

CMSC 06 Scottsdale AZ

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

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**Reynolds Sir J.R.
Therapeutic Uses &
Toxic Effects
of Cannabis Indica.
(*Lancet* 1890)**

**"One of the most valuable
medicines we possess..."**

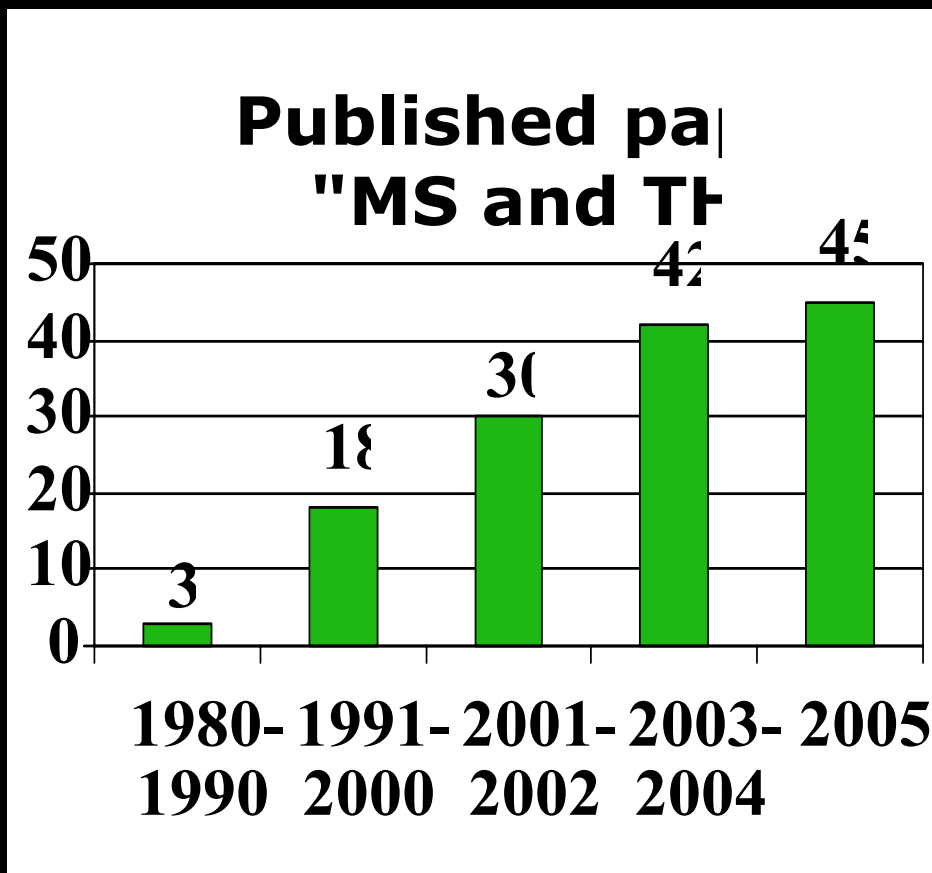
Sirven JI and Berg AT

**Marijuana as a treatment
for Epilepsy and MS ?**

Neurology

2004;62:1924-25.

***....or is it cruelly hoaxing on
vulnerable patients who have
lost hope ?"***



**Use of
Cannabinoids
in MS :
Is it
evidence based ?**

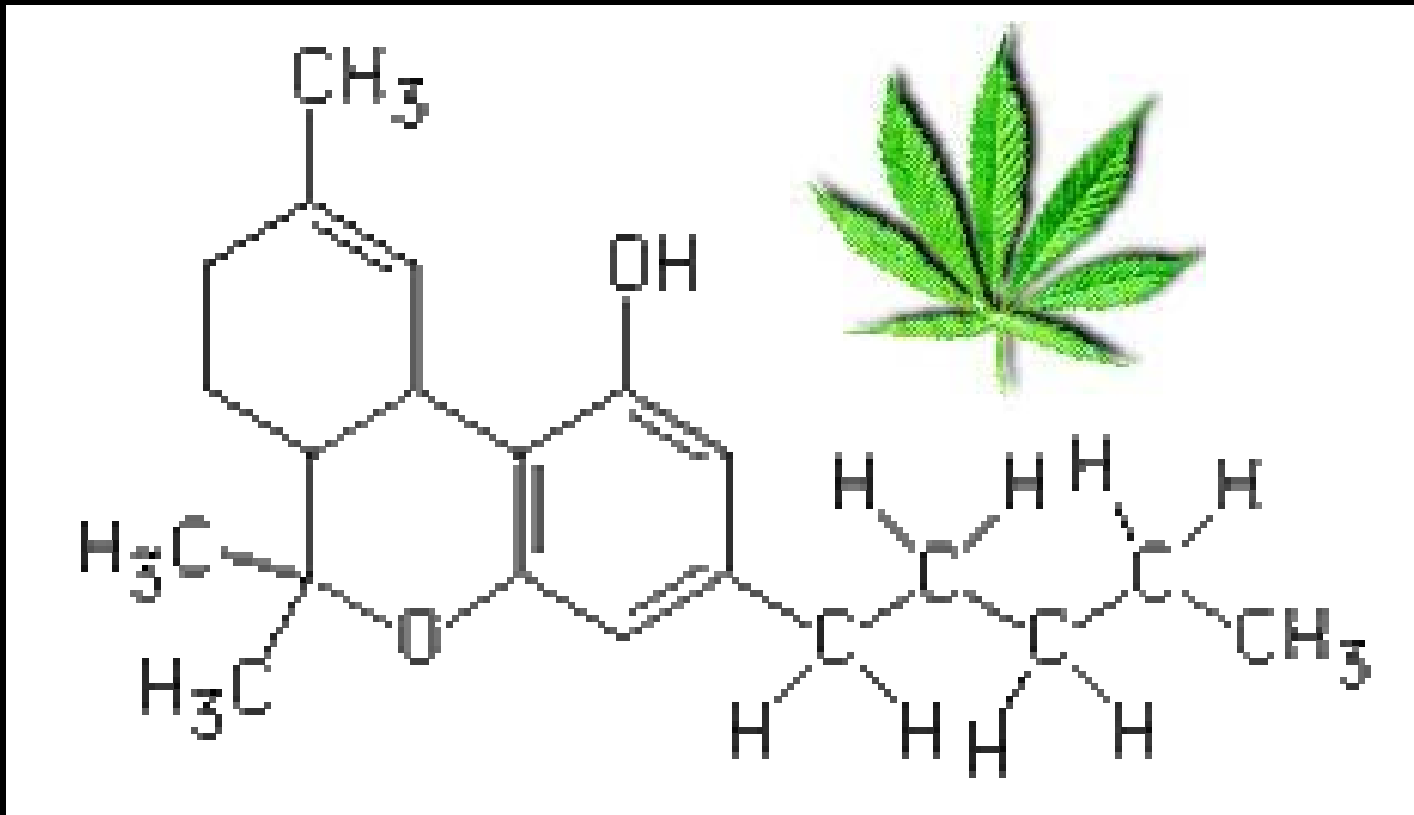
Properties of an ideal drug for MS?

- **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**
- **Promote sleep**

What about this molecule ?



Δ^9 -Tetrahydrocannabinol (THC)

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

Background knowledge I

- Neurodegenerative changes are of major importance in disease progression
(Trapp et al. *NEJM* 1998)

Background knowledge II

- Correlation axonal loss, reduced NAA and accumulation of permanent disability

(Bjartmar et al.
Ann.Neurology 2000)

Background knowledge III

- Likewise axonal damage is a feature in experimental allergic encephalomyelitis (EAE)
(Baker D et al. *J.Immunology* 1990)

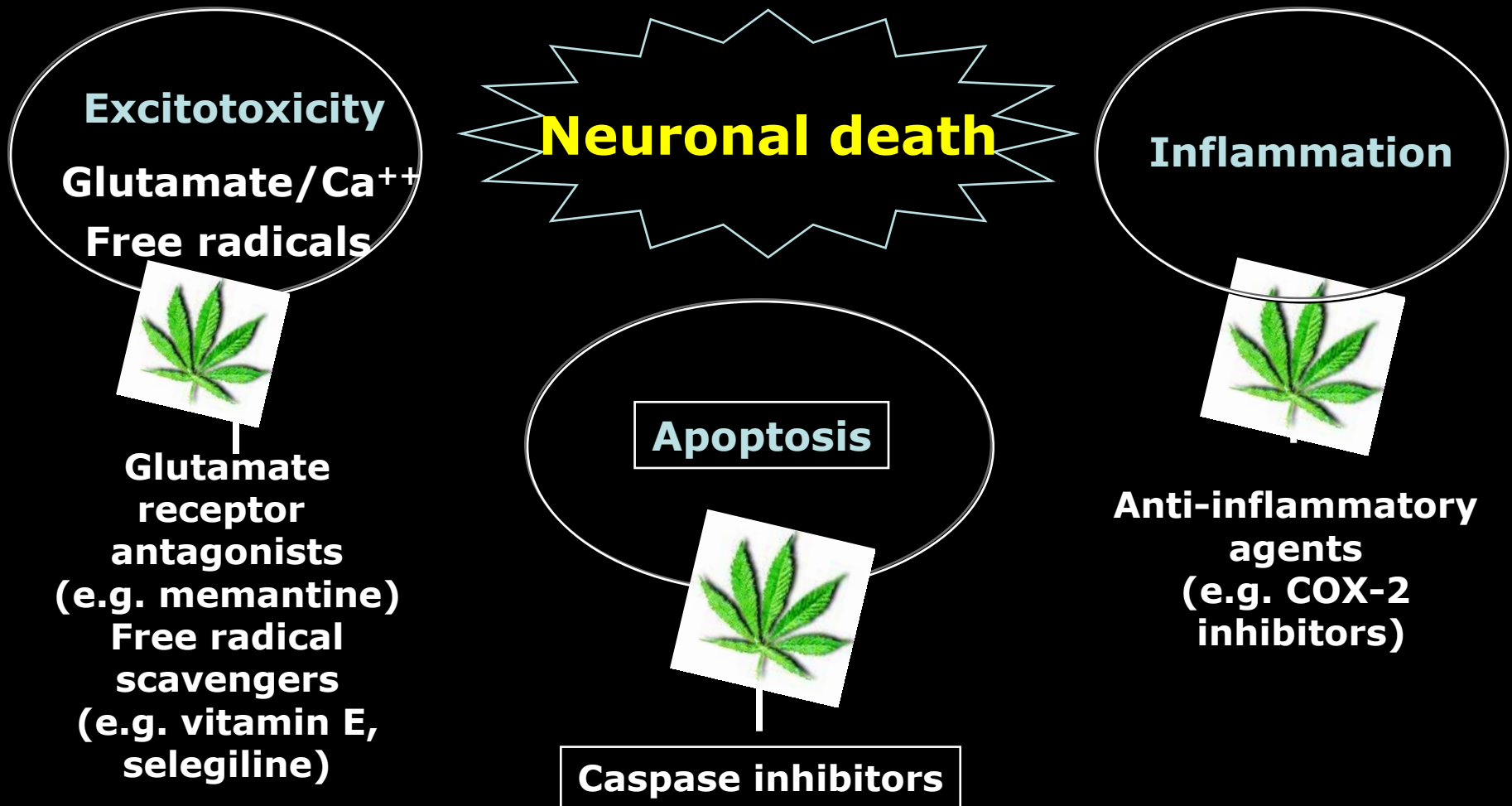
Cannabinoids slow down progression...

- **as anti-oxidants**

- **as neuroprotective agents**

- In *vitro* evidence that cannabinoids can reduce glutamate (=neurotoxin) release. (Hampson AJ et al. *Proc Natl Acad Sci USA* 1998)
- CB1 deficient mice tolerate inflammatory and exotoxic insult poorly and develop substantial neurodegeneration following immun attack. (Pryce G et al. *Brain* 2003)

Putative Factors Contributing to Neurodegeneration and Therapeutic Targets



Cannabinoids slow down progression...

- **as anti-oxidants**
- **as neuroprotective agents**
- CB1 receptor activation has been shown to reduce oligodendrocyte apoptosis in vitro (Molina- Holgado E. *J Neuroscience* 2002)
- Case report of women developing MS after receiving a CB1 antagonist for obesity (Van Oosten BW *Multiple Sclerosis* 2004)

• **Slow down progression** 

• **No serious side effects ?**

• **Low cost**

• **Favorable effect on symptoms**

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**

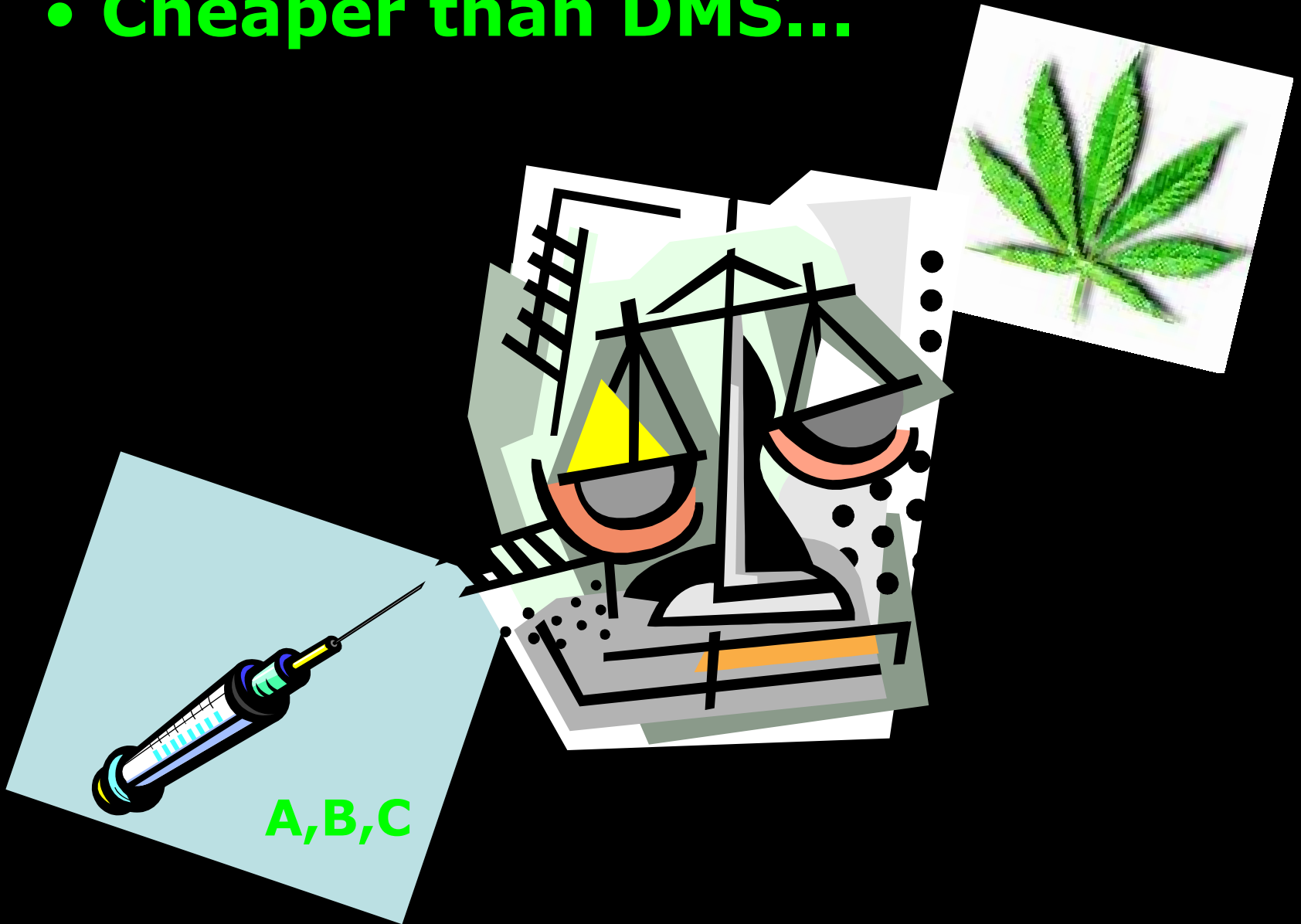
„Number of serious events are similar across the treatments, with slightly more events in the placebo group“

- **Wade DT et al. Mult Scler 2004**




„Most people achieved benefit without troublesome side effects“

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

- Cheaper than DMS...



A,B,C

- **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**
- **Promote sleep**

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

• **Lower spasticity** 

• **reduce pain ?**

• **Calm the bladder**

• **Increase mobility**

• **Promote sleep**

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**

- **Promote sleep**

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; Jaggar et al., 1998)**

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 ?**
- **Promote sleep**

CAMS Study- J.Zaijcek , *Lancet* 03

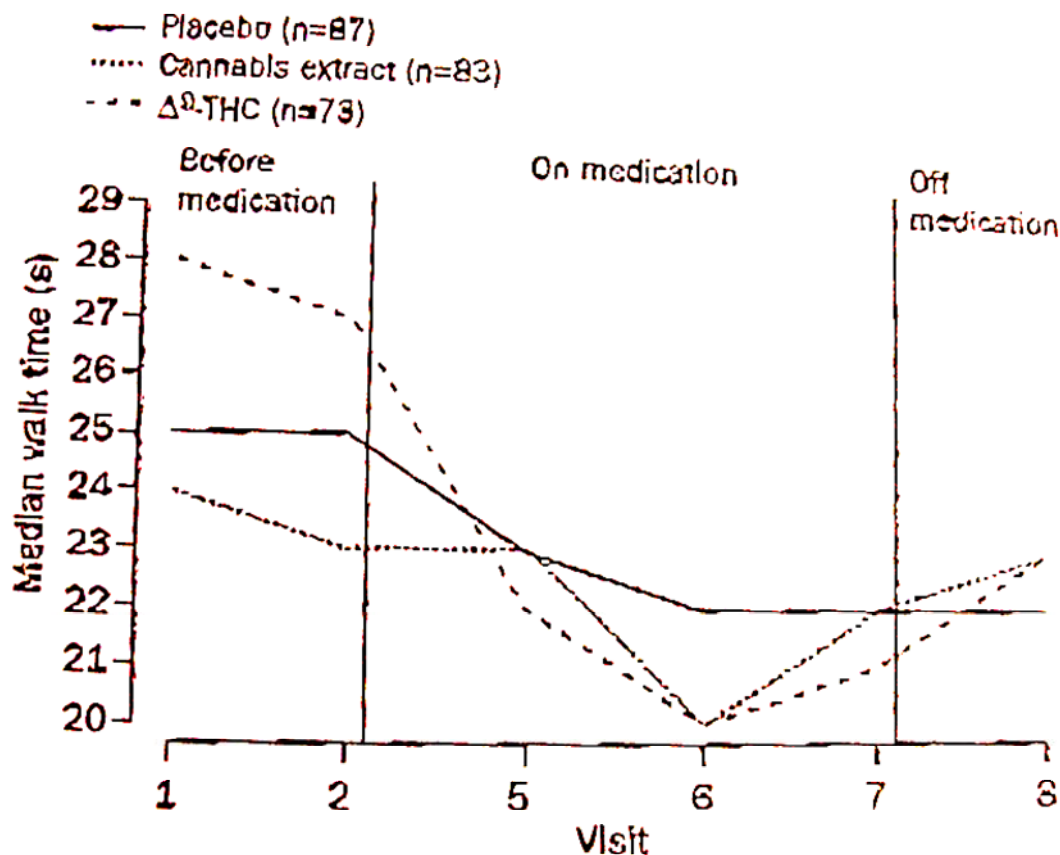


Figure 5: Median 10 m walk times by visit and treatment group. Only cases in which patients were ambulatory at baseline and walk information was available at all six visits included. In cases where patient was physically unable to walk a suitably large value was substituted.

- **Lower spasticity ✓**
- **reduce pain ✓**
- **Calm the bladder ✓**
- **Increase mobility ✓**
- **Promote sleep ?**

Promote sleep

- **Zaijcek 0.025**
- **Vaney 0.07**
- **Brady < 0.05 (only THC)**



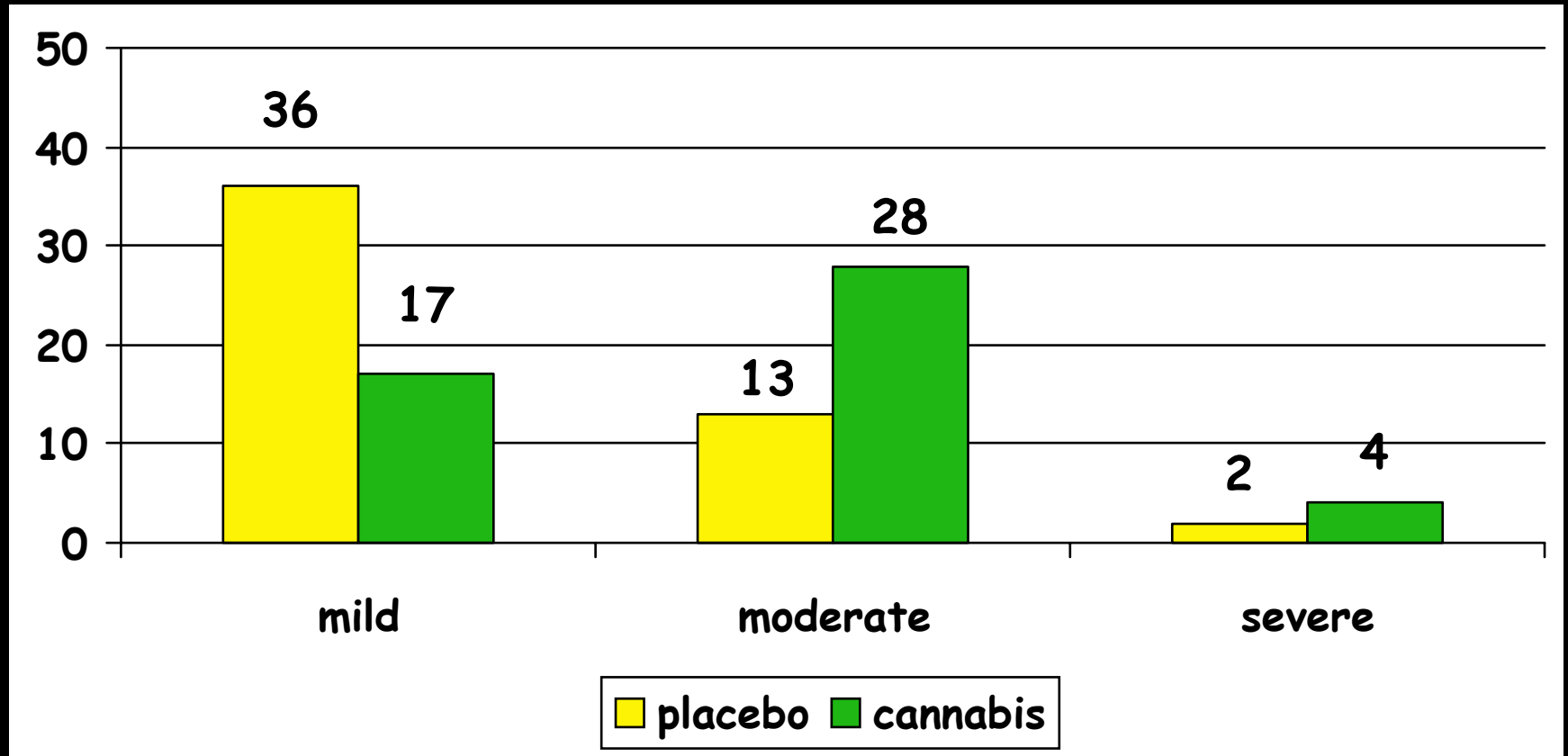
a panacea ! ?

Sorry, I have led you astray...

Was spasticity reduced according to the primary outcome measure ?

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)

However..

**There is not enough evidence
not to perform placebo
controlled trial with cannabis!**

Open questions for further studies:

- **Spray or Capsules ?**
- **Only THC or THC /CBD ?**
- **Inhibitors of cannabinoid degradation**
- **Long term effect...neuroprotection**

**In the meantime,
what should be are attitude ?**



**Hildegard von
Bingen
1098-1179**

**Prevalence of
medicinal cannabis
use among
patients 15 %.**

Clark AJ et al.
Neurology 2004

**... In the meantime, when other
treatment inadequately controls
spasticity, oral cannabinoids should be
considered...**

(L.Metz, *Lancet* 2003)