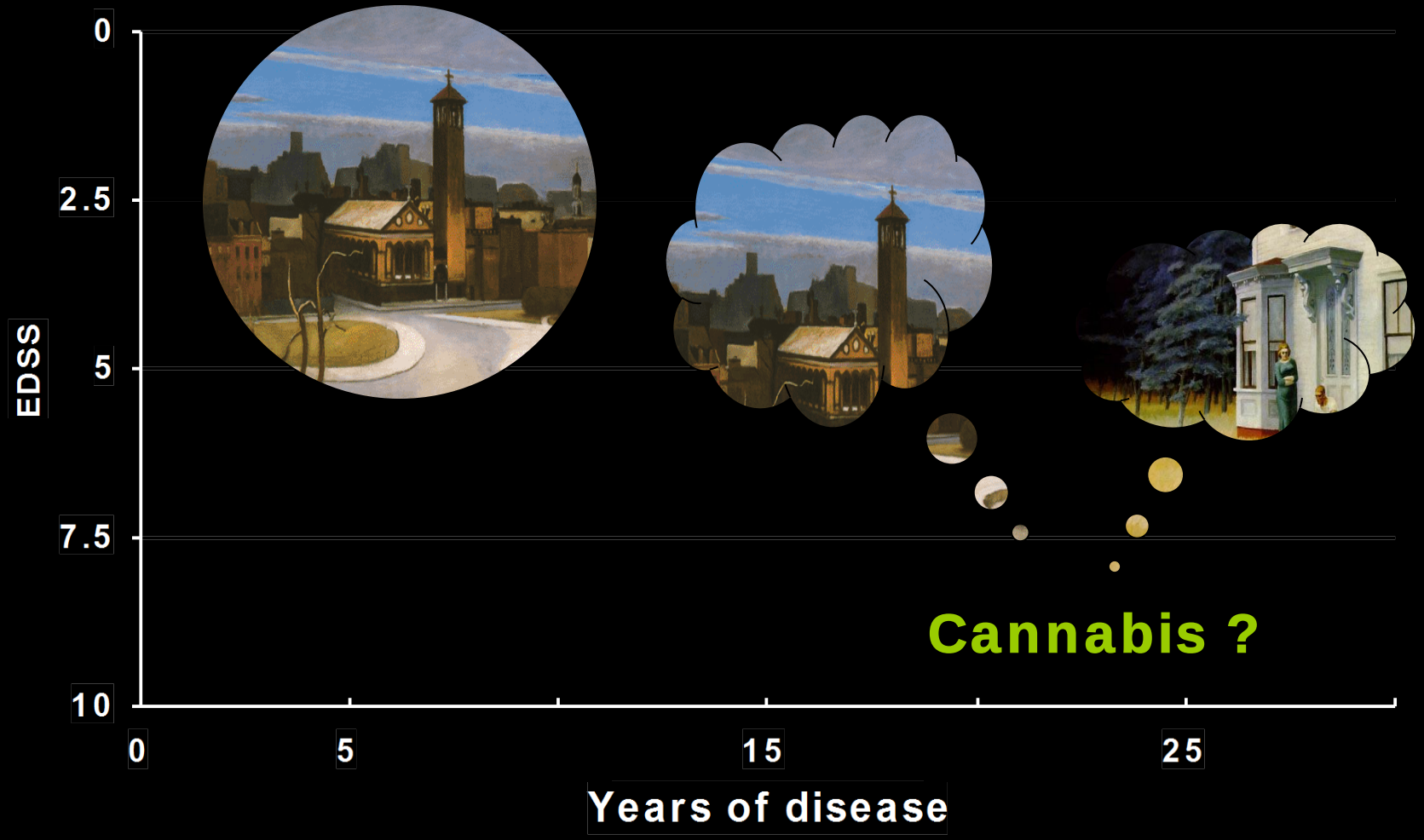
In the follow up study there was no difference in the relapse rate between THC and Placebo

Zajicek J.P. et al. *JNNP* 2005

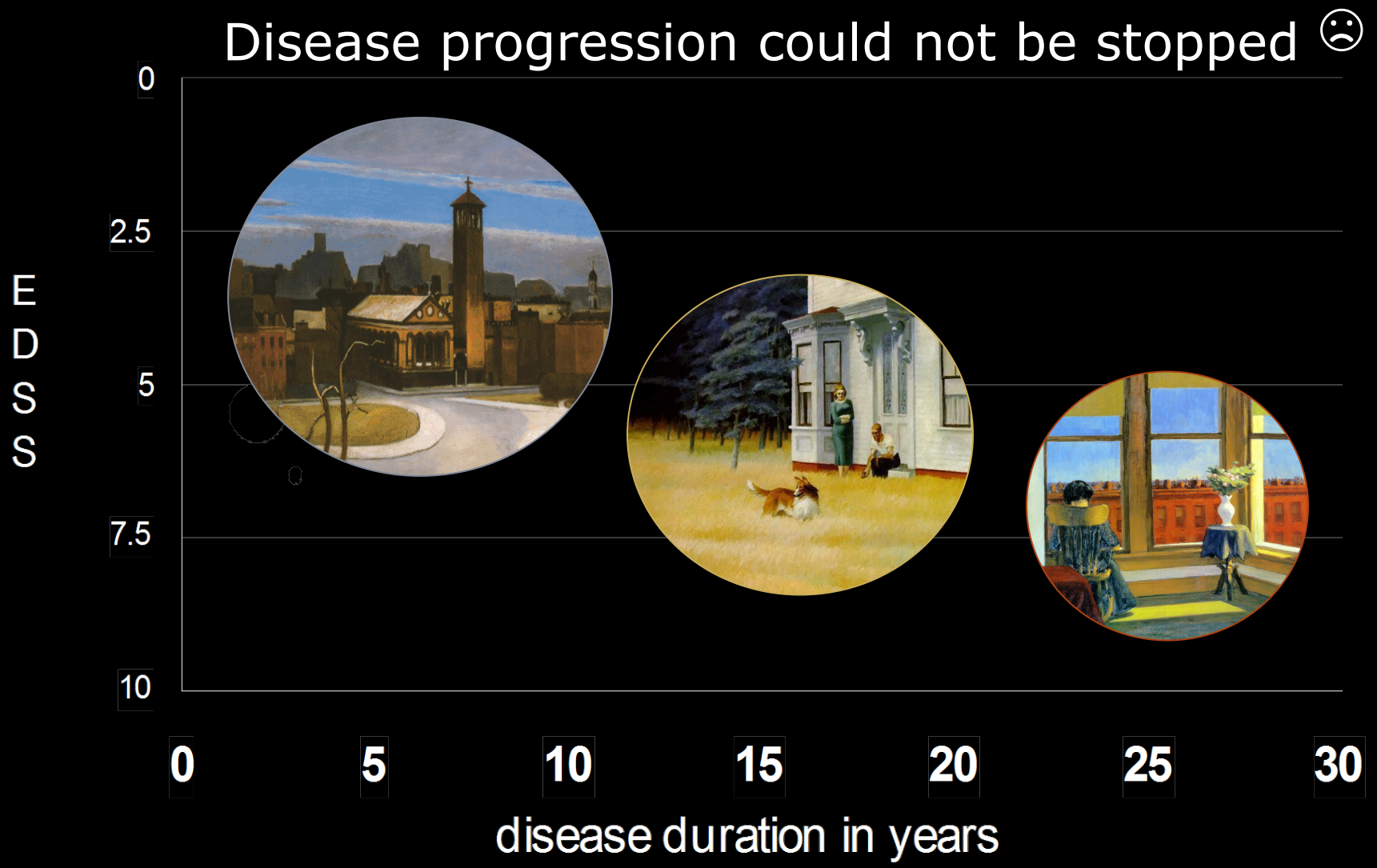


CUPID Study 2008-2011 in the UK with 500 PwMS (2Mio £)

Cannabinoid use in progressive inflammatory brain disease



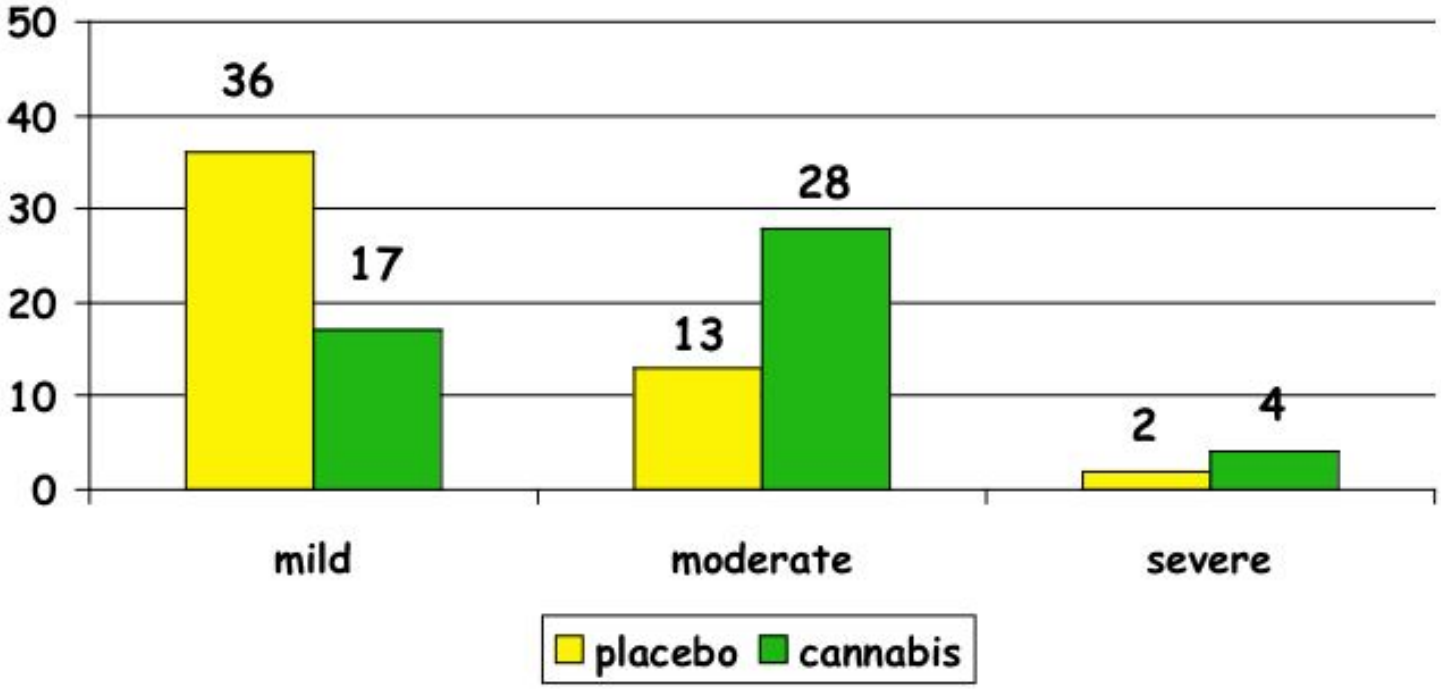
CUPID Study 2008-2011 in the UK with 500 PwMS (2Mio £)



Spasticity as the primary outcome measure was not significantly reduced

Study	n	Ashworth	Spasm / well being
Ungerleider 1987	13	ns	improved
Killestein 2002	16	ns	worse with THC
Zaijcek 2003	667	ns	improved
Vaney 2004	57	ns	Only trends in favour of THC

Side effects were more pronounced in the cannabis group !



Drop out rate = 12 % (7/57)

Reduced the dose =26 % (13/50)

Effects of cannabis on cognition in patients with MS

A psychometric and MRI study

Bennis Pavisian, BAH, Bradley J. MacIntosh, PhD, Greg Szilagyi, BScH, Richard W. Staines, PhD, Paul O'Connor, MD, and Anthony Feinstein, PhD, MD

Conclusions: Patients with MS who smoke cannabis are more cognitively impaired than nonusers. Cannabis further compromises cerebral compensatory mechanisms, already faulty in MS. These imaging data boost the construct validity of the neuropsychological findings and act as a cautionary note to cannabis users and prescribers.

Neurology. 2014 May 27; 82(21): 1879–1887.

Multiple sclerosis

management of multiple sclerosis in primary and secondary care

Issued: October 2014

NICE clinical guideline 186

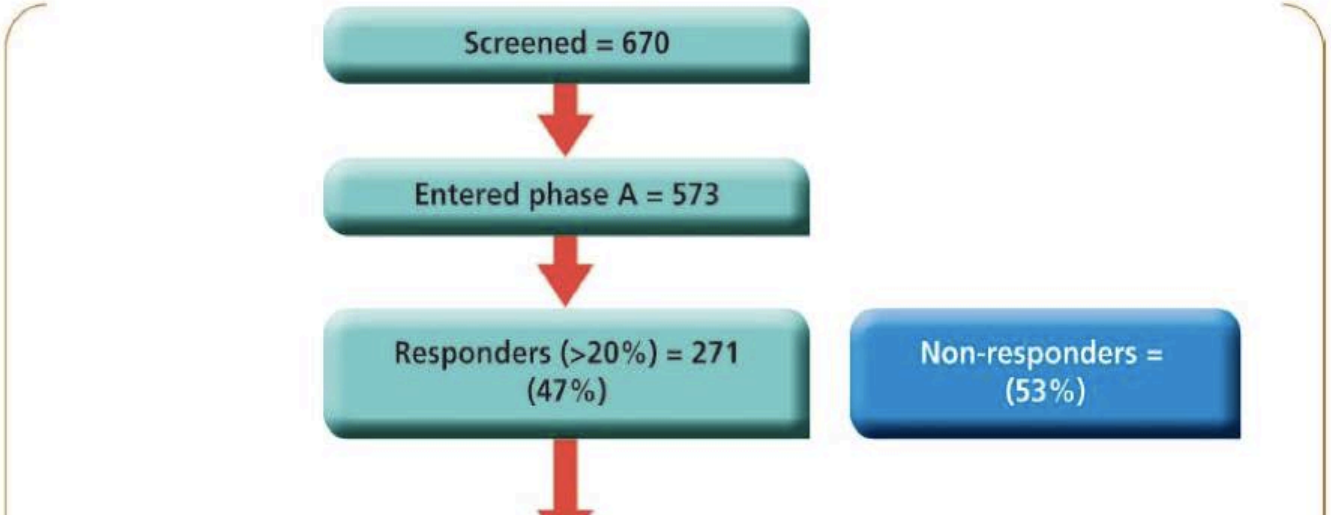
guidance.nice.org.uk/cg186

1.5.23 Do not offer Sativex to treat spasticity in people with MS because it is not a cost effective treatment[9].

Verkehrsfähige Cannabismedikamente SATIVEX®

Sativex third pivotal clinical trial: Patients' disposition

sativex
Delta-9-tetrahydrocannabinol/Cannabidiol



Sativex third pivotal clinical trial results:

Patients improving ≥30% from baseline at the 4 + 12th week

sativex
Delta-9-tetrahydrocannabinol/Cannabidiol

Novotna et al, European Journal of Neurology 2011

Almirall

One shouldn’t throw the baby with the bath water…

SPECIAL ARTICLE

Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders

Report of the Guideline Development Subcommittee of the American Academy of Neurology

Barbara S. Koppel, MD, FAAN
John C.M. Brust, MD, FAAN
Terry Fife, MD, FAAN
Jeff Bronstein, MD, PhD
Sarah Youssof, MD
Gary Gronseth, MD, FAAN
David Gloss, MD

Correspondence to American Academy of Neurology: guidelines@aan.com

ABSTRACT

Objective: To determine the efficacy of medical marijuana in several neurologic conditions.

Methods: We performed a systematic review of medical marijuana (1948–November 2013) to address treatment of symptoms of multiple sclerosis (MS), epilepsy, and movement disorders. We graded the studies according to the American Academy of Neurology classification scheme for therapeutic articles.

Results: Thirty-four studies met inclusion criteria; 8 were rated as Class I.

Conclusions: The following were studied in patients with MS: (1) Spasticity: oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannabinol (THC) are probably effective, for reducing patient-centered measures; it is possible both OCE and THC are effective for reducing both patient-centered and objective measures at 1 year. (2) Central pain or painful spasms (including spasticity-related pain, excluding neuropathic pain): OCE is effective; THC and nabiximols are probably effective. (3) Urinary dysfunction: nabiximols is probably effective for reducing bladder voids/day; THC and OCE are probably ineffective for reducing bladder complaints. (4) Tremor: THC and OCE are probably ineffective; nabiximols is possibly ineffective. (5) Other neurologic conditions: OCE is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson disease. Oral cannabinoids are of unknown efficacy in non-chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy. The risks and benefits of medical marijuana should be weighed carefully. Risk of serious adverse psychopathologic effects was nearly 1%. Comparative effectiveness of medical marijuana vs other therapies is unknown for these indications. **Neurology® 2014;82:1556–1563**

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY.

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Objective: To determine the efficacy of medical marijuana in several neurologic conditions.

levodopa-induced dyskinesias in patients with Parkinson disease. Oral cannabinoids are of unknown efficacy in non-chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy. The risks and benefits of medical marijuana should be weighed carefully. Risk of serious adverse psychopathologic effects was nearly 1%. Comparative effectiveness of medical marijuana vs other therapies is unknown for these indications. *Neurology*® 2014;82:1556-1563

MS:

(1) **Spasticity:** oral cannabis extract (OCE) is effective, and nabiximols and tetrahydrocannabinol (THC) are probably effective, for reducing patient- centered measures

(2) **Central pain or painful spasms** (including spasticity-related pain, excluding neuropathic pain): OCE is effective; THC and nabiximols are probably effective.

(3) **Urinary dysfunction**: nabiximols is probably effective for reducing bladder voids/day;

Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

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CONCLUSIONS AND RELEVANCE There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

... In the meantime, when other treatment inadequatly controls spasticity, oral cannabinoids should be considered... (L.Metz, *Lancet* 2003)

The therapeutic value of cannabinoids in MS: real or imaginary ?

...ve drugs on the web building
...r a new species of indian spider
r BR et al. *Indian Med Sci* 1969; 10:550-8

Danke für ihre Aufmerksamkeit