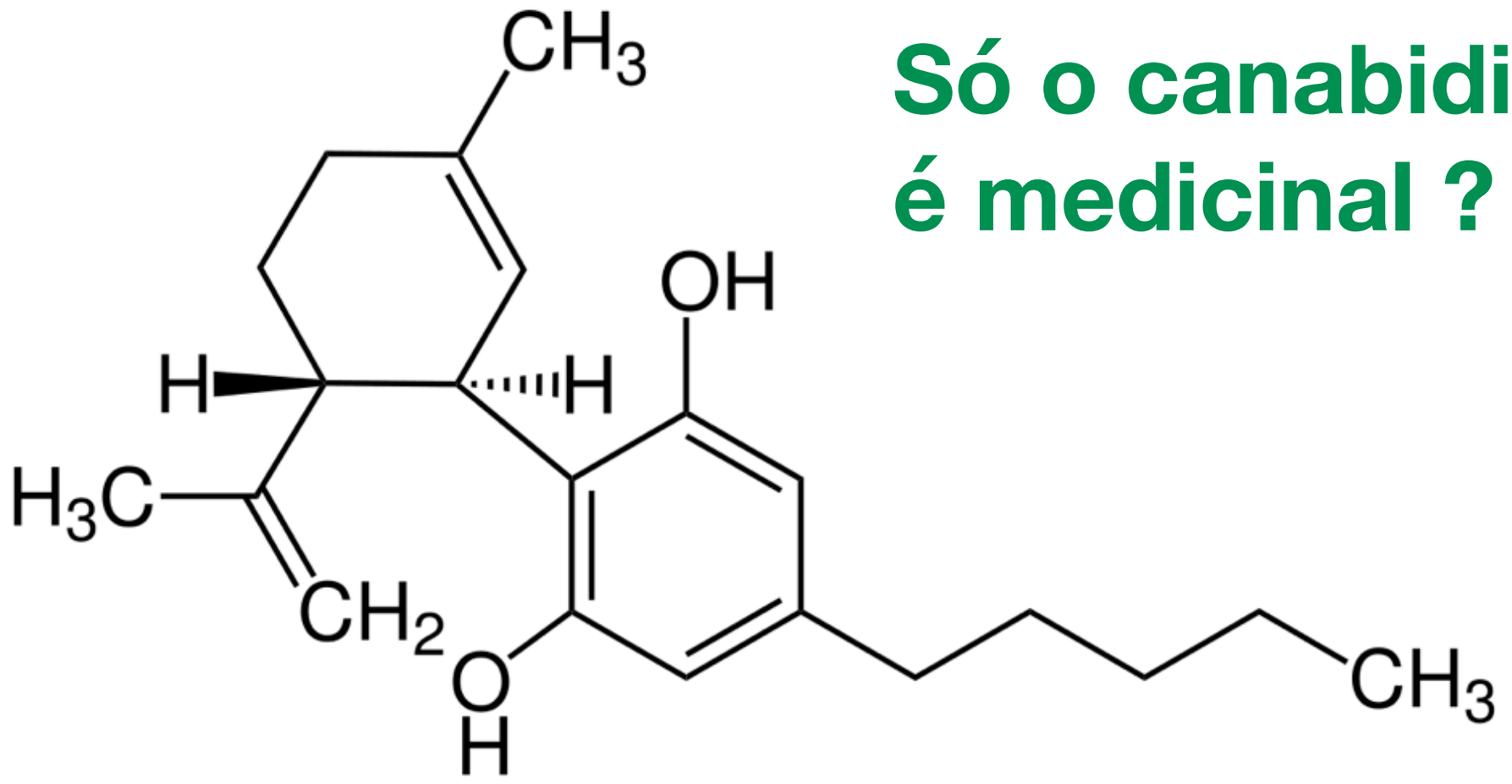
CÂMARA DOS DEPUTADOS
COMISSÃO ESPECIAL - PL 0399/15 - MEDICAMENTOS
FORMULADOS COM CANNABIS



Só o canabidiol é medicinal ?

http://bit.ly/maconha-versus-CBD
http://bit.ly/efeito-entourage

Contribuições por Dr. Fabricio Pamplona
Apresentado em 10/12/2019

UNIVERSIDADE FEDERAL
DE SANTA CATARINA

MAX-PLANCK-GESELLSCHAFT

INSTITUTO D'OR
PESQUISA E ENSINO

Entourage
PHYTOLAB

CannMed

ICRS

TEDx

SXSW

3 produtos já registrados no mundo

THC

THC/CBD

CBD

Dronabinol (THC)

Eur Neurol. 2017 Nov; 78(5-6): 320–329.
Published online 2017 Oct 26. doi: 10.1159/000481089: 10.1159/000481089

Dronabinol Is a Safe Long-Term Treatment Option for Neuropathic Pain Patients

Sebastian Schimrigk,[a,*] Martin Marziniak,[b] Christine Neubauer,[c] Eva Maria Kugler,[c] Gudrun Werner,[c] and Dimitri Abramov-Sommariva[c]

[a]Märkische Kliniken GmbH, Klinikum Lüdenscheid, Klinik für Neurologie, Lüdenscheid, Germany
[b]Kbo-Isar-Amper-Klinikum München-Ost, Klinik für Neurologie, Haar, Germany
[c]Department Clinical Research International, Bionorica SE, Neumarkt, Germany

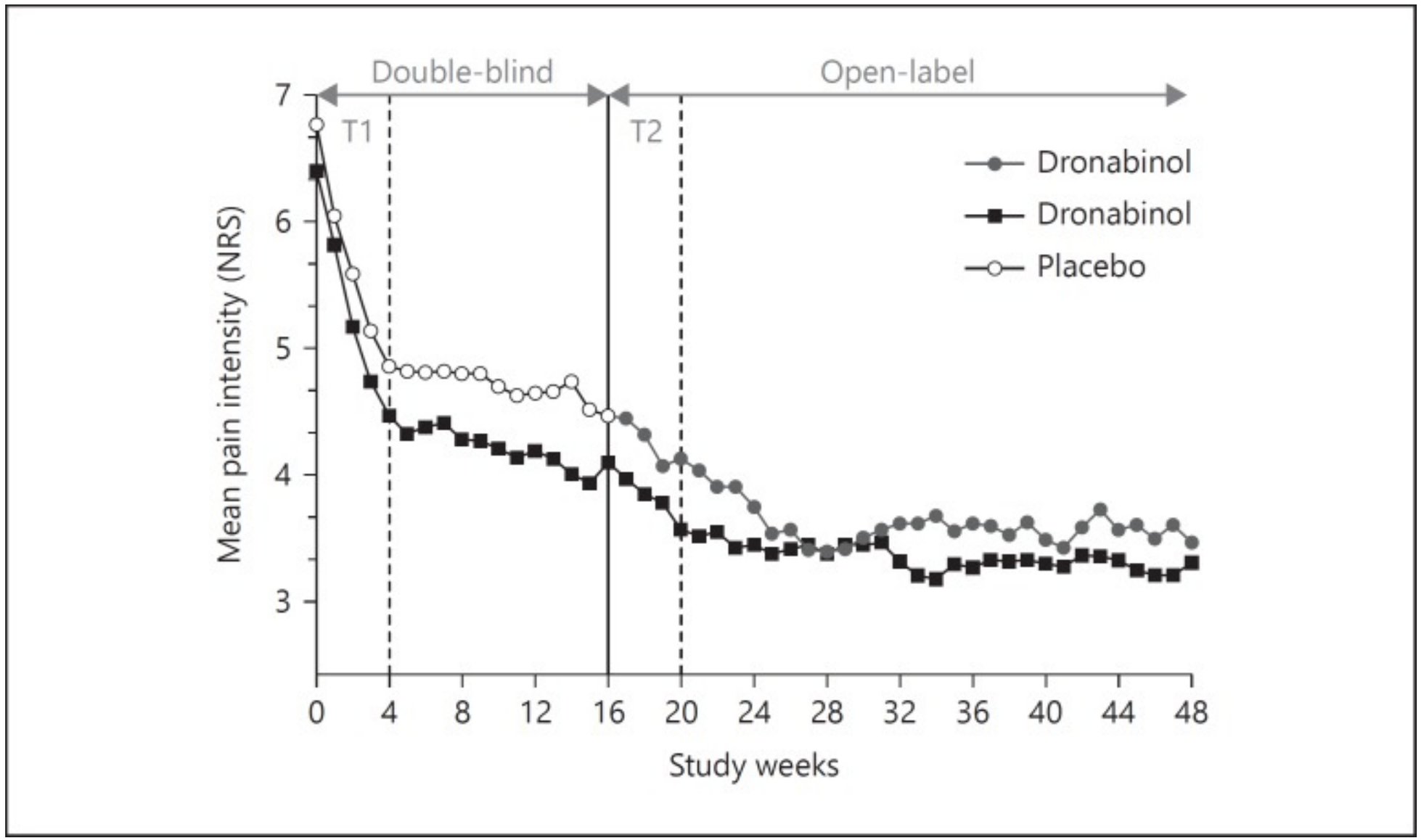
Critério
Pacientes com dor neuropatia crônica (NRS para dor >4)
Mantido tratamento com amitriptilina/gabapentina,
tramadol se necessário em dor aguda

Tratamento
Dose-alvo THC (7.5 - 15 mg), titulação em 2.5 mg a cada 5 dias
16 semanas vs. placebo + 32 semanas follow-up + 48 follow-up

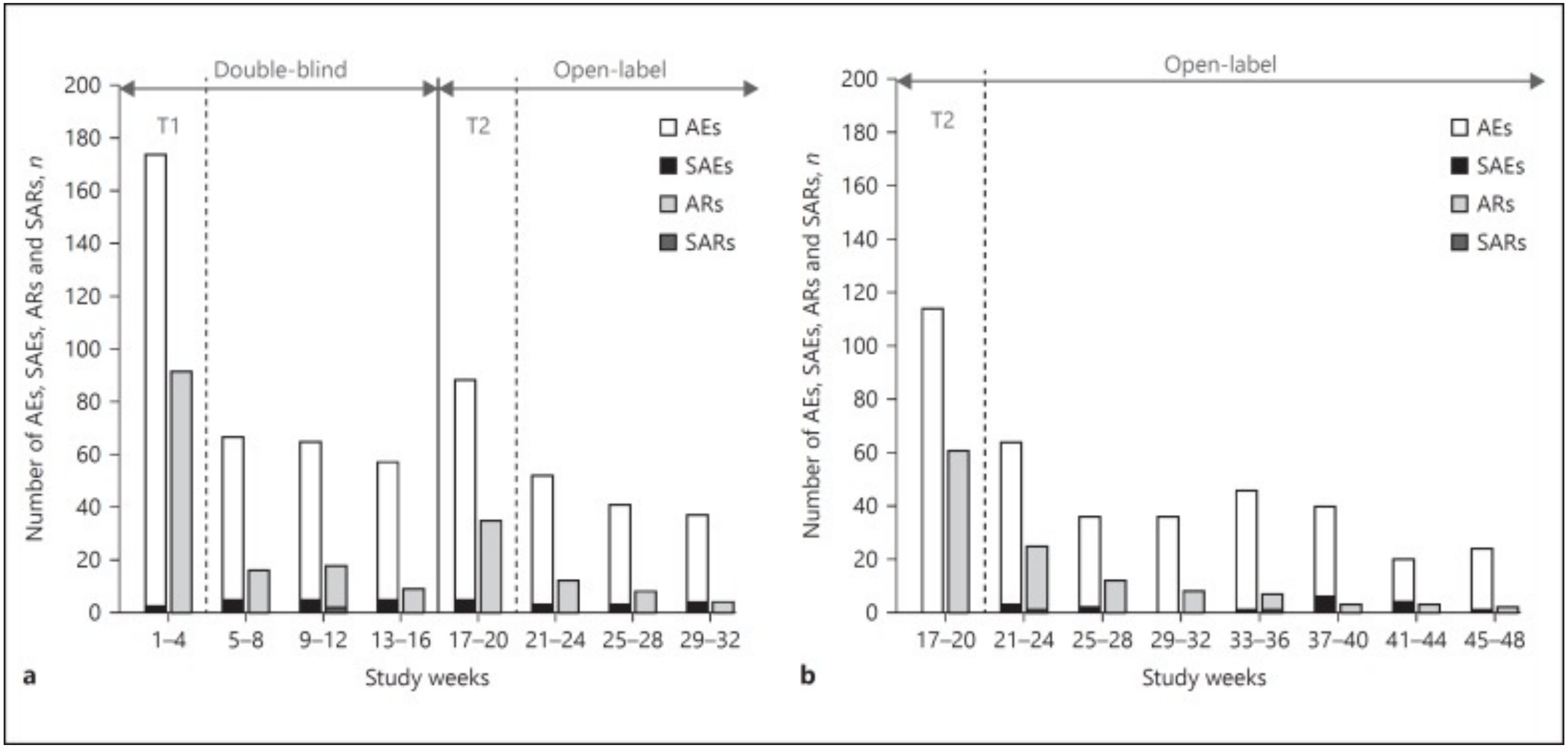
Avaliação
NRS para dor (1-11) e SF-36 para QoL
Ocorrências de EA, SEA, sinais vitais e bioquímicos

Dronabinol (THC)

Dose média: 12.7 mg/dia v.o.
Tempo de tratamento médio: 382 dias (aprox. 1 ano)
240 pacientes vs placebo / 100 pacientes follow-up



Dronabinol (THC)



Sativex (THC:CBD)

Clin Ther. 2007 Sep;29(9):2068-79.

Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial.

Rog DJ[1], Nurmikko TJ, Young CA.

Author information

Abstract

BACKGROUND: Central neuropathic pain (CNP), pain initiated or caused by a primary lesion or dysfunction of the central nervous system, occurs in ~28% of patients with multiple sclerosis (MS). Delta(9)-Tetrahydrocannabinol/cannabidiol (THC/CBD), an endocannabinoid system modulator, has demonstrated efficacy for up to 4 weeks in randomized controlled trials in the treatment of CNP in patients with MS.

OBJECTIVE: The purpose of this extension was to establish long-term tolerability and effectiveness profiles for THC/CBD (Sativex (R), GW Pharmaceuticals plc, Salisbury, United Kingdom) oromucosal spray in CNP associated with MS.

METHODS: This uncontrolled, open-label trial was an indefinite-duration extension of a previously reported 5-week randomized study in patients with MS and CNP. In the initial trial, patients were randomized to placebo or THC/CBD. Patients were only required to maintain their existing analgesia in the randomized study. In the open-label trial they could vary their other analgesia as required. All patients (placebo and THC/CBD) who completed the randomized trial commenced the open-label follow-up on THC/CBD (27 mg/mL: 25 mg/mL). Patients titrated their dosage, maintaining their existing analgesia. The primary end point of the trial was the number, frequency, and type of adverse events (AEs) reported by patients. Secondary end points included changes from baseline in 11-point numerical rating scale (NRS-11) neuropathic pain score, hematology and clinical chemistry test results, vital signs, trial drug usage, and intoxication visual analogue scale scores.

RESULTS: Sixty-six patients were enrolled in the randomized trial; 64 (97%) completed the randomized trial and 63 (95%) entered the open-label extension (race, white, 100%; sex, male, 14 [22%]; mean [SD] age, 49 [8.4] years [range, 27-71 years[). The mean (SD) duration of open-label treatment was 463 (378) days (median, 638 days; range, 3-917 days), with 34 (54%) patients completing >1 year of treatment with THC/CBD and 28 (44%) patients completing the open-label trial with a mean (SD) duration of treatment of 839 (42) days (median, 845 days; range, 701-917 days). Mean NRS-11 pain scores in the final week of the randomized trial were 3.8 in the treatment group and 5.0 in the placebo group. In the 28 (44%) patients who completed the 2-year follow up, the mean (SD) NRS-11 pain score in the final week of treatment was 2.9 (2.0) (range, 0-8.0). Fifty-eight (92%) patients experienced > or =1 treatment-related AE. These AEs were rated by the investigator as mild in 47 (75%) patients, moderate in 49 (78%), and severe in 32 (51%). The most commonly reported AEs were dizziness (27%), nausea (18 %), and feeling intoxicated (11%). Two treatment-related serious AEs (ventricular bigeminy and circulatory collapse) were judged to be treatment-related. Both serious AEs occurred in the same patient and resolved completely following a period of discontinuation. Eleven (17%) patients experienced oral discomfort, 4 persistently. Regular oral examinations revealed that 7 (11%) patients developed white buccal mucosal patches and 2 (3%) developed red buccal mucosal patches; all cases were deemed mild and resolved. Seventeen (25%) patients withdrew due to AEs. The mean number of sprays and patients experiencing intoxication remained stable throughout the follow-up trial.

CONCLUSIONS: THC/CBD was effective, with no evidence of tolerance, in these select patients with CNP and MS who completed approximately 2 years of treatment (n = 28). Ninety-two percent of patients experienced an AE, the most common of which were dizziness and nausea. The majority of AEs were deemed to be of mild to moderate severity by the investigators.

Sativex (THC:CBD)

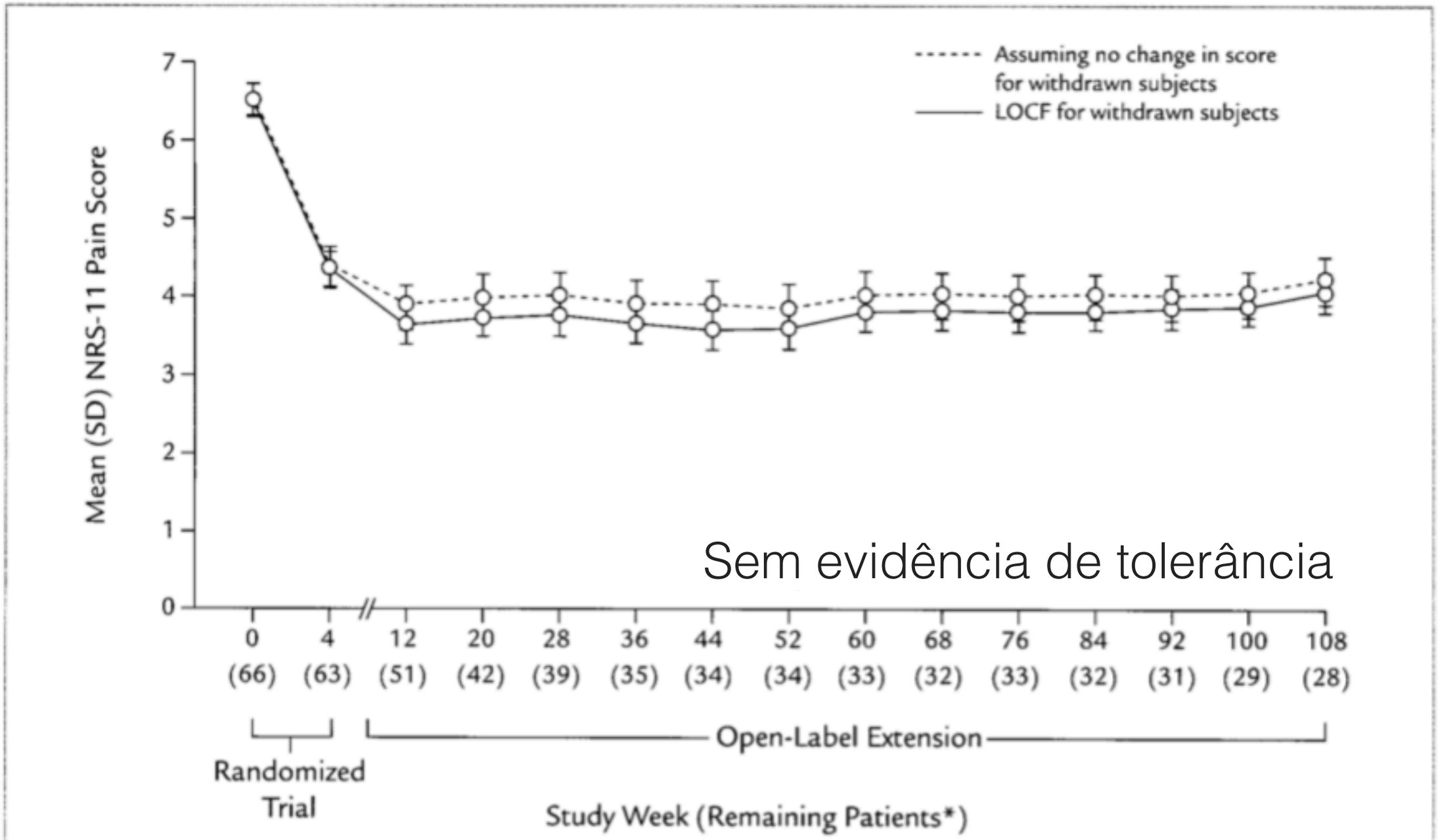


Figure 2. Mean (SD) 11-point numerical rating scale (NRS-11) pain scores throughout the randomized[6] and open-label trial with last-observation-carried-forward (LOCF) for withdrawn patients. *The number of patients remaining on trial at each time point are for illustrative purposes.

Sativex (THC:CBD)

Poucos EAs
EAs comuns a outros medicamentos SNC

Table II. Treatment-related adverse events (AEs) occurring in >5% of patients with multiple sclerosis (MS) receiving Δ^9-tetrahydrocannabinol/cannabidiol.

AEs	Patients, No. (%)
Patients with ≥1 AE	58 (92.1)
Gastrointestinal disorders	
Nausea	11 (17.5)
Diarrhea	6 (9.5)
Mouth plaque	6 (9.5)
Vomiting, NOS	5 (7.9)
Constipation	4 (6.3)
Dry mouth	4 (6.3)
Mouth ulceration	4 (6.3)
Tooth discoloration	4 (6.3)
General disorders and administration-site conditions	
Feeling intoxicated	7 (11.1)
Edema, peripheral	6 (9.5)
Fatigue	4 (6.3)
Weakness	4 (6.3)
Nervous system disorders	
Dizziness	17 (27.0)
Balance impaired, NOS	6 (9.5)
Headache, NOS	5 (7.9)
MS aggravated	5 (7.9)
Respiratory, thoracic, and mediastinal disorders	
Pharyngitis	4 (6.3)

NOS = not otherwise specified.

Sativex (THC:CBD)

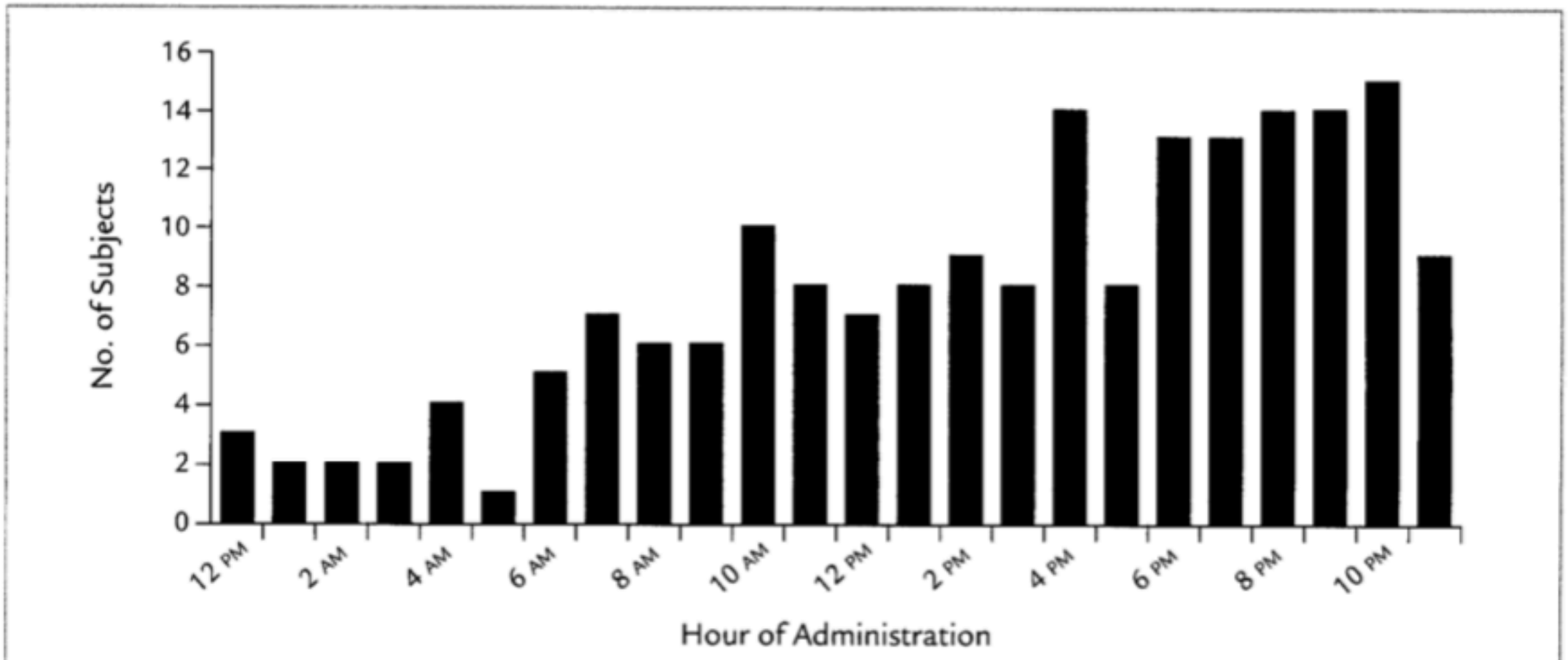


Figure 3. Time of Δ^9-tetrahydrocannabinol/cannabidiol administration by number of patients taking ≥1 spray in each hour on ≥1 of the last 7 days of treatment in patients with multiple sclerosis who completed the open-label trial (n = 28).

Padrão peculiar de auto-administração

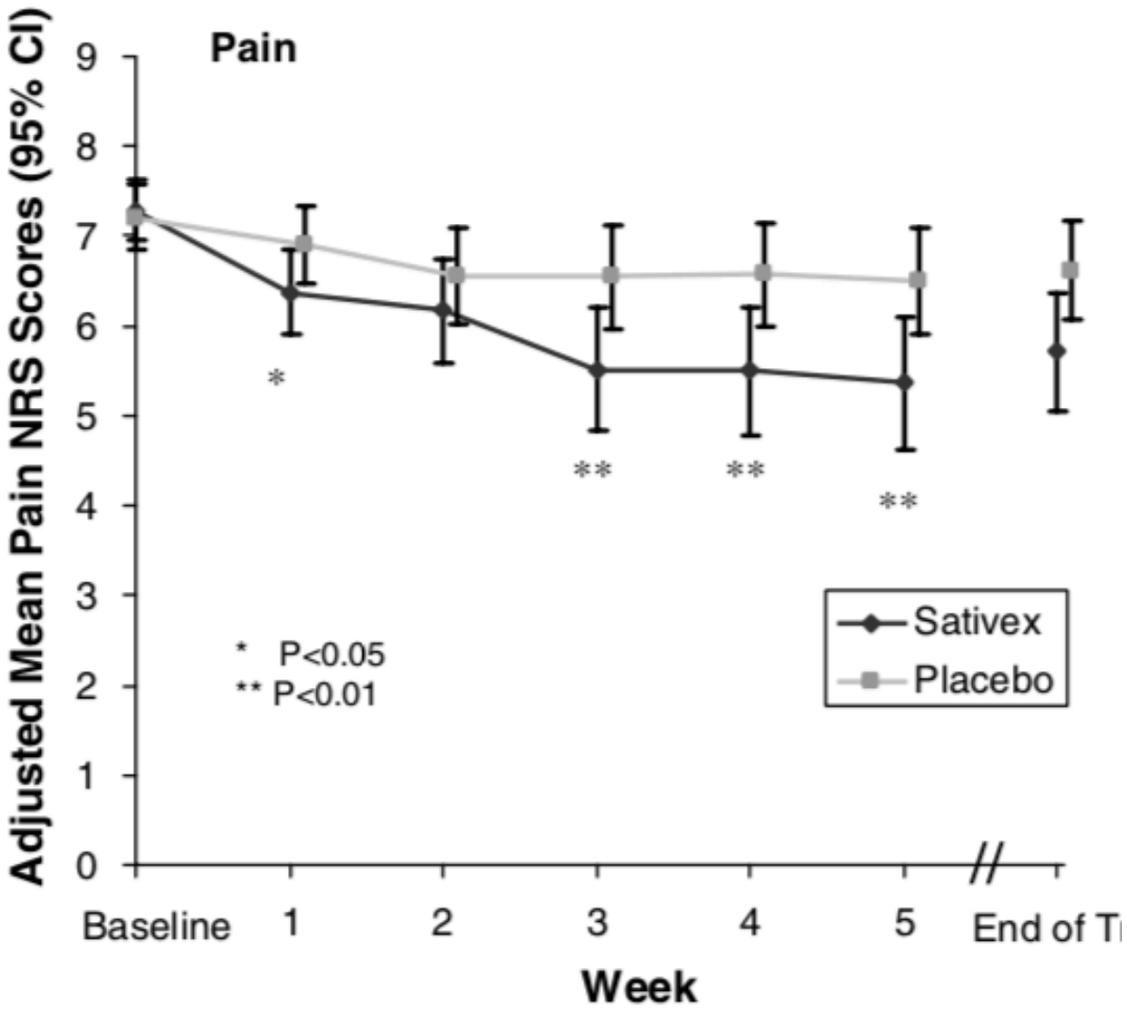
Sativex (THC:CBD)

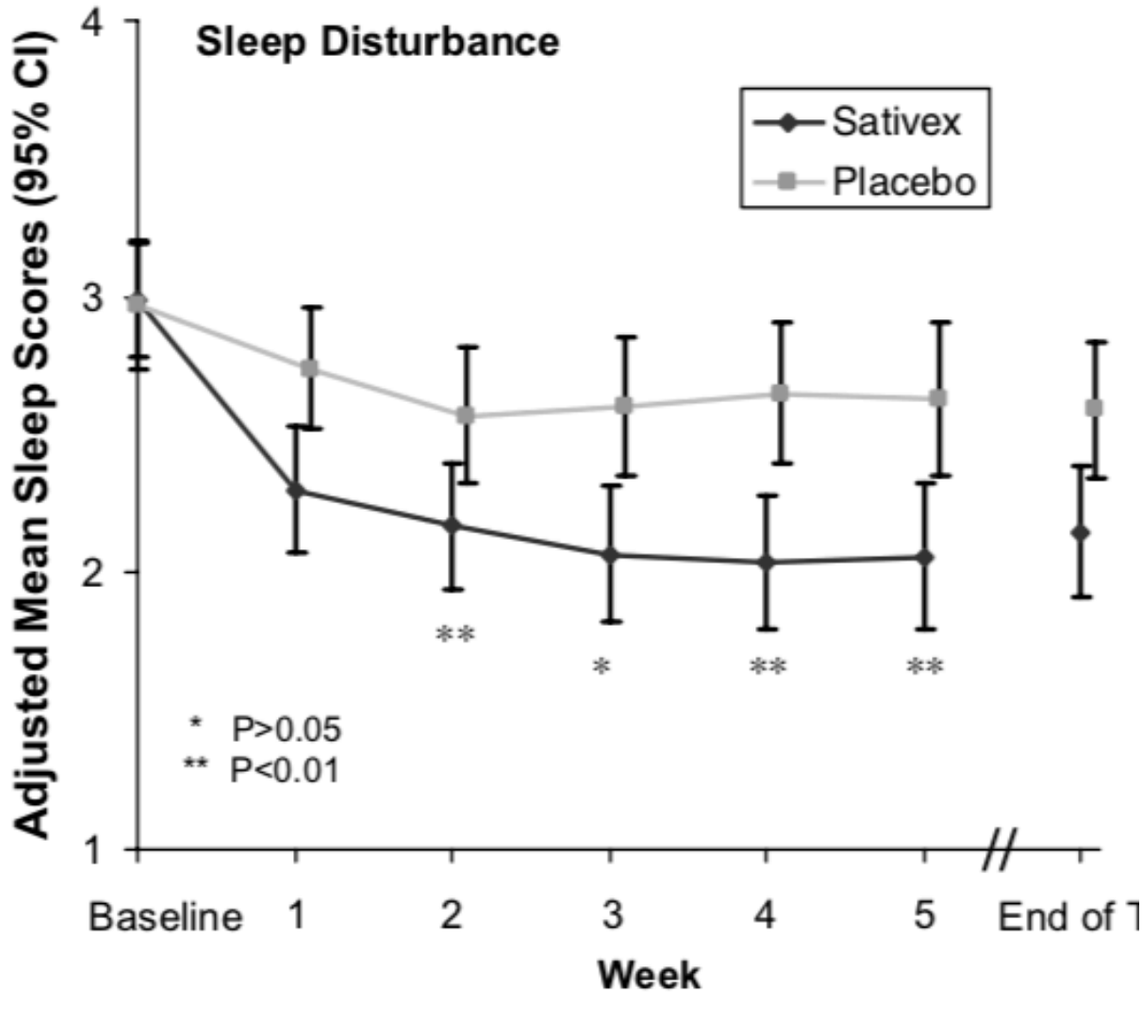
Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

Turo J. Nurmikko [a,*], Mick G. Serpell [b], Barbara Hoggart [c], Peter J. Toomey [d], Bart J. Morlion [e], Derek Haines [f]

Cannabinoids are known to have analgesic properties. We evaluated the effect of oro-mucosal sativex, (THC: CBD), an endocannabinoid system modulator, on pain and allodynia, in 125 patients with neuropathic pain of peripheral origin in a five-week, randomised, double-blind, placebo-controlled, parallel design trial. Patients remained on their existing stable analgesia. A self-titrating regimen was used to optimise drug administration. Sixty-three patients were randomised to receive sativex and 62 placebo. The mean reduction in pain intensity scores (primary outcome measure) was greater in patients receiving sativex than placebo (mean adjusted scores −1.48 points vs. −0.52 points on a 0–10 Numerical Rating Scale ($p = 0.004$; 95% CI: −1.59, −0.32). Improvements in Neuropathic Pain Scale composite score ($p = 0.007$), sleep NRS ($p = 0.001$), dynamic allodynia ($p = 0.042$), punctate allodynia ($p = 0.021$), Pain Disability Index ($p = 0.003$) and Patient's Global Impression of Change ($p < 0.001$) were similarly greater on sativex vs. placebo. Sedative and gastrointestinal side effects were reported more commonly by patients on active medication. Of all participants, 18% on sativex and 3% on placebo withdrew during the study. An open-label extension study showed that the initial pain relief was maintained without dose escalation or toxicity for 52 weeks.

Sativex (THC:CBD)





Sativex (THC:CBD)

Table 5
Treatment emergent adverse events (AEs) experienced by 3 or more subjects (~ 5%) receiving sativex compared with placebo and the % of subject who withdrew due to these AEs

Adverse event	Number (%) of patients experiencing AEs		Number (%) of patients who withdrew due to AE	
	Sativex ($N = 63$)	Placebo ($N = 62$)	Sativex ($N = 63$)	Placebo ($N = 62$)
Dizziness	18 (28.6)	9 (14.5)	2 (3.2)	0
Nausea	14 (22.2)	7 (11.3)	1 (1.6)	0
Fatigue	13 (20.6)	5 (8.1)	0	0
Dry mouth	11 (17.5)	3 (4.8)	0	0
Vomiting	8 (12.7)	3 (4.8)	2 (3.2)	0
Feeling drunk	6 (9.5)	1 (1.6)	1 (1.6)	0
Headache	6 (9.5)	9 (14.5)	0	0
Diarrhoea	4 (6.3)	0	2 (3.2)	0
Nasopharyngitis	4 (6.3)	2 (3.2)	0	0
Anorexia	4 (6.3)	0	1 (1.6)	0
Somnolence	4 (6.3)	1 (1.6)	0	1 (1.6)
Abdominal pain upper	3 (4.8)	1 (1.6)	0	0
Disturbance in attention	3 (4.8)	0	0	0
Memory impairment	3 (4.8)	0	0	0

The Brief Repeatable Battery of Neuropsychological Tests (BRB-N) was given to 85 patients (43 randomised to sativex and 42 to placebo). No difference was seen between groups assessed for cognitive function with this method at the beginning and end of treatment (Table 6).

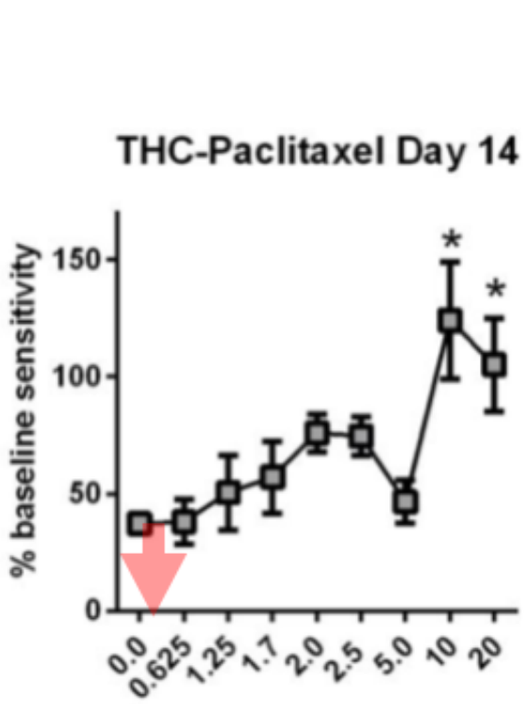
Intoxication scores (SD) remained low throughout the study, peaking after the self-titration week at 8.0 (15.4) for sativex and 3.0 (7.9) for placebo on a 0–100 scale, respectively. Five patients on sativex and 2 patients on placebo scored more than 40/100 during the maintenance period.

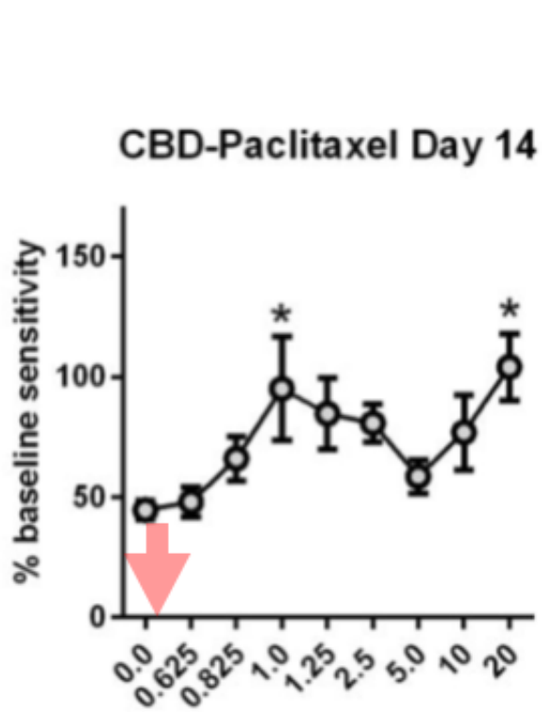
CBD+THC: Sinergia

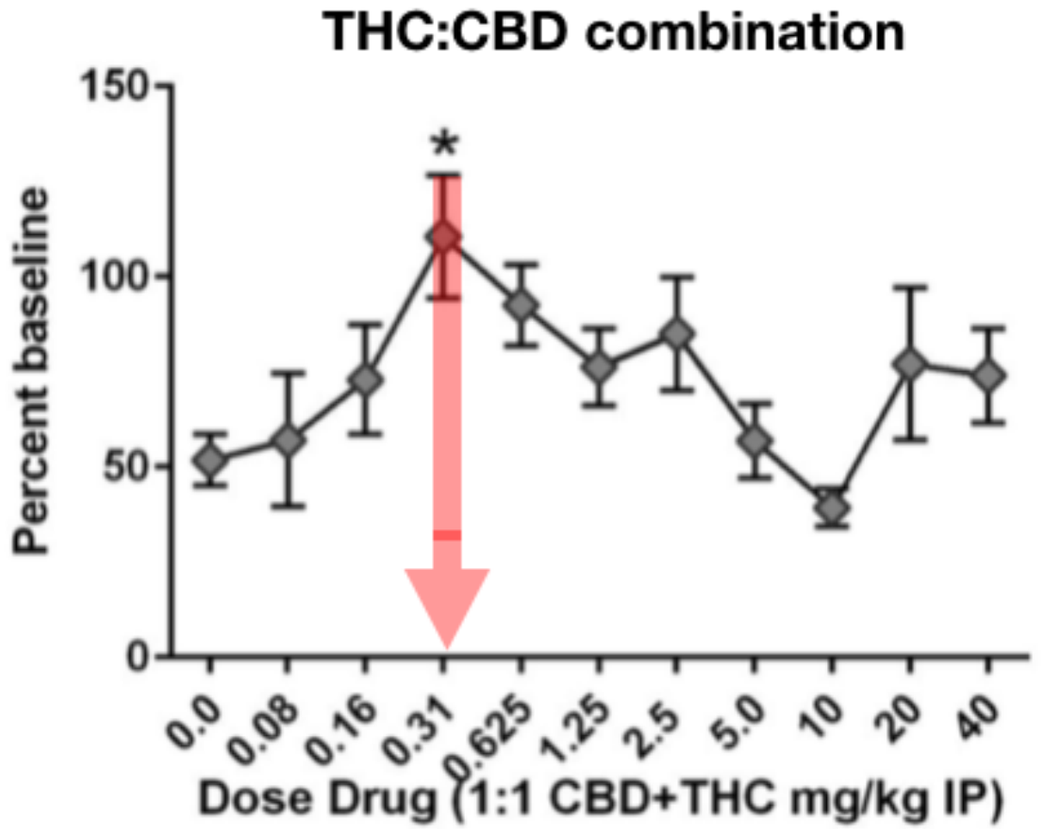
Br J Pharmacol. 2017 Sep;174(17):2832-2841. doi: 10.1111/bph.13887. Epub 2017 Jul 27.

Single and combined effects of Δ^9 -tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain.

King KM[1], Myers AM[1], Soroka-Monzo AJ[1], Tuma RF[1], Tallarida RJ[1], Walker EA[2], Ward SJ[1].







https://www.ncbi.nlm.nih.gov/pubmed/28548225

frontiers in Neurology

Potential Clinical Benefits of CBD-Rich *Cannabis* Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis

***Fabricio A. Pamplona*[1]*, *Lorenzo Rolim da Silva*[2] *and Ana Carolina Coan*[3]**

[1] *Entourage Phytolab, São Paulo, Brazil,* [2] *Bedrocan Brasil, São Paulo, Brazil,* [3] *UNICAMP, Campinas, Brazil*

TABLE 2 | Efficacy of treatments in the reduction of convulsive seizures (heterogeneous population).

References	Patients	Reported improvement	>50%	>70%	Mean daily dose (mg/kg/day)
Total reports	**670**	**399/622**	**216/553**	**83/311**	**(2–50 mg/kg)**
Mean	**100%**	**64%**	**39%**	**27%**	**15.0 mg/kg**
CBD pure (6)	137	37%	37%	22%	22.9 mg/kg
CBD pure (7)	7	86%	71%	57%	22 mg/kg
CBD pure (8)	13	85%	70%	46%	24.6 mg/kg
CBD pure (9)	18	72%	50%	22%	37.7 mg/kg
CBD pure (10)	48	NR	42%	NR	28.2 mg/kg
CBD-rich extract (11)	19	84%	74%	42%	7.0 mg/kg
CBD-rich extract (12)	117	85%	NR	NR	4.3 mg/kg
CBD-rich extract (28)	75	57%	33%	NR	NR
CBD-rich extract (13)	74	89%	34%	18%	<10 mg/kg
CBD-rich extract (14)	43	83%	67%	42%	3.2 mg/kg
CBD-rich extract (15)	119	49%	24%	NR	NR

Endpoints: any improvement reported, improvement > 50% ("clinical responder") and >70%, and average dose reported. NR, not reported; ?, inconclusive.

Óleo de cânhamo “full spectrum”

Potencialmente
> 100 canabinóides
400+ compostos únicos

CANABINOIDES

Principais
CBD (18-25%)
Δ9-THC (0.3-1%)

Outros <1%
CBN
THCV
CBG
CBC
Δ8-THC

TERPENOS

Mais comuns
Mirceno
Limoneno
Pineno
Humuleno

Medical use of Cannabis by elder patients

Study with 2736 patients in Israel

Only 25% had previous experience

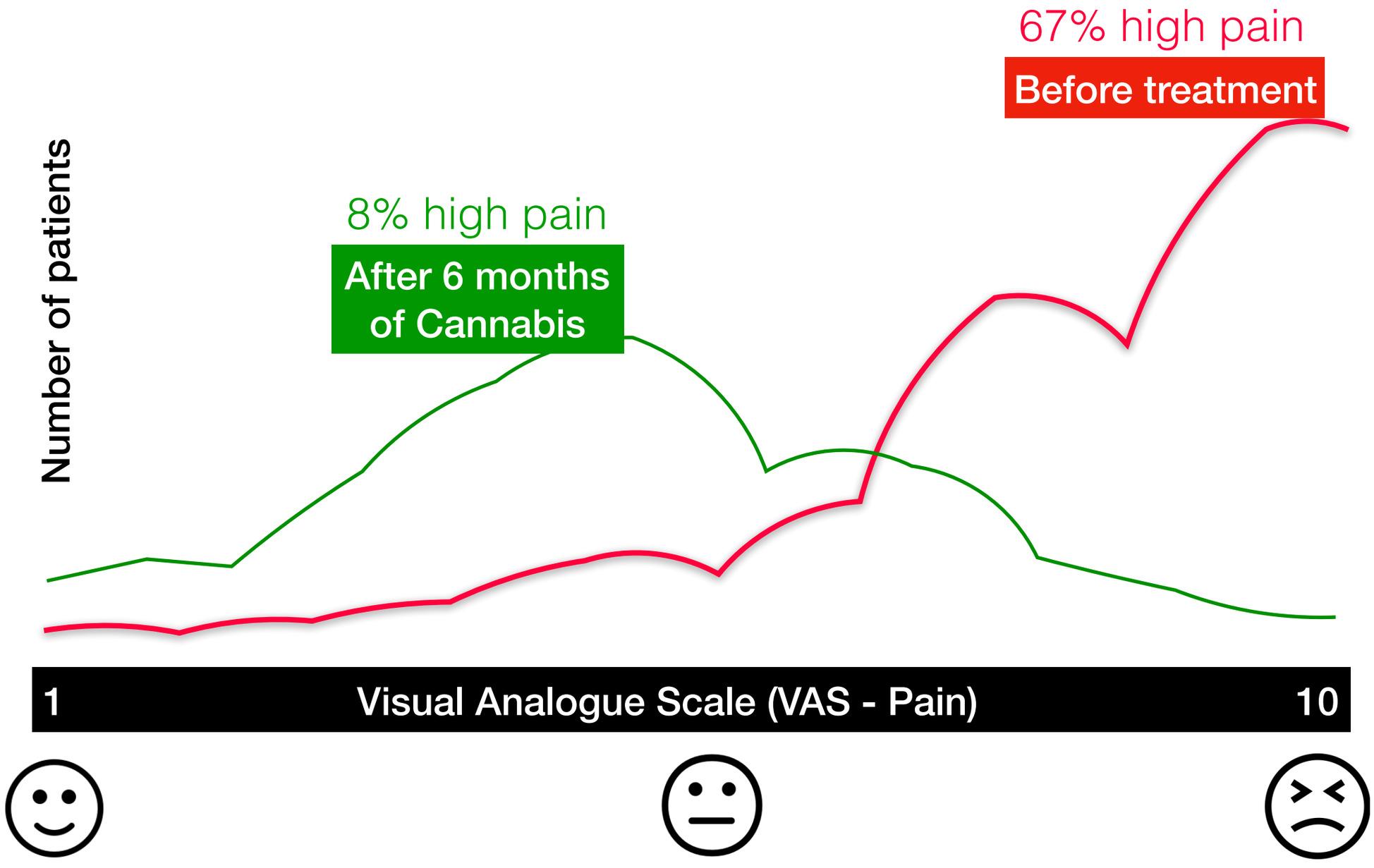
93% declared improvement in their conditions with Cannabis treatment

The vast majority used for **pain** and/or **cancer** management

Abuhasira et al (2018) Eur J Intern Med 49: 44-50. Epidemiological characteristics, safety and efficacy of medical Cannabis in the elderly. https://www.ncbi.nlm.nih.gov/pubmed/29398248

Medical use of Cannabis by elder patients

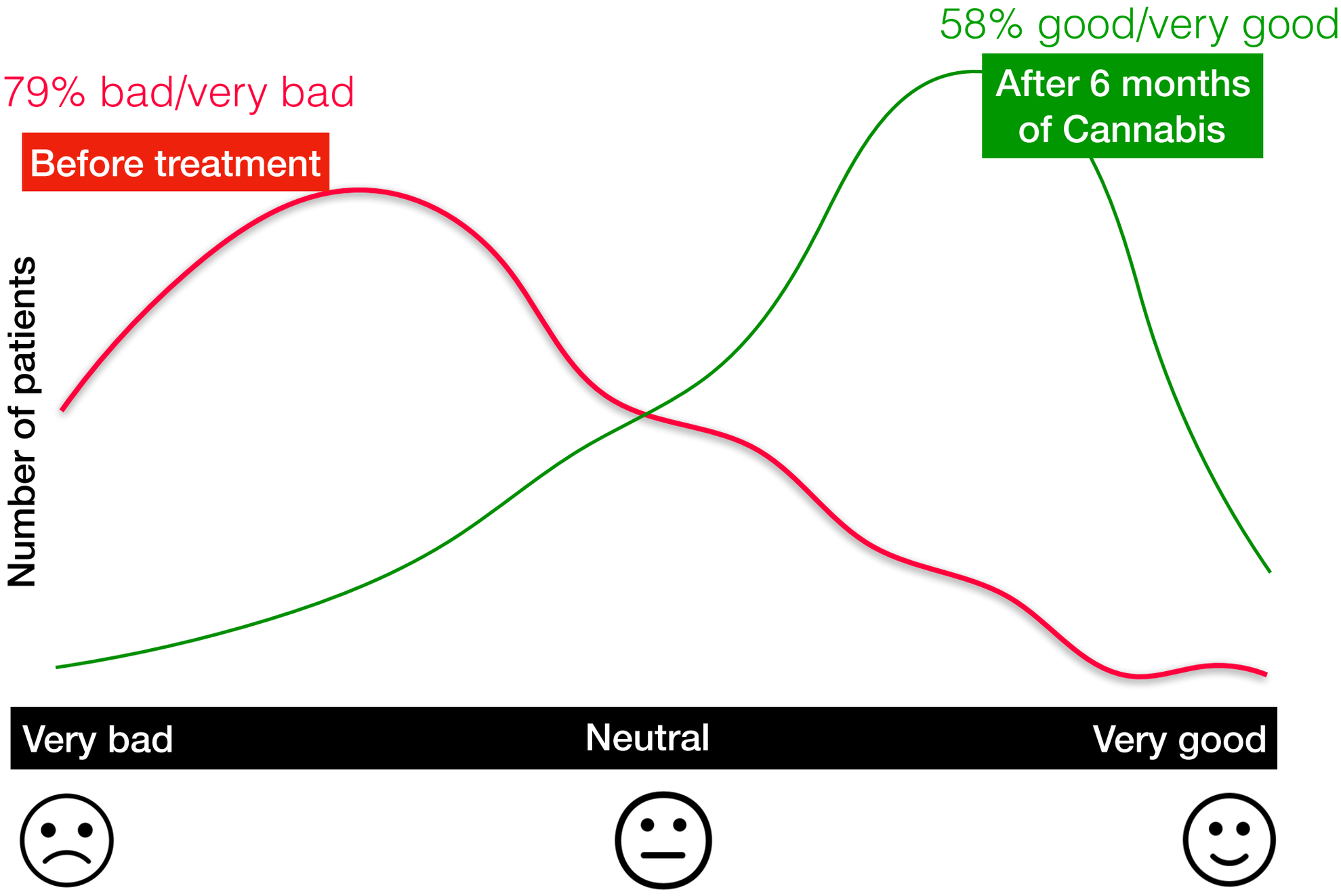
[Pain intensity] Lines drawn based on the population distribution (histogram)



Abuhasira et al (2018) Eur J Intern Med 49: 44-50. Epidemiological characteristics, safety and efficacy of medical Cannabis in the elderly. https://www.ncbi.nlm.nih.gov/pubmed/29398248

Medical use of Cannabis by elder patients

[Quality of Life] Lines drawn based on the population distribution (histogram)



Abuhasira et al (2018) Eur J Intern Med 49: 44-50. Epidemiological characteristics, safety and efficacy of medical Cannabis in the elderly. https://www.ncbi.nlm.nih.gov/pubmed/29398248

Medical use of Cannabis by elder patients

[Types of treatment]

Preferred compositions

54%

15-18% THC
<1% CBD
(Myrcene-dominant strain)
(night, sedative)

27%

20-23% THC
<1% CBD
(Pinene-dominant strain)
(day, uplifting)

19%

1% THC
16% CBD
(Myrcene-dominant strain)
(day/night, sedative)

Abuhasira et al (2018) Eur J Intern Med 49: 44-50. Epidemiological characteristics, safety and efficacy of medical Cannabis in the elderly. https://www.ncbi.nlm.nih.gov/pubmed/29398248

Medical use of Cannabis by elder patients

[Adverse events]

Dizziness
10%

Dry mouth
7%

Somnolence
4%

Weakness
2%

Nausea
2%

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Health Canada

Information for Health Care Professionals

Cannabis (marihuana, marijuana) and the cannabinoids

Informações completas como auxílio à prescrição médica
Mais de 40 aplicações clínicas descritas

https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids.html

https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/information-medical-practitioners.html