Universitätsklinikum
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HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

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New treatments for spasticity and other symptoms

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Multiple Sclerosis Therapy

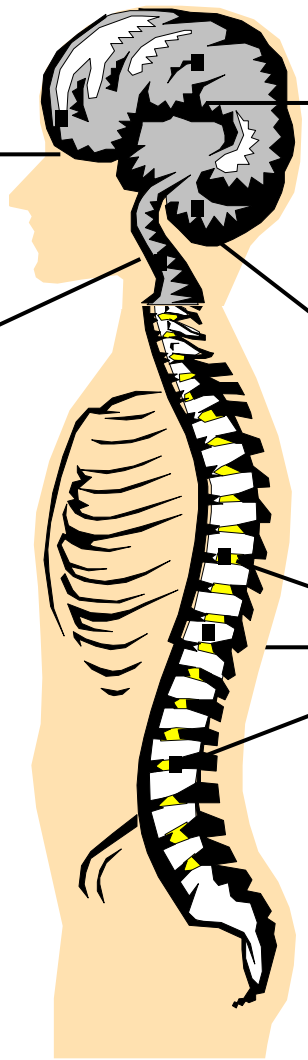
Causal Therapy

Immunmodulation-> Treatment of the underlying “autoimmune disease“:
-> Investment into the future

Symptomatic Therapy

Therapy of the symptoms of the disease:
->“immediate (?) relief from symptoms“

Multiple Sclerosis: Scope of Symptoms



Optic Nerve

- Blurred vision
- Reduced colour
- Visual field deficit

Brainstem

- Articulation
- Swallowing
- Eye movements

Cerebrum

- Mentation
- Concentration
- Fatigue

Cerebellum

- Articulation
- Coordination
- Tremor, vertigo

Spinal cord

- Sensory symptoms
- Spasticity
- Palsy
- Sphincter dysfunction
- Sexual dysfunction

➢And many others, often nonspecific symptoms!

Ten most common MS Symptoms
(UK survey)

Symptom	Patients experiencing the symptom (%)	Patients rating the impact of the symptom as 'moderate' or 'severe' (%)
Fatigue	96	88
Balance and dizziness problems	92	74
Loss of mobility	91	79
Sensory problems	88	54
Bladder problems	87	70
Loss of memory and concentration	87	52
Spasticity	**82**	**54**
Vision problems	82	41
Pain	81	50
Bowel problems	74	45

†n = 2265.
Adapted from [8].

Fampridine

Early Studies I

Nature Vol. 283 7 February 1980

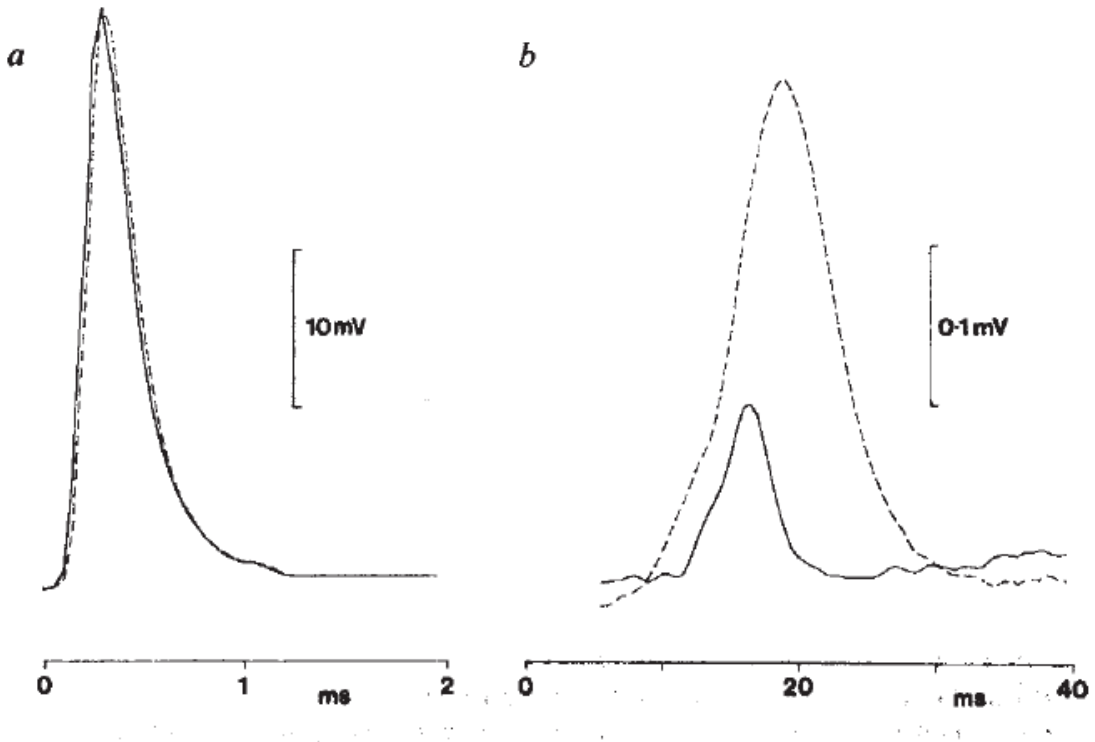


Fig. 1 Effect of 4AP on compound action potential in rat dorsal root, showing myelinated (*a*) and unmyelinated (*b*) fibre components separately. Each trace is the mean of eight, obtained with a digital signal averager. Solid lines, control; dashed lines, following application of 4 mM 4AP.

Sherrat et al. 1980

Aminopyridine-MOA

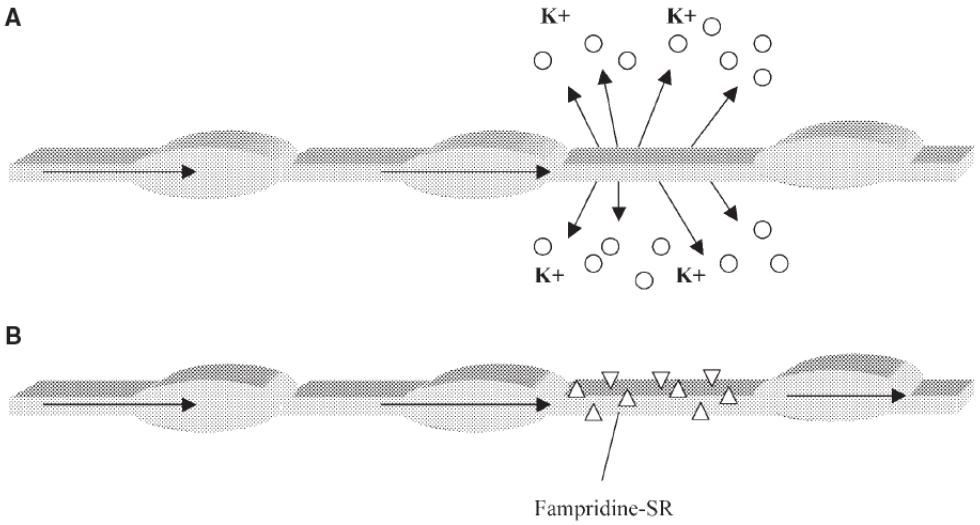


Figure 1. Downstream effects of sustained-release (SR) fampridine. A: In multiple sclerosis, demyelination of axons exposes voltage-gated potassium channels, diminishing formation of a normal action potential and limiting neuronal conduction. B: With fampridine-SR, exposed voltage-gated potassium channels are blocked, restoring neuronal conduction and action potential formation.

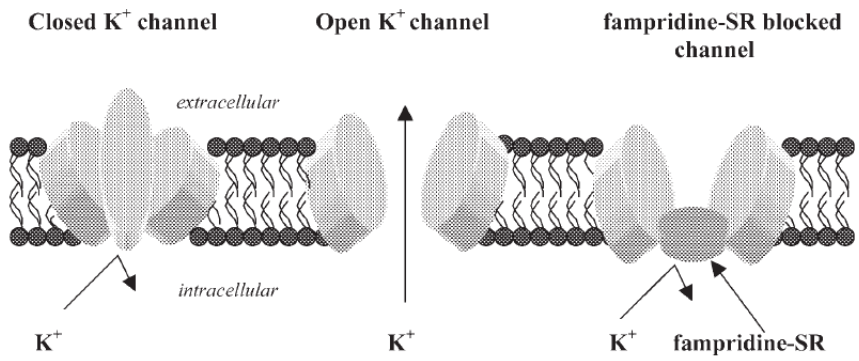
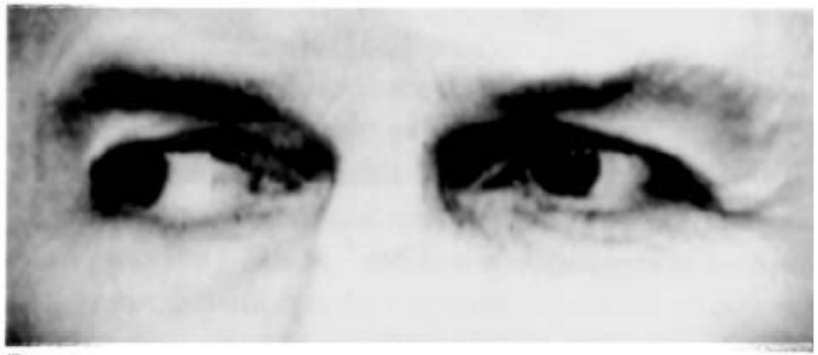


Figure 2. Mechanism of action of sustained-release (SR) fampridine.

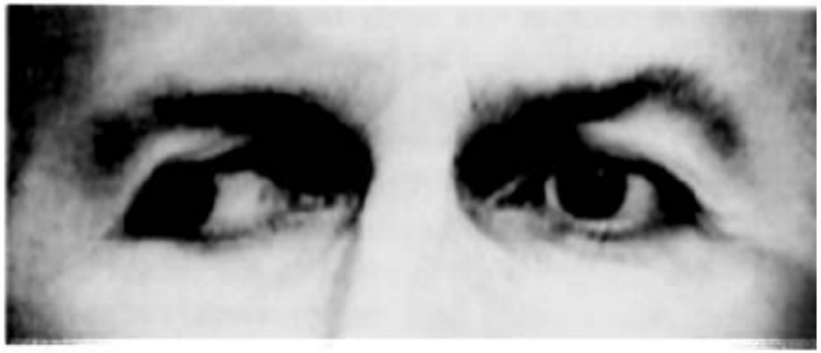
Korenke et al., 2008

Early Studies II

A



B



C

Fig 5. Reversible improvement from left internuclear ophthalmoplegia in the patient shown in Figure 4. (A) Before 4-aminopyridine (4-AP); (B) 75 minutes after 20 mg 4-AP; (C) reversal 220 minutes after 20 mg 4-AP. (Videotaped material.)

Stefoski et al. 1987

P-Kinetics of unsustained Formulation

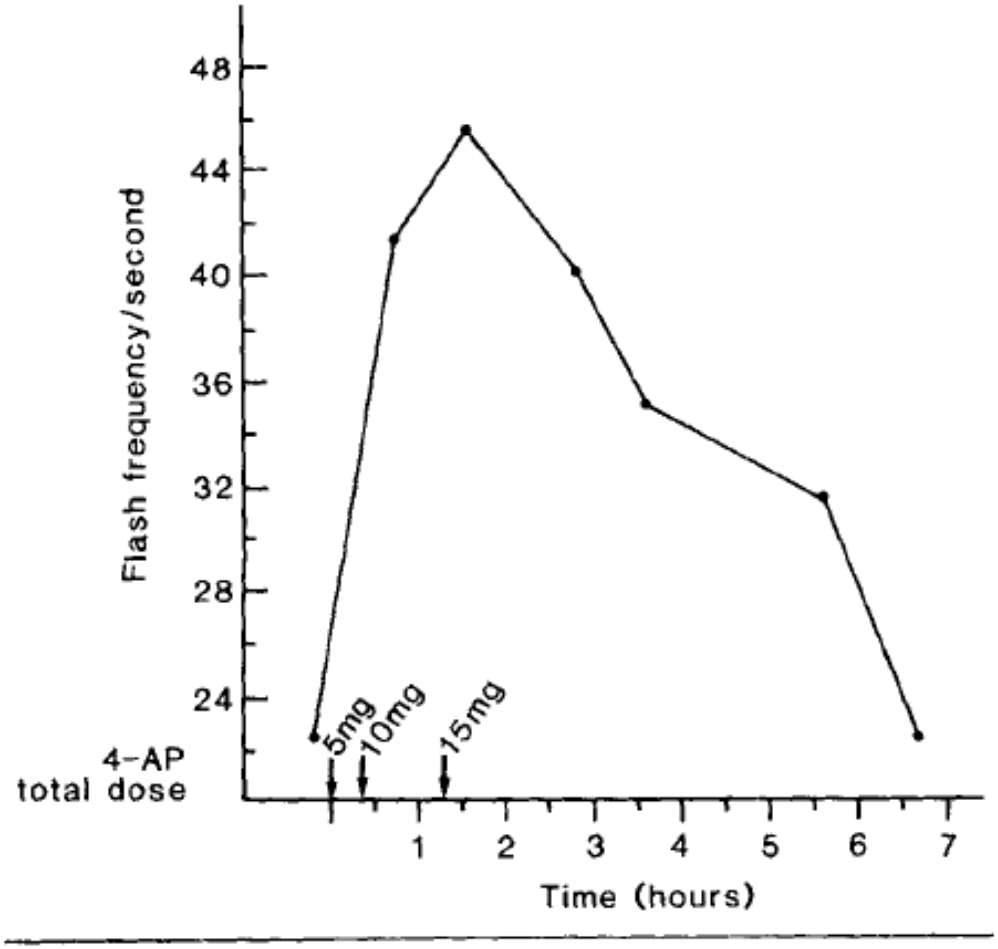


Fig 2. Reversible improvement in critical flicker-fusion frequency after administration of 4-aminopyridine (4-AP) in a patient with multiple sclerosis with right optic nerve involvement (see text).

Stefoski et al. 1987

P-Kinetics of unsustained Formulation

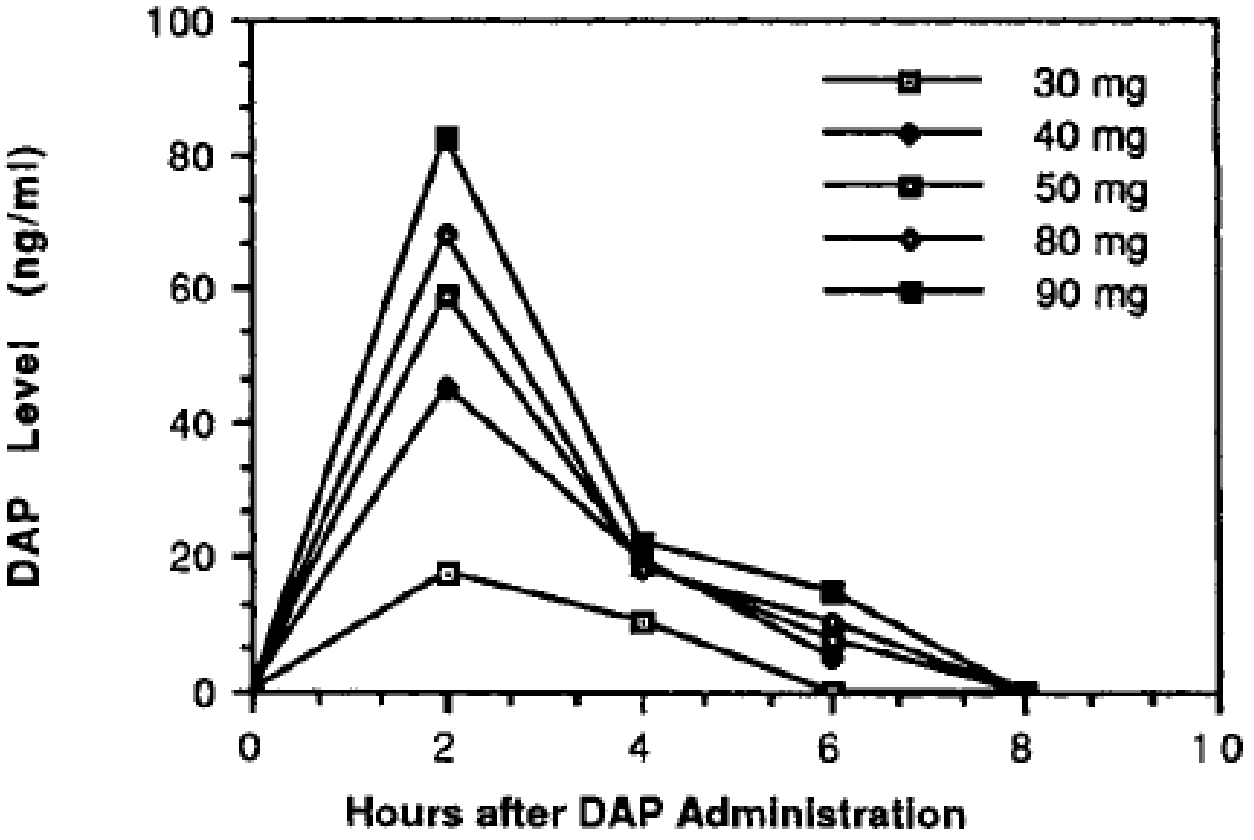


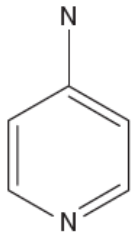
Fig 2. Serial levels of 3,4-diaminopyridine (DAP) in Patient 1, with increasing doses demonstrating consistency in pharmacokinetics at different doses in a single patient.

Bever et al. 1990

Dalfampridine (Biogen-Idec / Acorda)

- 4-aminopyridine, sustained release (SR)
- Modifies axonal function

  -> Duration of action potential increases
- 10 mg Dalfampridine 2x/d (N=119) vs. Placebo (N=120)
- Timed 25 ft walk test

Drug name	Fampridine-SR
Phase	Phase III
Indication	Multiple sclerosis
Pharmacology description	Potassium channel antagonist
Route of administration	Alimentary, by mouth Alimentary, general
Chemical structure	
Pivotal trial(s)	1) MS-F202 study 2) Study MS-F203 3) Study MS-F204

Phase III Trial: Extended Release Oral Dalfampridine in Multiple Sclerosis (MSF204)

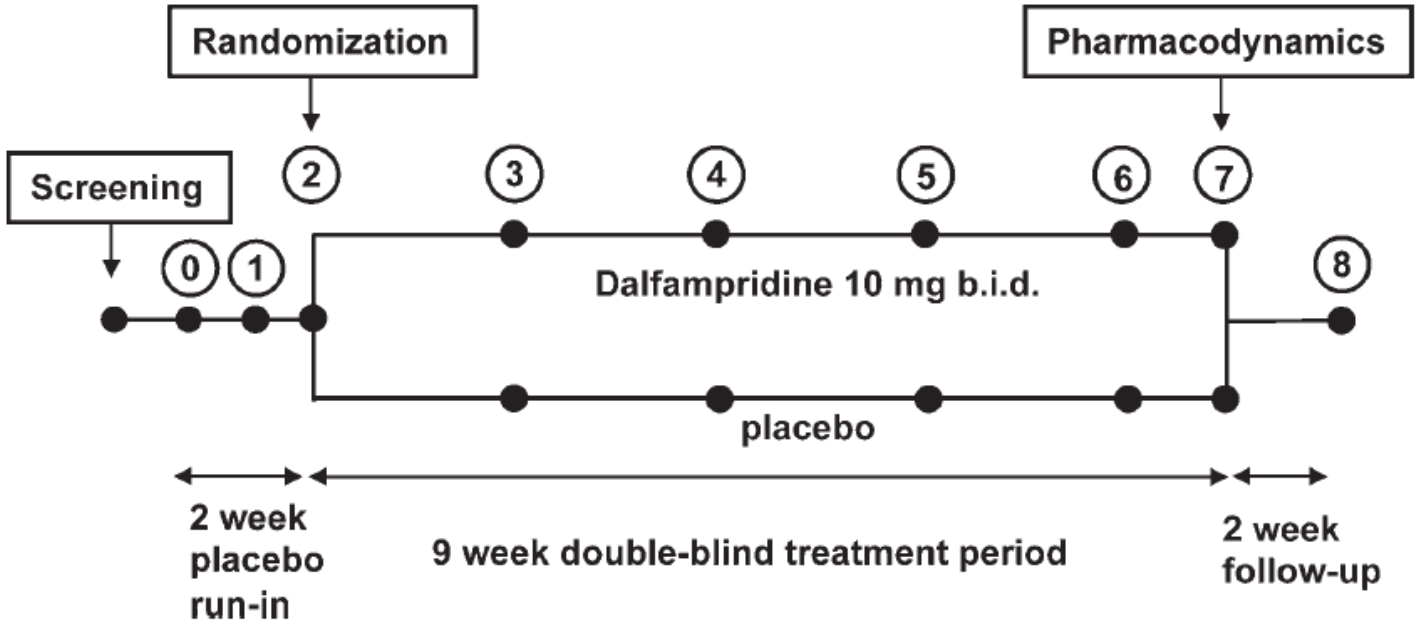
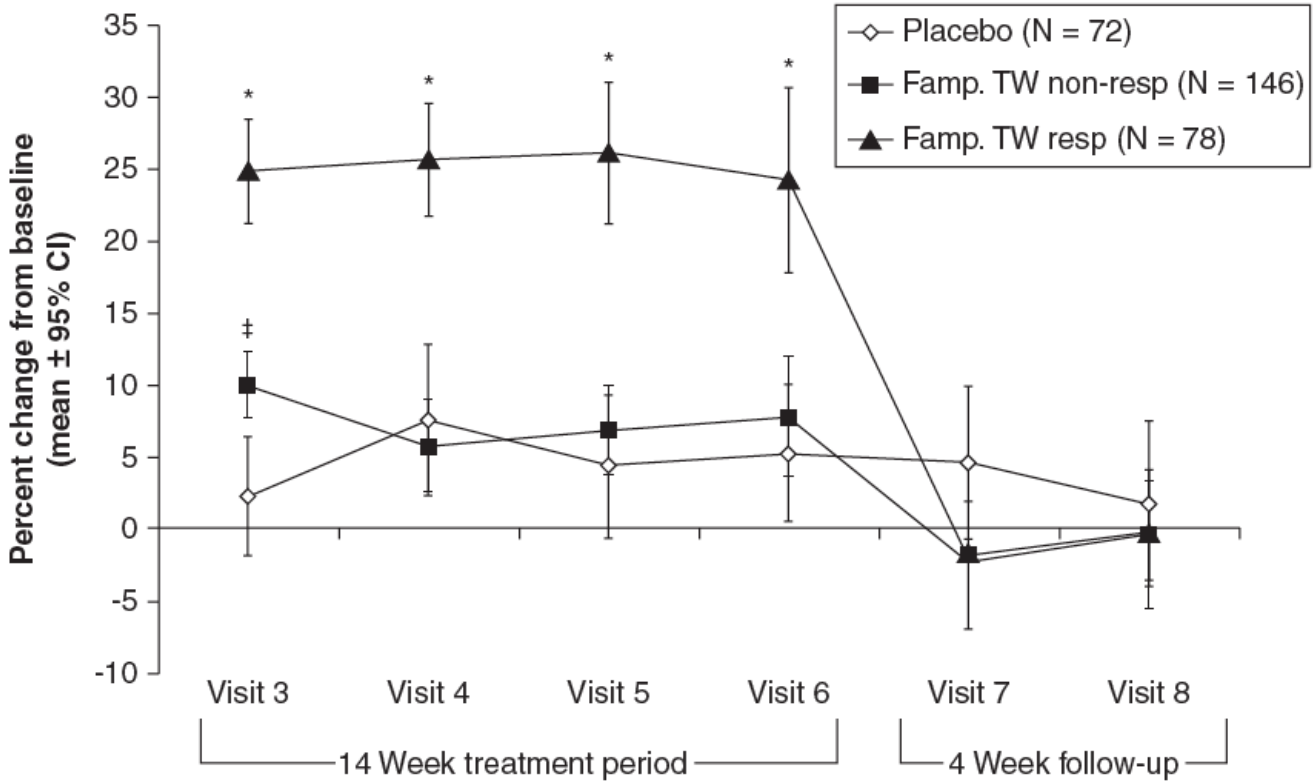


FIGURE 1: Diagram of the study schedule and design, with study visits shown by circled numbers. b.i.d. = twice daily.

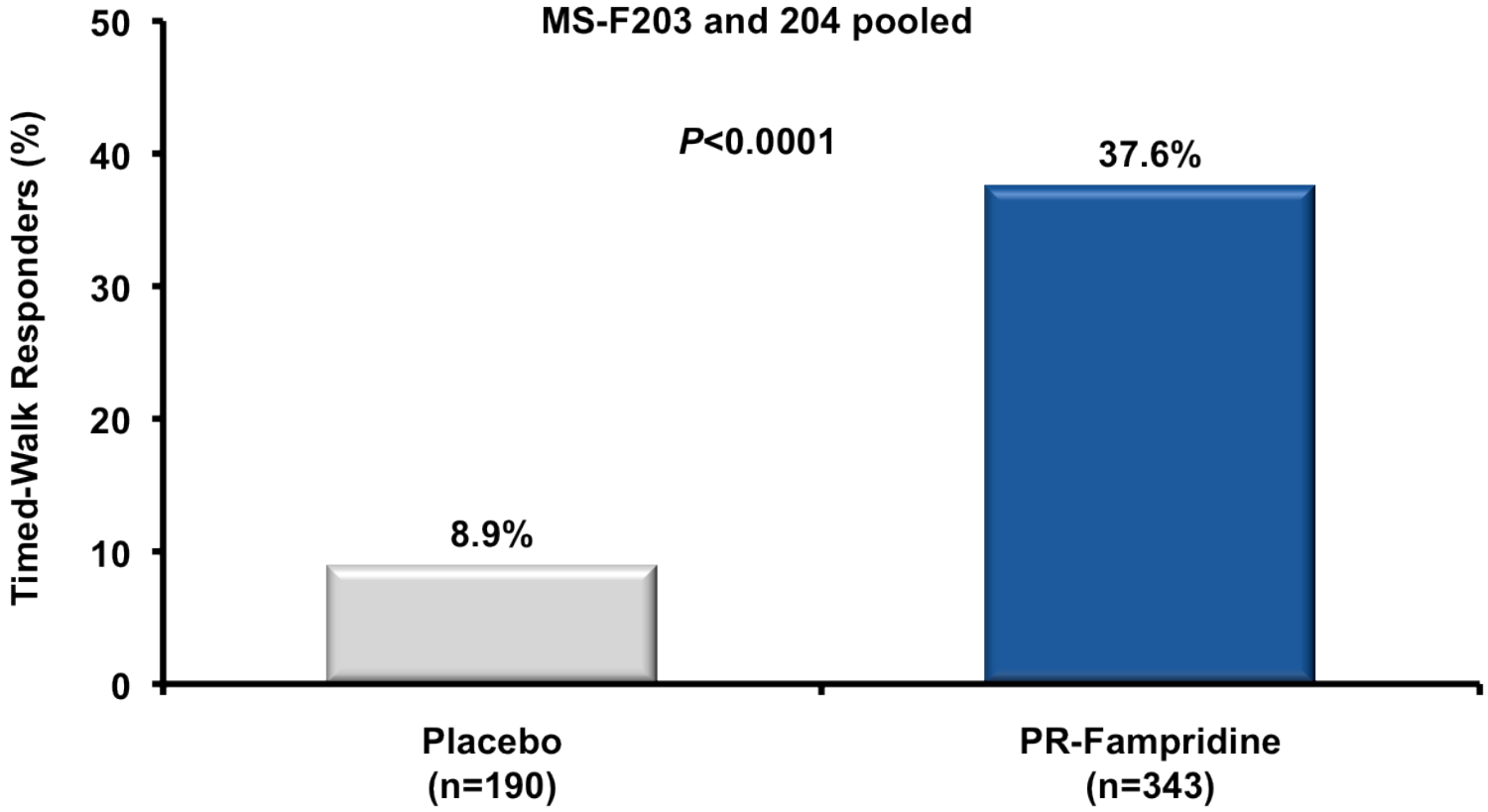
Dalfampridine

Figure 1. MS-F203 trial design and primary end point–response criterion. (MS-F204 utilized a shortened 9 week stable dose phase, without an alteration in the number of visits.)



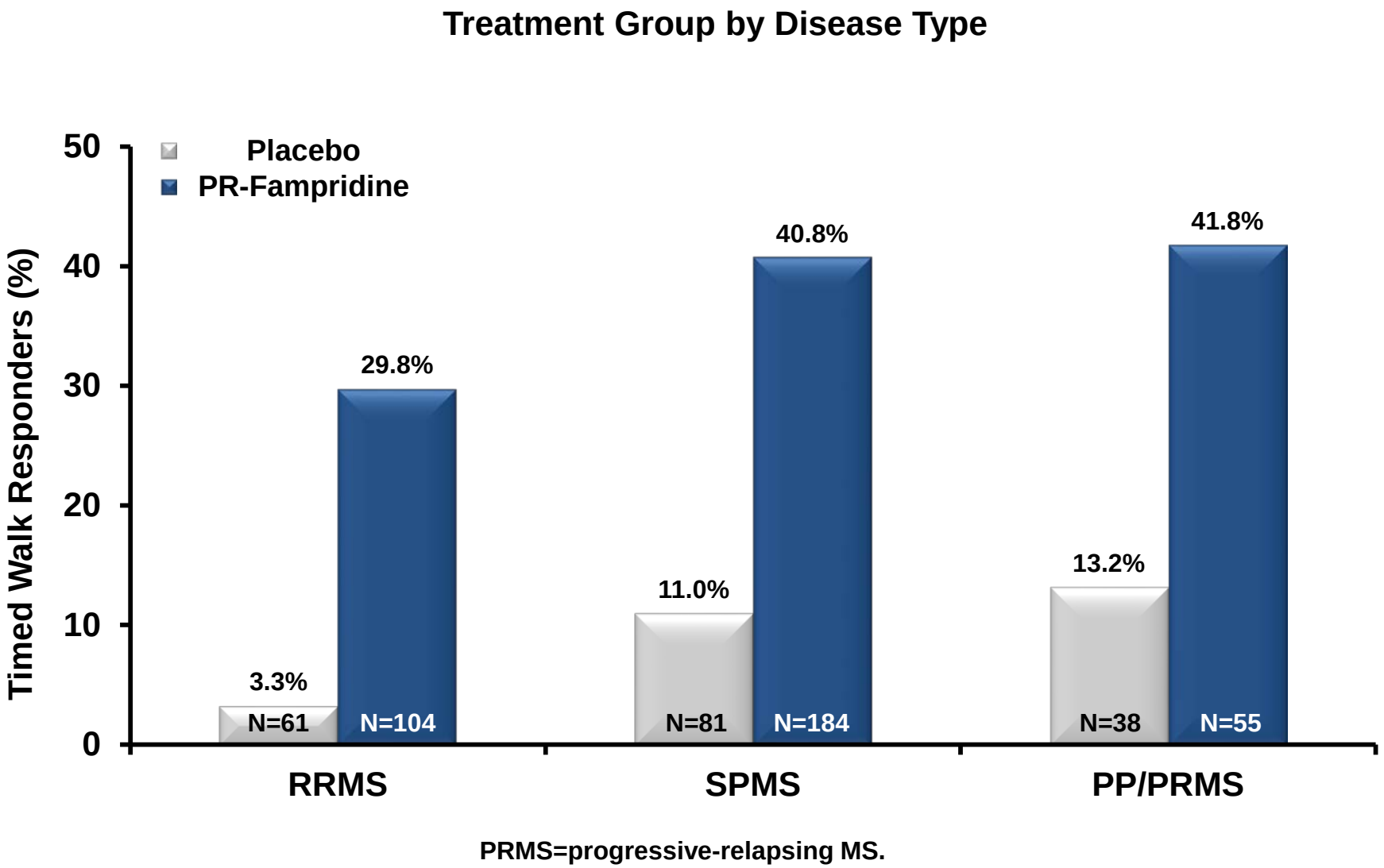
Primary Outcome: Percentage of Timed-Walk Responders (Pooled)

- **Across trials, approximately 38% of patients treated with PR-fampridine showed a consistent increase in walking speed (timed-walk responders)**



MS-F203 Goodman et al. Lancet 2009; MS-F204 Goodman et al. Ann Neurol 2010. Biogen Idec data on file.

PR-Fampridine Shows Consistent Effects Regardless of MS Type



PRMS=progressive-relapsing MS.

MS-F203 Goodman et al. Lancet 2009; MS-F204 Goodman et al. Ann Neurol 2010. Biogen Idec data on file.

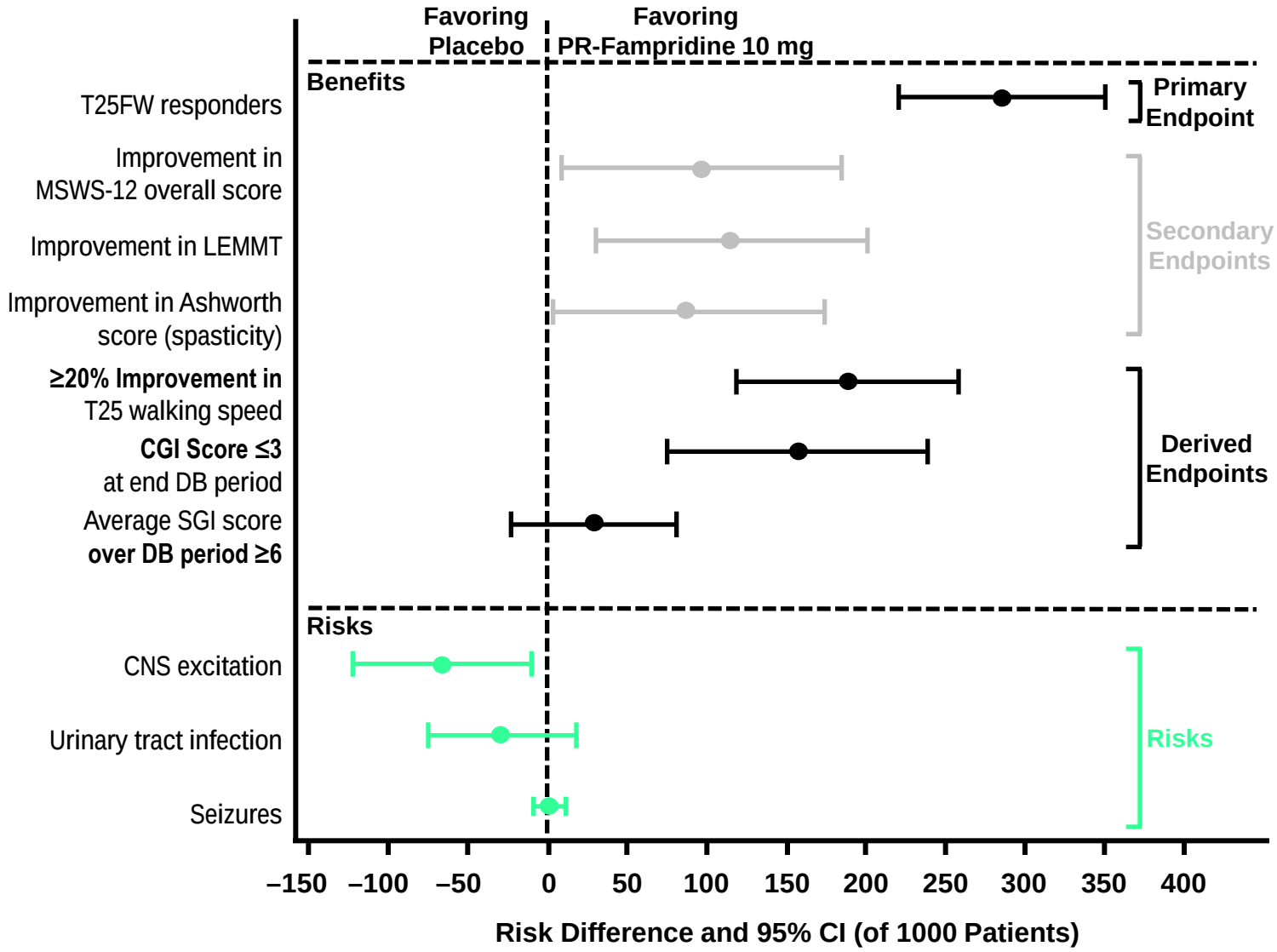
Phase 3 Studies: Most Frequent Adverse Events (AEs)

	Placebo (n=191)	PR-Fampridine (n=348)
Urinary tract infection	**10.5%**	**14.9%**
Falls	**16.2%**	**14.4%**
Insomnia	**2.6%**	**8.9%**
Dizziness	**2.6%**	**8.3%**
Headache	**2.6%**	**6.9%**
Nausea	**2.1%**	**6.9%**
Asthenia	**4.7%**	**6.6%**
Upper respiratory tract infection	**7.9%**	**6.0%**
Back pain	**1.6%**	**5.7%**
Balance disorder	**2.1%**	**5.7%**
Fatigue	**3.1%**	**5.2%**

Studies MS-F203 and MS-F204: all AEs seen in >5% of PR-fampridine–treated patients.

MS-F203 Goodman et al. Lancet 2009; MS-F204 Goodman et al. Ann Neurol 2010. Biogen Idec data on file.

Quantitative Benefit-risk Profile for PR-Fampridine



DB=double-blind; CNS=central nervous system.

Biogen Idec, data on file.

€ Fampridine $

WARENKORB | POSITIONEN: 0

VERLAUF

Artikel ähnlich wie: 4-AMINOPYRIDIN ZUR SYNTHESE Inhalt pro Packung: 10 G...

Artikelnr	Beschreibung	Preis	
8011110010	4-AMINOPYRIDIN ZUR SYNTHESE Inhalt pro Packung: 10 G R-Nummer: R 28-36/38 S-Nummer: S 28-36/37-45 CAS-Nummer: 504-24-5 WGK-Nummer: 3 Gefahrenzeichen: T+ UN-Nummer Landverkehr: 2671 Bezeichnung Landverkehr: Aminopyridine ADR-Nummer: 6.1, II UN-Nummer Seeversand: 2671 Bezeichnung Seeversand: ...	41,80 Euro für 1 Verpackung	1 Bestellen
8011110025	4-AMINOPYRIDIN ZUR SYNTHESE Inhalt pro Packung: 25 G R-Nummer: R 28-36/38 S-Nummer: S 28-36/37-45 CAS-Nummer: 504-24-5 WGK-Nummer: 3 Gefahrenzeichen: T+ UN-Nummer Landverkehr: 2671 Bezeichnung Landverkehr: Aminopyridine ADR-Nummer: 6.1, II UN-Nummer Seeversand: 2671 Bezeichnung Seeversand: ...	79,30 Euro für 1 Verpackung	1 Bestellen

Retail-Price Dalfampridine (AMPYRA ®) in the USA:

12.672,- USD / year (= 7,2 g)

7,2 g 4-Aminopyridin: 22,83 € (30,50 $)

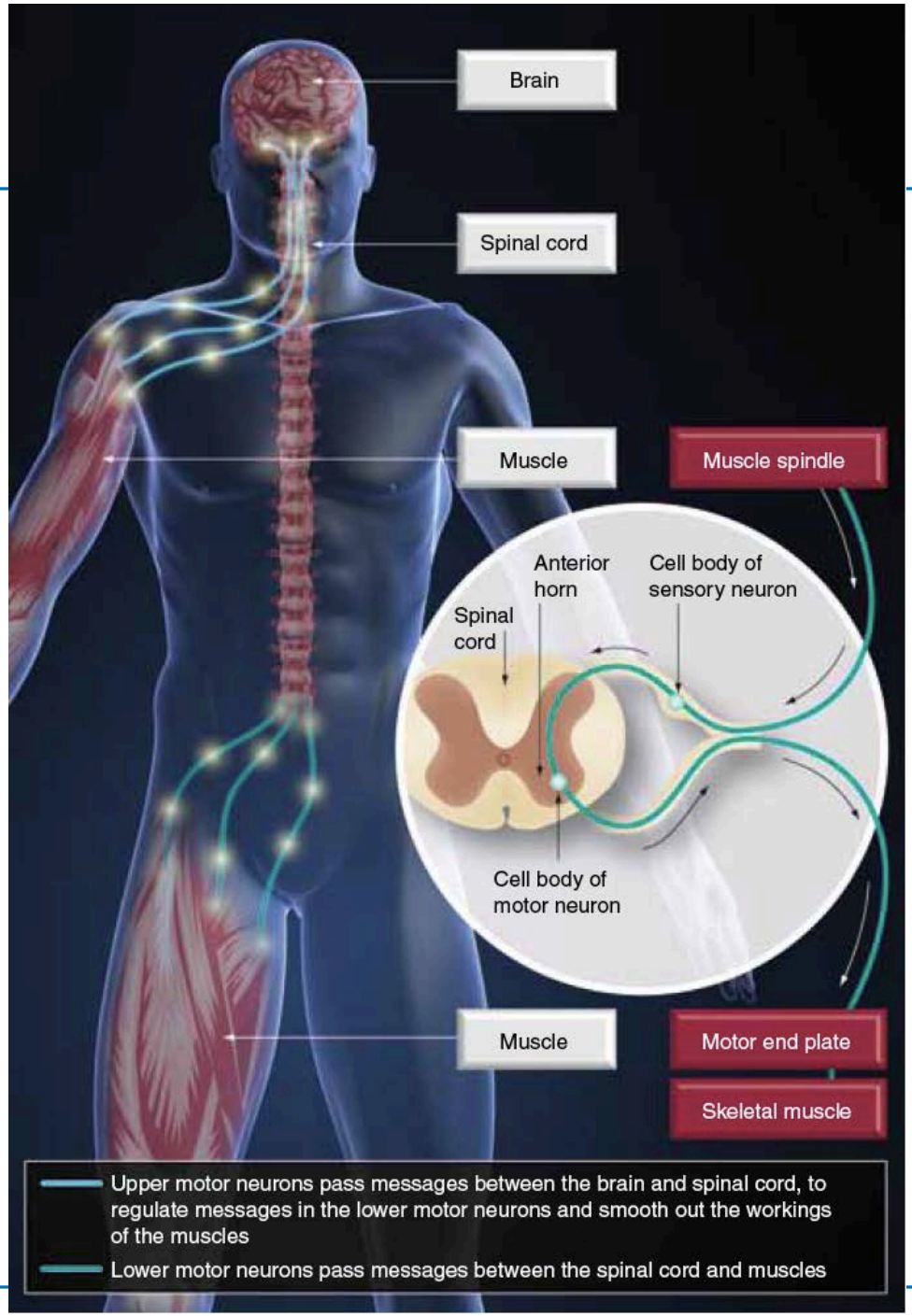
-> 41.500 %

Ten most common MS Symptoms
(UK survey)

Symptom	Patients experiencing the symptom (%)	Patients rating the impact of the symptom as 'moderate' or 'severe' (%)
Fatigue	96	88
Balance and dizziness problems	92	74
Loss of mobility	91	79
Sensory problems	88	54
Bladder problems	87	70
Loss of memory and concentration	87	52
Spasticity	**82**	**54**
Vision problems	82	41
Pain	81	50
Bowel problems	74	45

†n = 2265.
Adapted from [8].

The stretch-reflex arc in MS spasticity



EUSPASM: *"disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles."*
Stevenson VL. *Clin Rehab* 2010

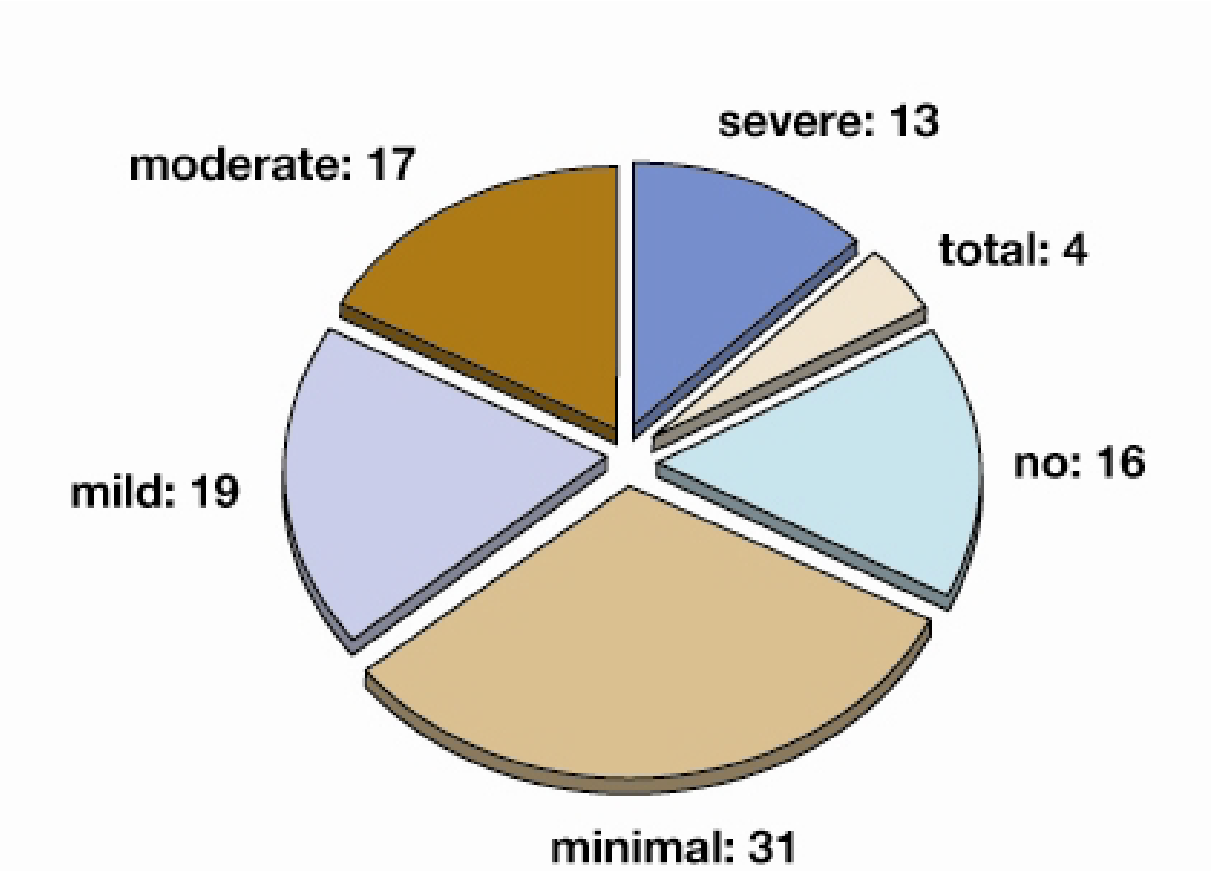
Patient description: "an unusual tightening of muscles that feels like leg stiffness, jumping of legs, a repetitive bouncing of the foot, muscle cramping in the legs or arms, legs going out tight and straight or drawing up".
Rizzo et al. *Mult Scler* 2004

MS spasticity: causes

- Result of myelin and nerve fibre degradation
- MS plaques inhibit supraspinal control of reflex activity
- ->Impairment of functional movements of muscles of the extremities and of the trunk.
- Progressive damage -> loss of inhibition and a disruption of the stretch-reflex arc

Bavikatte & Gaber Br J Med Pract 2009; 2: 29-34;
Springhouse. Handbook of signs and symptoms. LWW, 2005.

MS spasticity severity
(% from US survey of > 20000 patients)



Rizzo et al. *Mult Scler* 2004; 10: 589-95.

MS spasticity: symptom rating scales

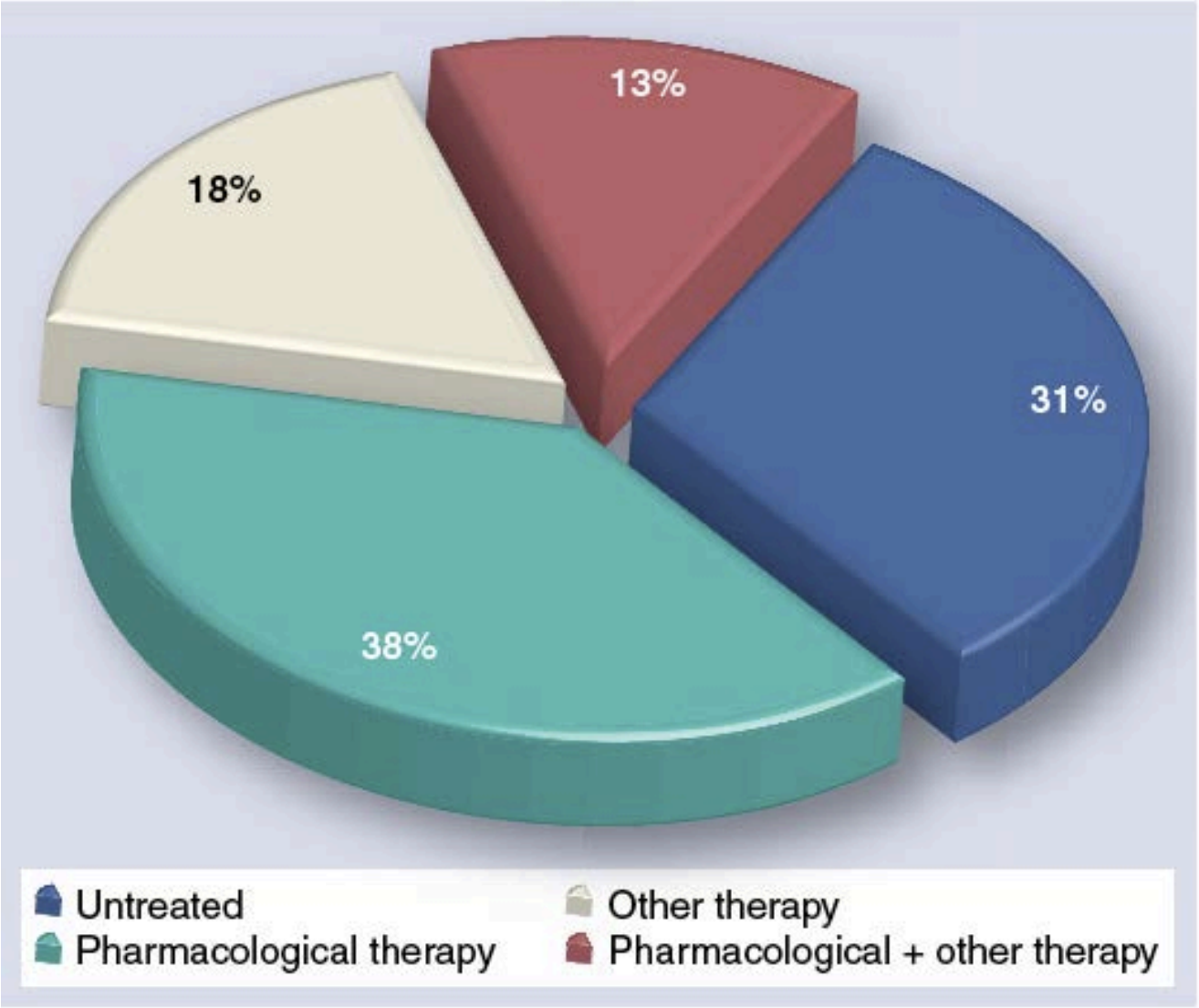
The most frequently used have been:

- Ashworth Scale/Ashworth (modified) Scale
- Numerical Rating Scale (NRS)
- Multiple Sclerosis Spasticity Scale (MSSS)
- Daily mean spasm score
- Tardieu Scale (rarely used today)

MS spasticity: conclusions

- Spasticity is one of the most disabling symptoms associated with MS.
- Like all MS symptoms, spasticity occurs as a result of myelin and nerve fibre degradation.
- The Ashworth scale is the most widely used rating scale for assessing the degree of spasticity.
- The NRS is a valid and sensitive diagnostic tool for determining the severity of spasticity.

Management of spasticity in MS patients



Haas 2011

Symptomatic Therapy for Spasticity (1)

Treatment of contributing factors

- Fever
- (Urinary tract) Infections
- (Infected) decubitus ulcer
- Beta-Interferon associated increase of spasticity

Symptomatic Therapy for Spasticity (2)

Physiotherapy

- Multimodal rehabilitation including intense physiotherapy to reduce the extent of motor deficits
- Passive movement of major joints (motordriven bicycle)
- If possible: Aerobic Fitnesstraining
- Important: Sufficient Intensity and frequency

Medication:

Substance (Drugname)	Dosage	Side effects
Baclofen (e.g. Lioresal)	5-120 mg/d	Fatigue, nausea, confusion, ataxia
Tizanidin (e.g. Sirdalud)	2-24 mg/d	Hypotonia, dry mouth, nausea
Gabapentin (e.g. Neurontin)	300 – 2400 (3600) mg/d	Vertigo, fatigue, weakness

Symptomatic Therapy for Spasticity (3)

- Oral anti-spasticity agents (z.B. Baclofen/Lioresal®, Tizanidin/Sirdalud®)
  - cave: weakness
  - Increase dosage slowly (start with e.g. 3x2.5 mg Lioresal, 3x1 mg Sirdalud), -> maximum dosage according to effect, combine if necessary
- Botulinumtoxin A (z.B. Botox®)
- Intrathecal Baclofen (“Lioresal pump“)
- *Intrathecal Triamcinolon (Volon A)*
- *Cannabis*

Medical use of cannabis

- Cannabis has a long-history of use as both a medicine and as a recreational drug.
- Medically, street cannabis has been used to utilise it's antispastic, muscle relaxant and pain relief effects.
- In a UK survey of persons using cannabis medically (mostly smokers) between 1998 and 2002, almost 75% indicated that it was better or somewhat better than their previous treatment for MS or various pain states.

Ware et al. *Int J Clin Pract* 2005;59: 291-95.

Street cannabis: concerns/limitations

- Legal issues.
- Street cannabis lacks standardization and purity
- In recent herbal samples high levels of Tetrahydrocanabinol (THC, psychoactive cannabinoid) and low levels of Canabidiol CBD (antipsychotic cannabinoid) were reported .
- Largely smoked and this increases the risk of lung cancer, heart disease, etc.
- Smoked cannabis has variable pharmacokinetics, causing very high THC peaks, which lead to psychoactivity and other adverse events.

Chong et al. *Mult Scler* 2006; 12: 646-51.; Wade et al. *Mult Scler* 2006; q12: 639-45.; Aldington et al. *Eur Resp J* 2008; 31: 280-86.; Potter et al. *J Forensic Sci* 2008; 53: 90-4.

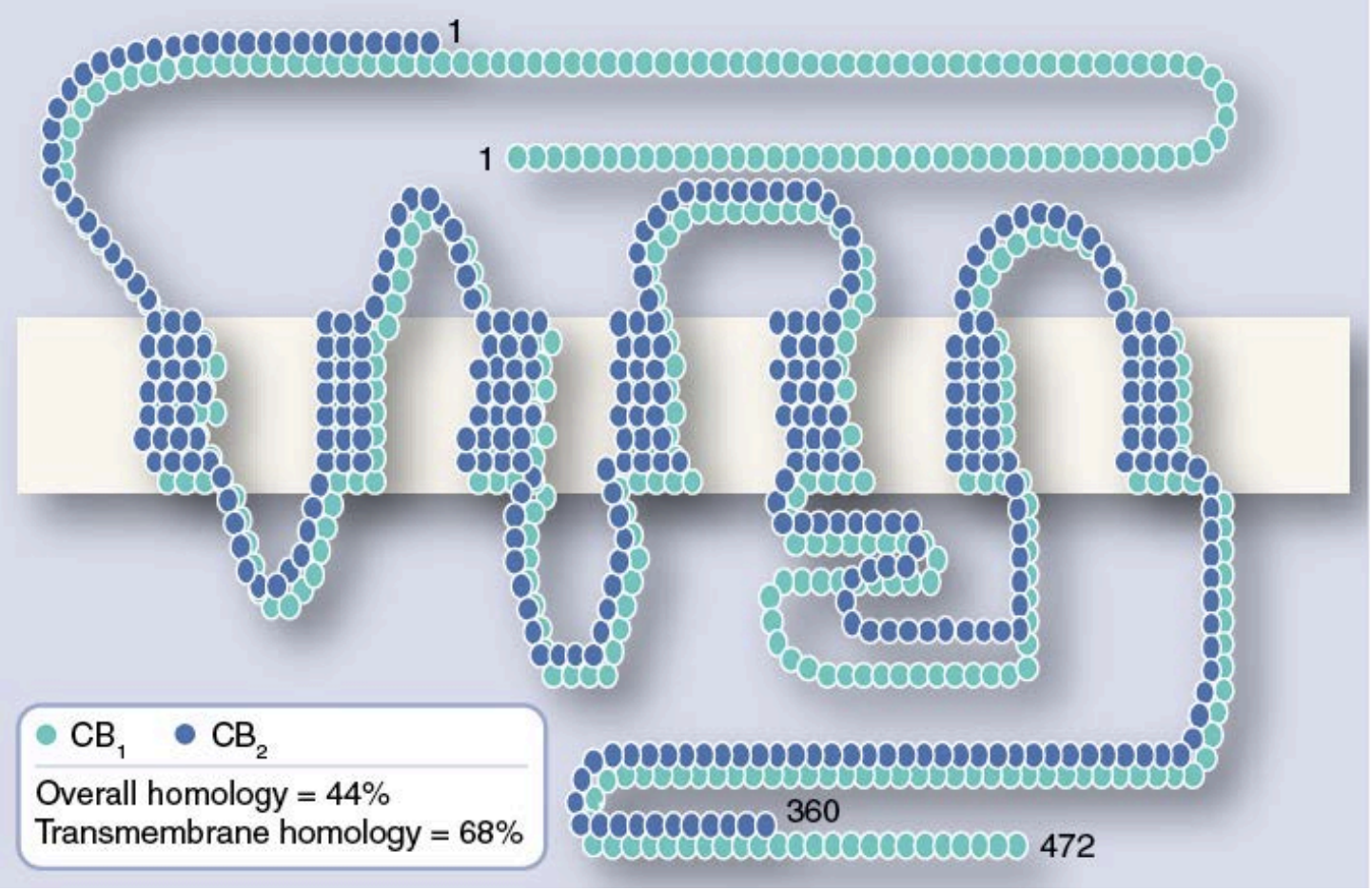
The endocanabinoid system

- 1990 breakthrough in the field of canabinoid research: CB_1 receptor was discovered by Matsuda *et al*.
- 1992 Discovery of anandamide (endocanabinoid) by Devane *et al.*
- 1993 Discovery of CB_2 receptor by Munro *et al*.
- During the last 10 years the antispastic and analgesic effects of cannabinoids were investigated

New target for the regulation of physiological functions

Experimental studies showed, that the endocanabinoid system significantly changes in processes of spasticity.

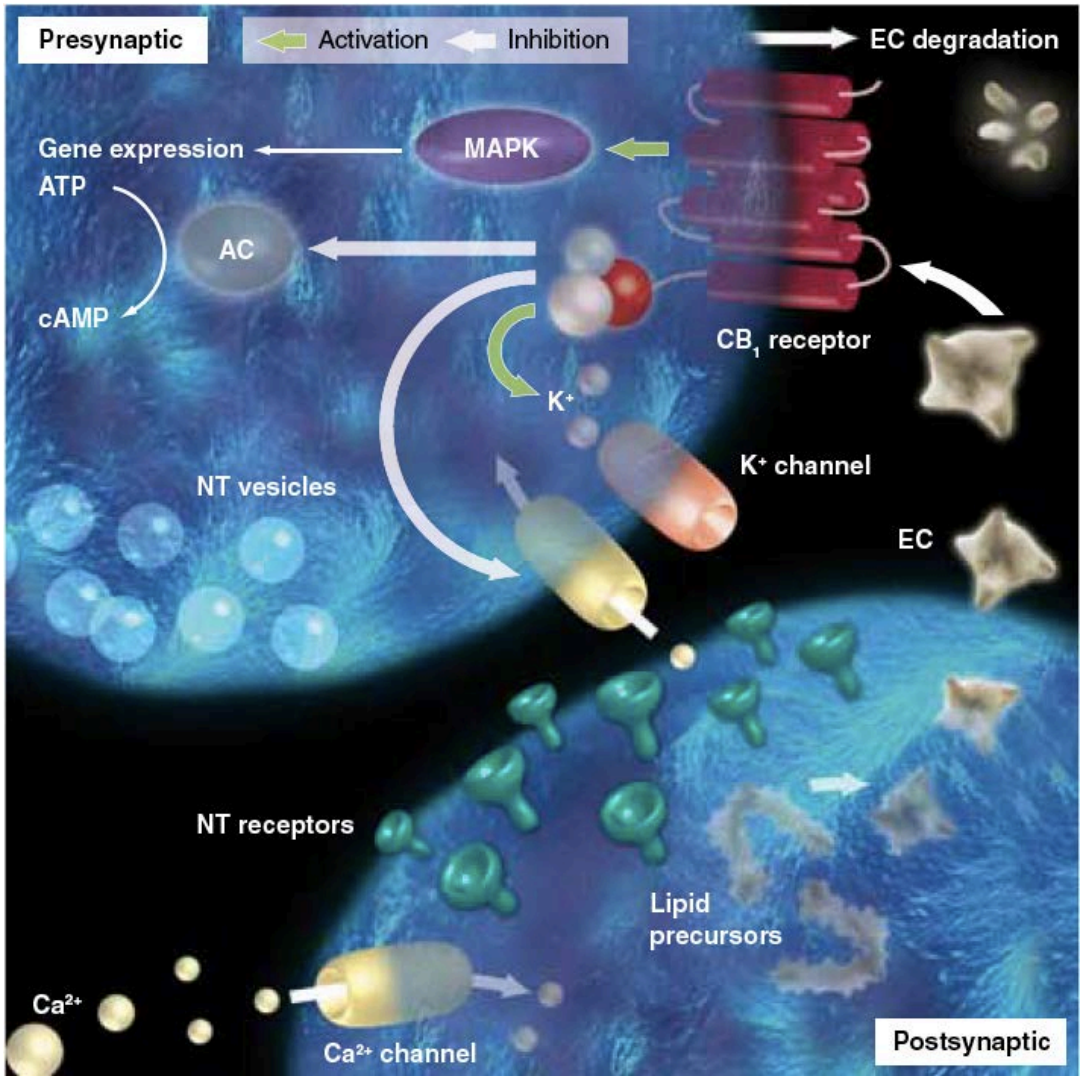
The protein sequences of CB1 and CB2 receptors



CB1 receptors: hippocampus, basal ganglia, cortex, cerebellum,hypothalamus, pituitary, limbicstructure and gastrointestinal tract.

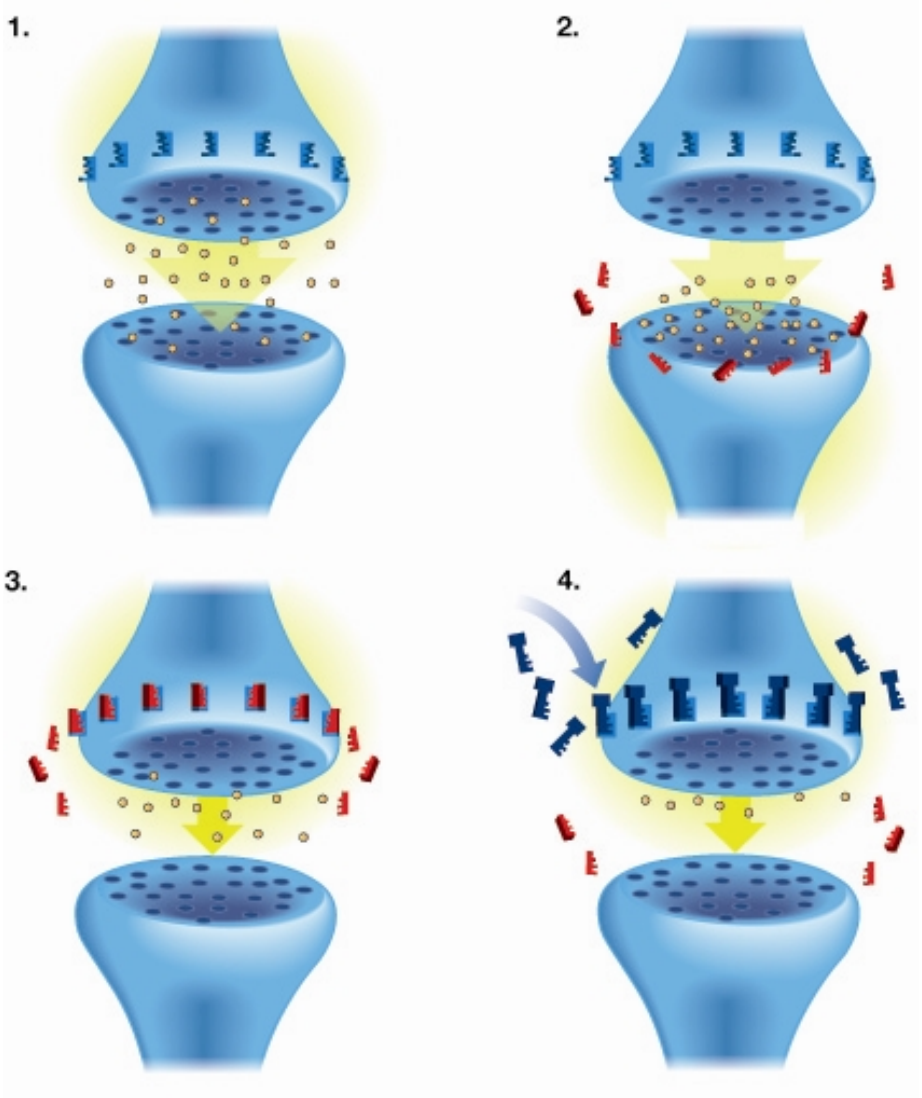
CB2 receptors: immune cells and tissues and bone.

Endocannabinoids act as retrograde neuromodulators



CB: Cannabinoid; EC: Endocannabinoid; NT: Neurotransmitter

Cannabinoids: mechanism of action



1. A nerve impulse reaching the synapse stimulates the release of neurotransmitters (the yellow molecules). These cross the synapse and bind to receptors on the post-synaptic cell, initiating a series of events.

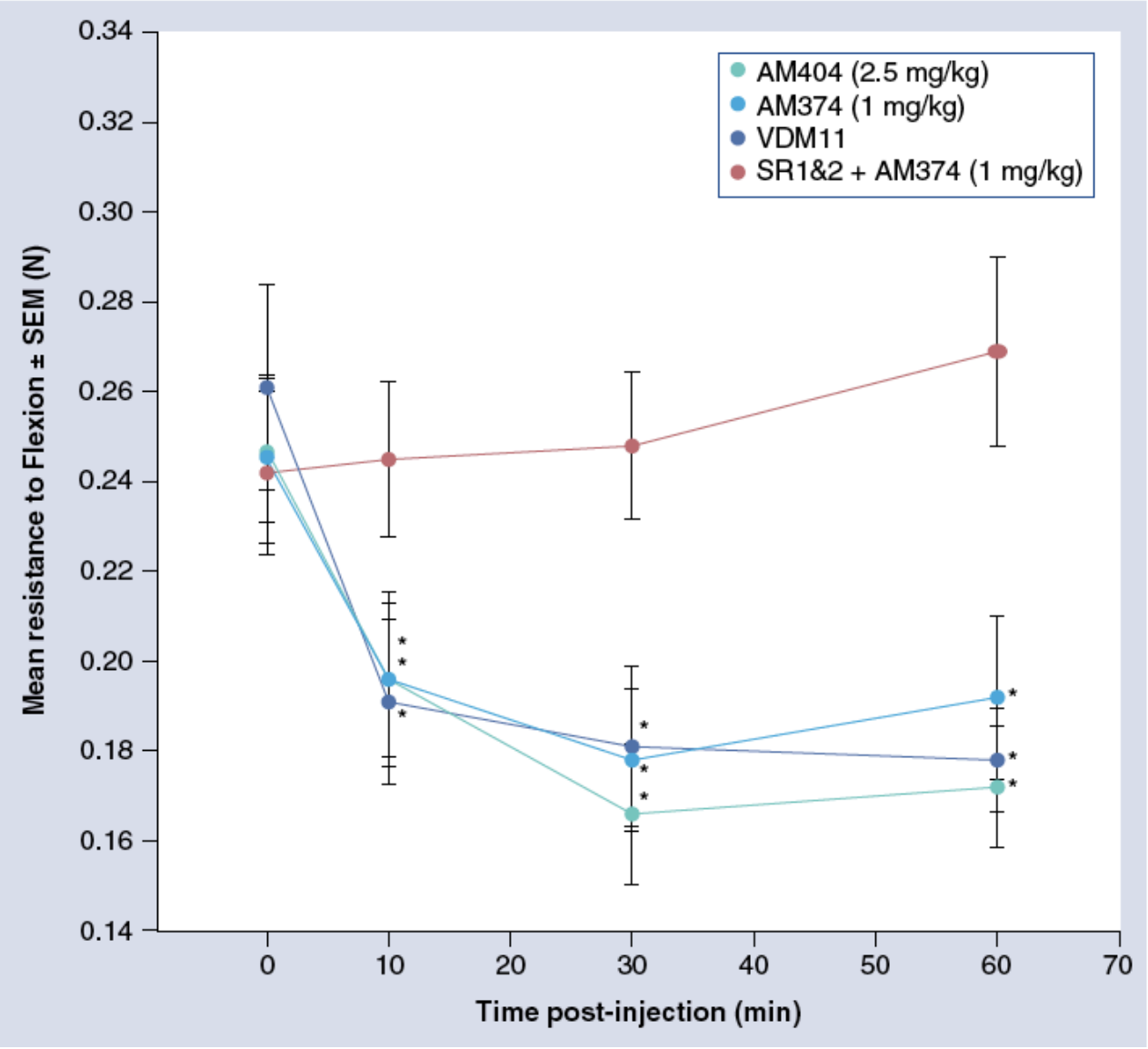
2. One of these events is the release of endocannabinoids (the red molecules) which are released locally, crossing the synapse in the opposite direction of the nerve impulse.

3. The endocannabinoids bind to pre-synaptic CB_1 receptors (the light blue receptors) inhibiting the release of further neurotransmitters, whether the neurotransmitters are inhibitory (e.g., GABA) or excitatory (e.g., glutamate). This is an example of negative feedback system.

4. Phytocannabinoids mimic the action of these endocannabinoids. In this way, they are able to augment the effect that endocannabinoids have in regulating the transmission of impulses from one nerve to another.

CNS forum. Cannabinoid receptors 2009.

Biozzi mice with chronic relapsing EAE
CB1 agonists ameliorate spasticity



*p < 0.001 compared with baseline

Collin et al. 2007

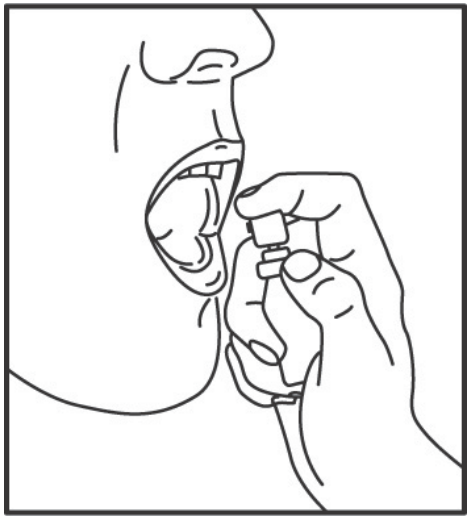
Rationale for the development of the standardised fix combination THC/CBD

- To produce a standardised medicinal product based upon the main active constituents of *Cannabis sativa,* tetrahydrocannabinol (THC) and cannabidiol (CBD).
- Formulated to ensure purity and stability.
- To administer in a way (oromucosal) which provides a satisfactory pharmacokinetic profile avoiding the high plasma levels and risks associated with smoking.
- To benefit from the synergistic interaction between CBD and THC, with a reduction in psychoactivity and enhanced cannabinoid-mediated clinical effects.

Perez *Drugs of Today* 2006; 42: 495-501; Potter et al. *J Forensic Sci* 2008; 53: 90-4.

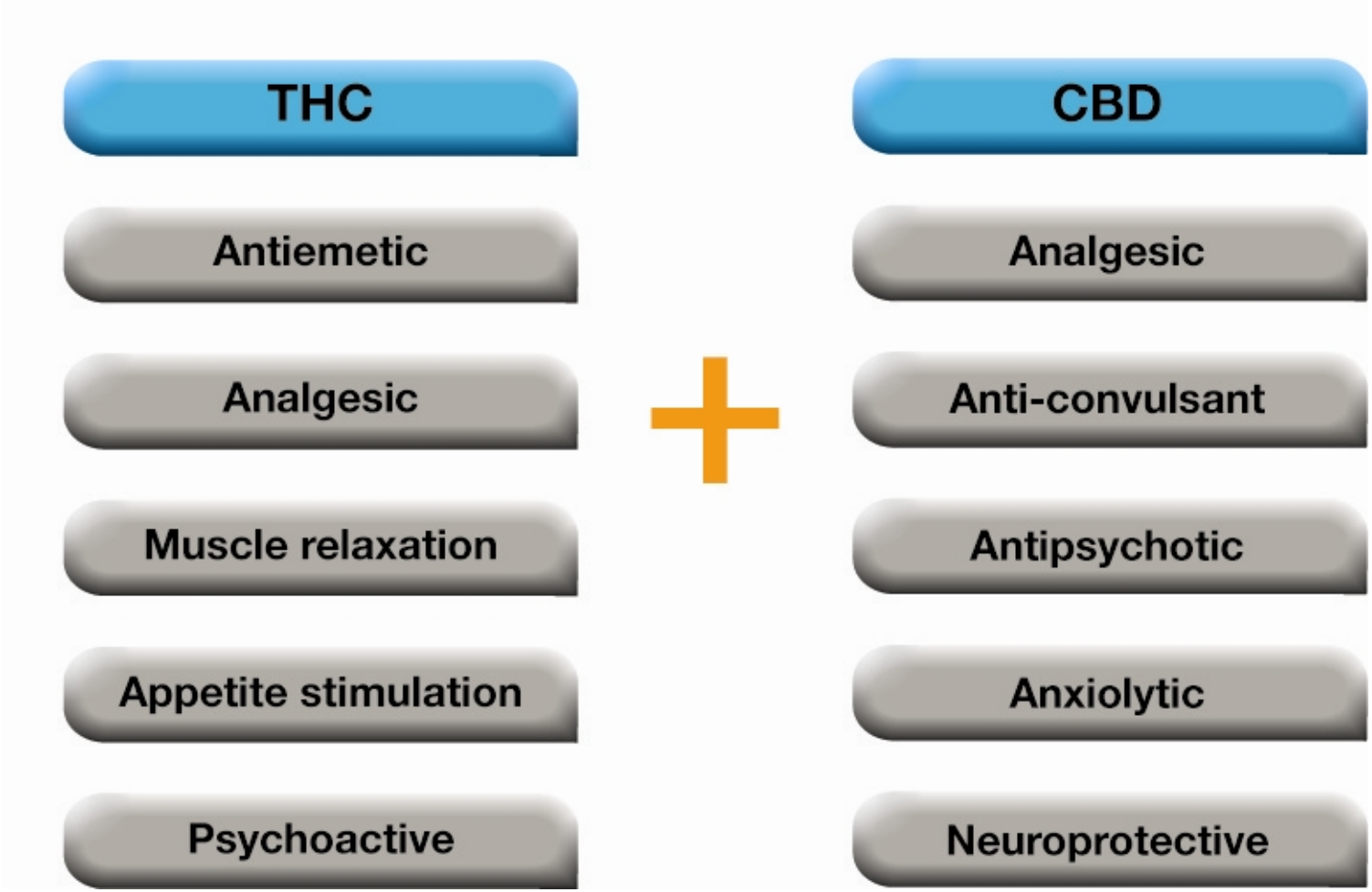
Standardized fix combination of THC/CBD

- Oromucosal spray contains two canabinoids, which act synergistically:
  - 1) Tetrahydrocanabinol (THC)
  - 2) Canabidiol (CBD)



- THC is a CB_1- and CB_2-receptor agonist
- CBD is a CB_1- receptor antagonist and prevent the psychoactive effects of THC

THC and CBD: synergy (complementary effects)

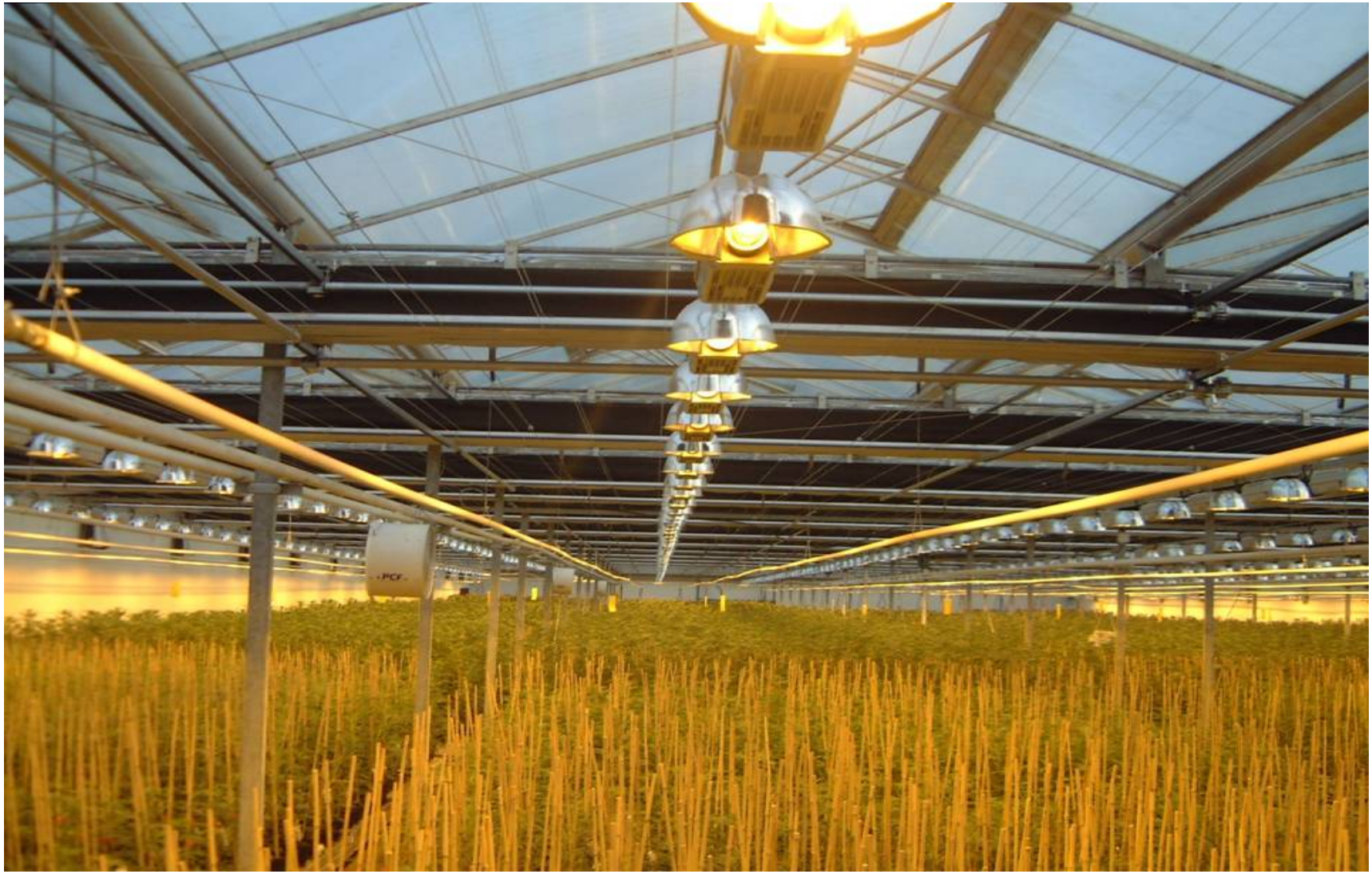


Russo & Guy *Med Hypotheses* 2006; 66: 234-46.

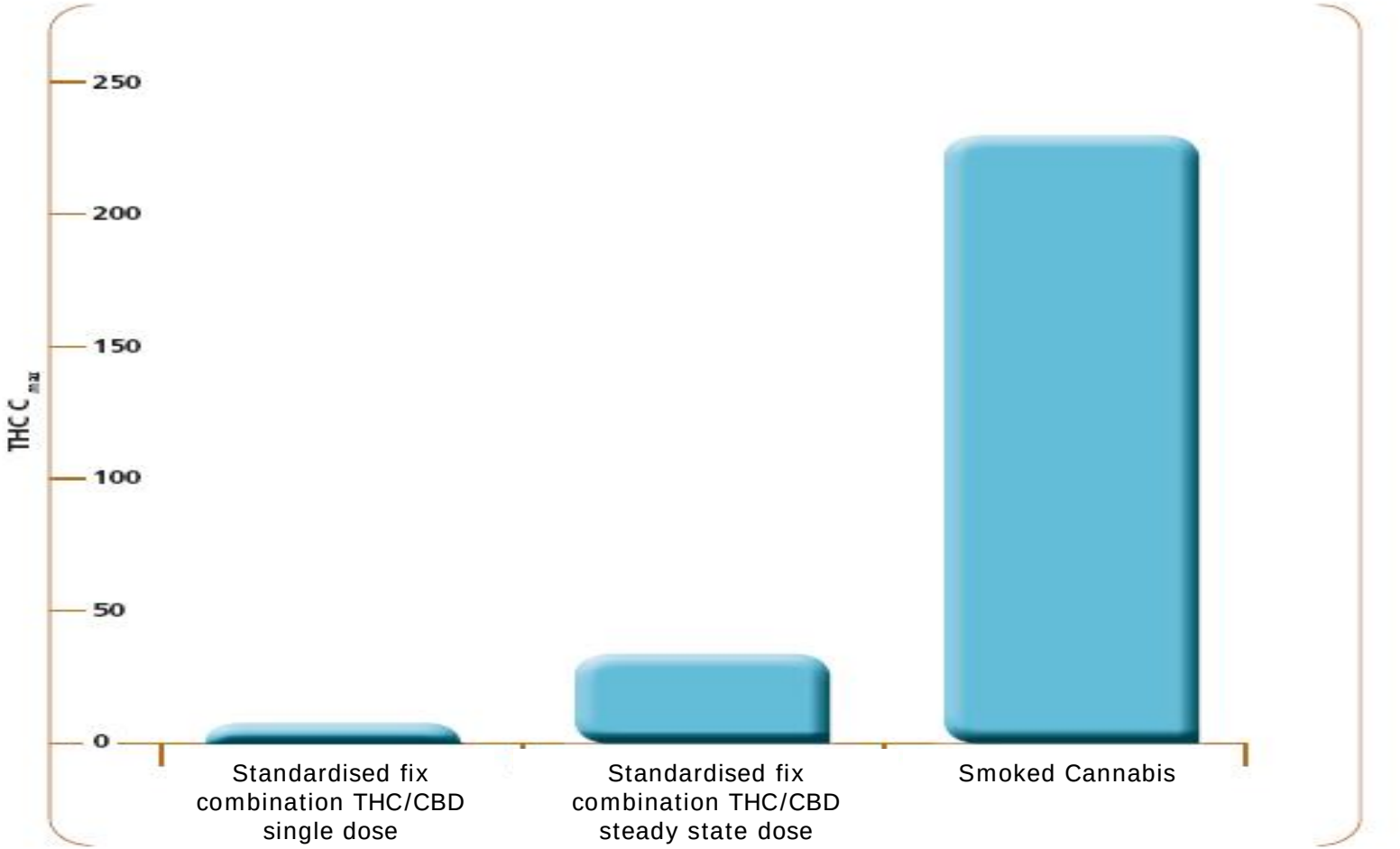
Standardised fix combination THC/CBD: Composition and production

- First-in-class endocannabinoid system modulator comprising THC + CBD.
- Cannabinoid-based medicine derived from *Cannabis sativa.*
- Prepared from 2 cloned chemovars of *C. sativa* to ensure standardisation and quality.
- 10ml amber vials with a pump for oromucosal application.

Standardised fix combination THC/CBD manufacturing: sophisticated cultivation



Maximum plasma THC levels with the standardised fix combination THC/CBD and Street Cannabis (smoked)



Guy & Stott In Parnham et al. (eds) Milestones in drug therapy: cannabinoids as therapeutics, 2005.

Clinical Overview (Phase III)

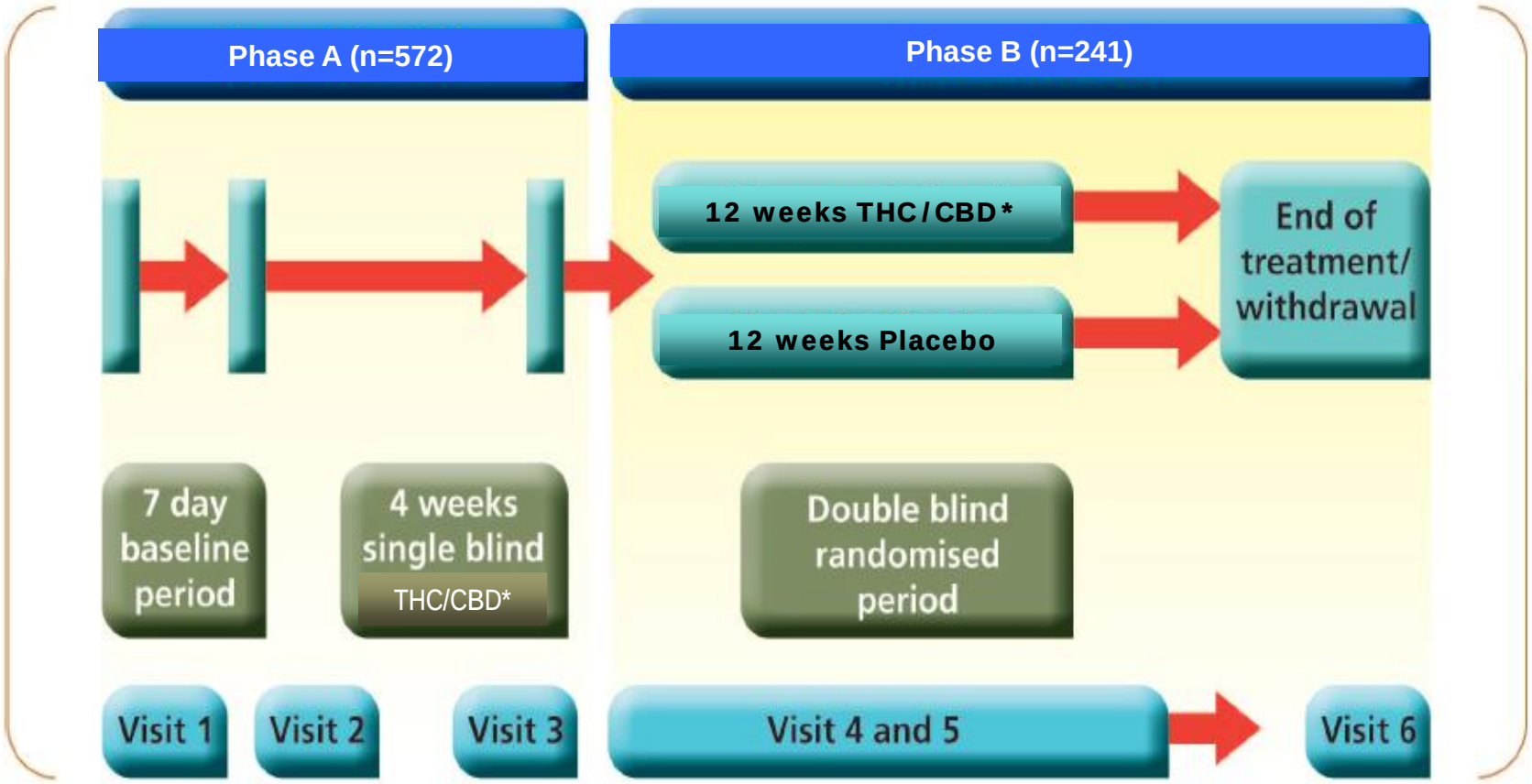
Author/publ. year	Patients n =	Type of study	Primary endpoint	Results
Wade 2004	160 / 3 centers	Pilot study	Score of five MS-symptoms: spasticity, spasms, bladder, tremor, pain (VAS)	1. endpoint: not sign.; 2. endpoint: spasticity alone: significant change
Collin 2007	189 / 12 centers	Pivotal study I	Change of spasticity (NRS)	Improvement statistically significant
Collin 2010	337	Pivotal study II	Change of spasticity (NRS)	PP: statistally significant
Novotna 2011	572 (Phase A) 241 (Phase B)	Pivotal study III	Change of spasticity (NRS)	Improvement statistically significant
Notcutt 2009	36	Tolerability	Time to failure of efficacy	Significance in favour of THC/CBD
Constantinescu 2006	444	Longterm safety study	Incidence of AEs and SAEs	Incidence comparable to short term studies
Wade 2006	137	Longterm safety study	Severity of worst symptoms (VAS)	Dosage & severity constant -> longterm efficacy

Standardized fix combination THC/CBD: third pivotal clinical trial

Status	Published (abstract available and full text pending)
Location	EU (multicentre)
Design	A 2-phase study: Phase A- single- blind response assessment and Phase B- a randomised, placebo-controlled, double-blind, parallel group study
Objective	To assess the efficacy and safety of the standardised fix combination THC/CBD vs. placebo in patients with MS spasticity
Participants and schedule	• N = 572 MS adult patients • MS with spasticity and an inadequate response to drug therapy • Single-blind the standardised fix combination THC/CBD for 4 week, with initial responders (improving 20% or more from baseline NRS score) randomised to the standardised fix combination THC/CBD or placebo for 12 more weeks • Participants continued with current therapies throughout the study
Follow-up	•14 day follow-up after controlled period of 12 weeks
Primary outcome	Change in Spasticity numerical rating scale (NRS) score
Secondary outcomes	• Improvement in NRS responses of 30% or more and 50% or more • Modified Ashworth scale of spasticity • Timed 10-metre walk and motricity index • Spasm frequency and sleep disruption • Barthel ADL index • Carer's global impression of change (CGIC) • Quality of Life

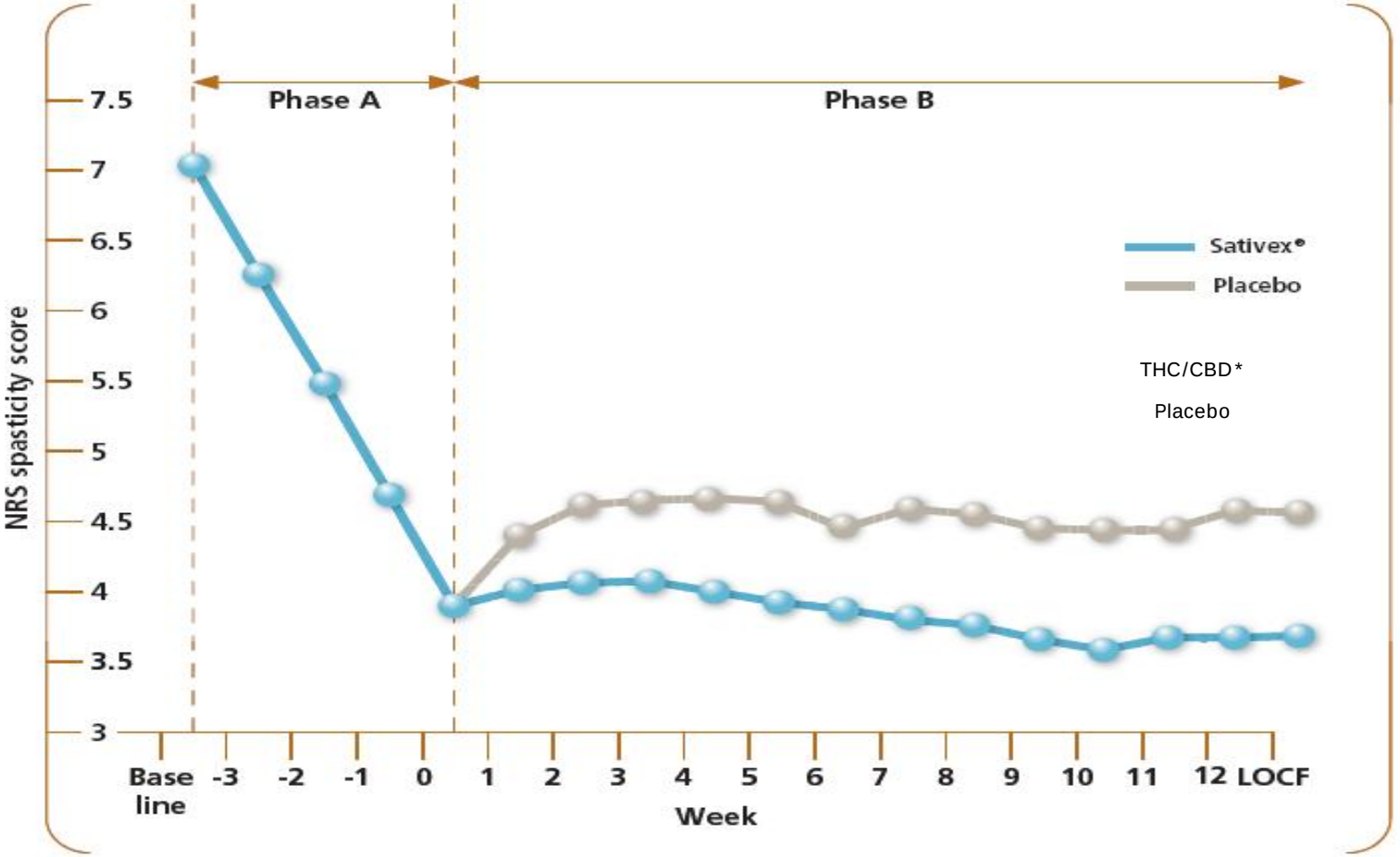
Novotna et al. *Eur J of Neurology* 2011

Standardised fix combination THC/CBD*: third pivotal clinical trial: two-phase study design



Novotna et al. *Eur J of Neurology* 2011

Standardized fix combination THC/CBD*: third pivotal clinical trial results: NRS resolution from phase A responders



Novotna et al. *Eur J of Neurology* 2011

Standardised fix combination THC/CBD third pivotal clinical trial: Well-being and quality of life (QoL)

- Barthel activities of daily living (ADL) ($p = 0.0067$).
- Physician, carer and patient global impression of change ($p = 0.0045$, $p = 0.0053$ and $p = 0.0234$, respectively).
- Sleep disruption NRS ($p < 0.0001$).
- Spasm frequency ($p = 0.0046$).
- QoL EQ-5D (0.48 to 0.57; +19%).
- QoL SF-36 Role Physical 0-100 (35.1 to 48.1; +37%).

Ambler et al. *Mult Scler* 2009; 15: S258; Montalbán & Wright *Mult Scler* 2009; 15: S272.

Standardised fix combination THC/CBD: adverse events (AEs)

- During the first 4 weeks of exposure dizziness (14-32%) and fatigue (12-25%) were the most common AEs.
- Usually mild to moderate and resolved quickly.
- When the recommended gradual “up titration” schedule was introduced the incidence of AEs was reduced.
- In clinical trials the rates of withdrawal due to AEs was low.
- The standardised fix combination THC/CBD does not exhibit the side effects typically associated with recreational cannabis use.

Wade et al. *Mult Scler* 2004; 10: 434-41; Wade et al. *Mult Scler* 2006; 12: 639-45; Collin et al. *Eur J Neurol* 2007; 14:290-96. Collin et al. *Mult Scler* 2007; 13: S129; Ambler et al. *Mult Scler* 2009; 15: S258.

Standardised fix combination THC/CBD: AEs listed in the SmPC

MeDRa System Organ Class disorders	Very common ≥1/10	Common ≥1/100 to <1/10
Infections and infestations		
Metabolism and nutrition		Anorexia (including ↓appetite), ↑ appetite
Psychiatric		Depression, disorientation, dissociation, euphoria
Nervous system	Dizziness	Amnesia, balance disorder, attention problems, memory impairment, somnolence, dysarthria, dysgeusia, lethargy
Eye		Blurred vision
Ear and labyrinth		Vertigo
Cardiac		
Vascular		
Respiratory, thoracic, mediastinal		
Gastrointestinal		Constipation, diarrhoea, nausea, dry mouth, glossodynia, vomiting, mouth ulcers, oral discomfort/pain,
General disorders and admin site	Fatigue	Application site pain, asthenia, feeling abnormal/drunk, malaise
Injury. Poisoning and procedural		fall

Treatment-related neurological AEs

Preferred Term	Standardised fix combination THC/CBD (n = 921)	Placebo (n = 853)
Disturbance in attention	37 (4%)	2 (0.2%)
Memory impairment	14 (1.5%)	4 (0.5%)
Amnesia	9 (1%)	1 (0.1%)
Coordination abnormal	5 (0.5%)	0
Cognitive disorder	2 (0.2%)	0
Depressed consciousness	2 (0.2%)	0

[From the standardised fix combination THC/CBD integrated safety analysis (Sept 1, 2007) from non-cancer studies.]

NB. These data do not include results from the third pivotal clinical trial which used the “up-titration” schedule and was associated with a significantly lower incidence of AEs.

Cognitive and Neuropsychiatric Effects

- Cognitive impairment occurs with the standardised fix combination THC/CBD, but in the majority of instances the symptoms were mild-to-moderate.
- Psychiatric AEs were also reported for the standardised fix combination THC/CBD , but they were mostly of mild-to-moderate severity.
- There is no evidence from RCTs that the standardised fix combination THC/CBD poses any long-term or irreversible neuropsychiatric or cognitive risk to patients

[From the standardised fix combination THC/CBD integrated safety analysis (May 11, 2007)]

Potential for abuse

- The standardised fix combination THC/CBD does not exhibit the psychostimulant effects typically associated with recreational cannabis use.
- Intoxication was reported to be very low during the course of short- and long-term studies.
- No association with signs of drug tolerance and in a long-term trial the mean dosage decreased slightly.
- No consistent withdrawal syndrome has been observed, and there is no evidence of drug misuse or abuse.
- Lower abuse potential than equivalent doses of dronabinol, which itself is considered to have minimal abuse potential, in 23 abuse-prone recreational marijuana users.

Wade et al. *Mult Scler* 2006;12: 639-45; Collin et al. *Eur J Neurol* 2007; 14:290-96; Schoedel et al. 2010.

Indication of standardized fix combination THC/CBD

Add-on treatment, for symptom improvement in patients with **moderate to severe spasticity** due to multiple sclerosis (MS), who have not responded adequately to other anti-spasticity medication

Standardised fix combination THC/CBD clinical efficacy: conclusions

- Results from well-controlled RCTs provide conclusive evidence of the efficacy of the standardised fix combination THC/CBD in MS-related spasticity.
- Randomized withdrawal of the standardised fix combination THC/CBD treatment provided definitive proof of long-term efficacy.
- The standardised fix combination THC/CBD not only reduced the symptoms associated with MS-spasticity, it also increased the ability of the patient to perform certain tasks and improved the perception of patients and their carers regarding functional status.

Standardized fix combination THC/CBD

Approved in:	Approval expected in:
United Kingdom	Germany
Spain	Denmark
Czech republic	Sweden
Canada	Italy
New Zealand	Austria

Summary

- Standardised fix combination THC/CBD well tolerated
- Dizziness and fatigue are the most common AEs
- Most AEs are mild to moderate
- Only few withdrawals due to unwanted effects.
- Fix combination THC/CBD does not appear to pose risks of long-term or irreversible neuropsychiatric or cognitive impairment

- Famprine increases mobility in 1/3 of patients, currently not approved in EU, expensive