Hospital Clínico San Carlos

SaludMadrid

Comunidad de Madrid

Spasticity and walking impairment: early to recognise and to treat

Prof. Dr. Celia Oreja-Guevara

Head of Multiple Sclerosis Unit

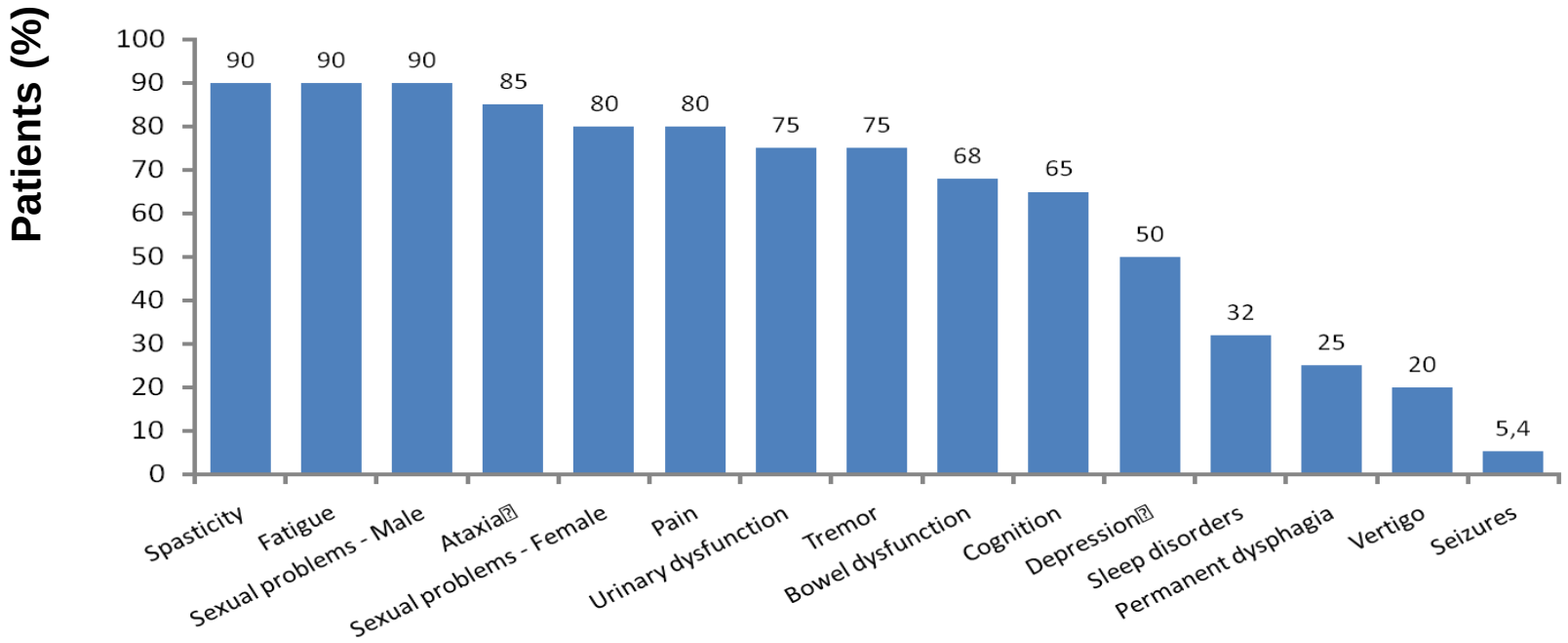
Hospital Clínico San Carlos, Madrid

Spain

Disclosures

Dr. Celia Oreja-Guevara received honoraria for consultancy and/or speaking from Biogen-Idec, Genzyme, Bayer-Schering, Merck-Serono, Roche, Teva and Novartis

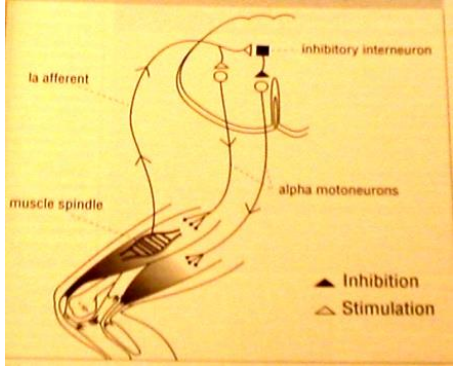
Prevalence of co-morbidities and associated symptoms in patients with MS



- The numerous symptoms and co-morbidities associated with MS can negatively impact patient quality of life (QoL), and places a burden on carers, family, friends and other support networks
- Many MS-related symptoms are frequently ignored in assessments of disease status and often thought not to be associated with the disease

Correia de Sá J, et al. Ther Adv Neurol Disord 2011; 4:139–168.

Spasticity: a common symptom in patients with MS



Spasticity is one of the most common and disabling symptoms in MS patients and approximately 84% of patients with MS experience spasticity during their lifetime

Spasticity in MS is a chronic symptom which can cause pain, spasms, gait disorders, urinary dysfunction, sleep alterations and daily life activity impairment.

Oreja-Guevara C. et al., Expert Rev Neurother 2012 Apr;12:3-8

Spasticity is common in MS

- Most MS patients complain of spasticity:

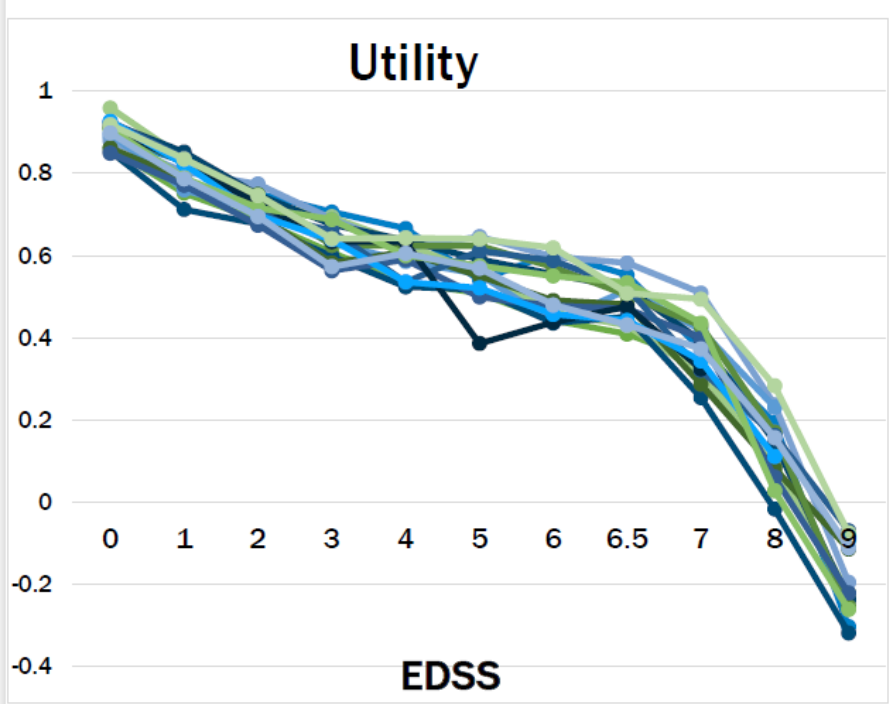
	No spasticity	Minimal-mild spasticity	Moderate spasticity	Severe spasticity
% of patients (**n=20 969**)	15.7	50.3	17.2	16.8
Disability PDDS*, p≤0.0001	1.6	3.5	4.8	5.9
QoL (SF-36) (n=9244)	n=1492	n=4608	n=1530	n=1614
PCS**	47.4	39.3	32.7	28.7
MCS***	52.1	51.3	48.2	45.8

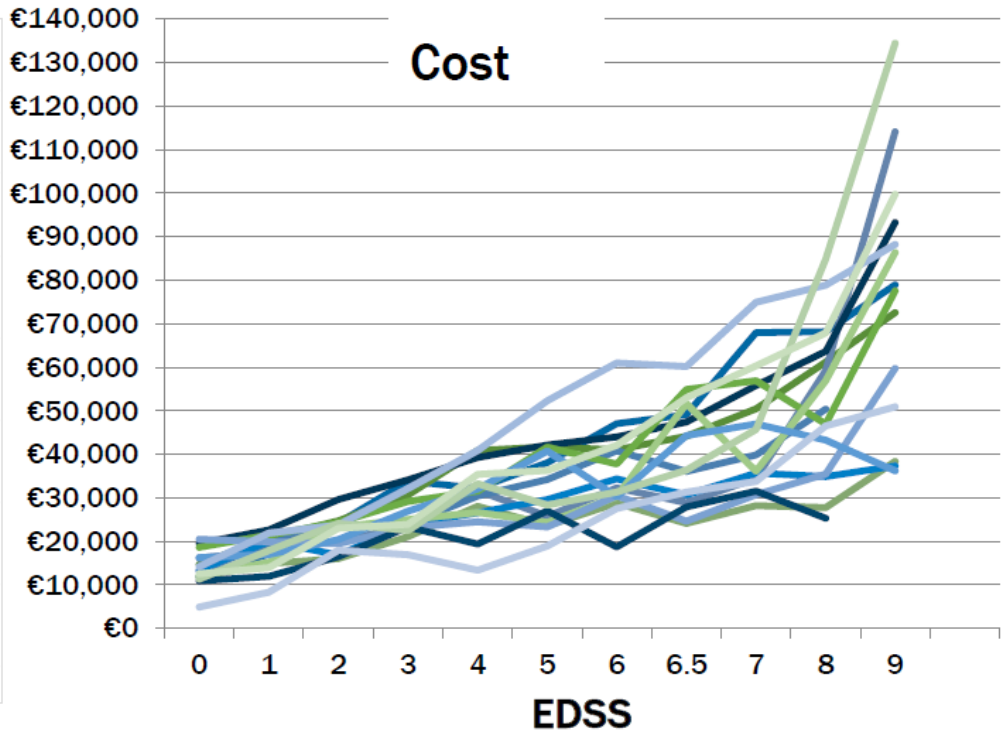
* Patient Determined Disease Steps; ** Physical Summary Score; *** Mental Summary Score

- Around 10.000 European MS patients present with spasticity requiring a baclofen pump or surgery, but the drawbacks of these techniques minimize their utility. Between 40 and 84 % of MS patients suffered from spasticity.

Rizzo et al. Mult Scler 2004; 10: 589-595

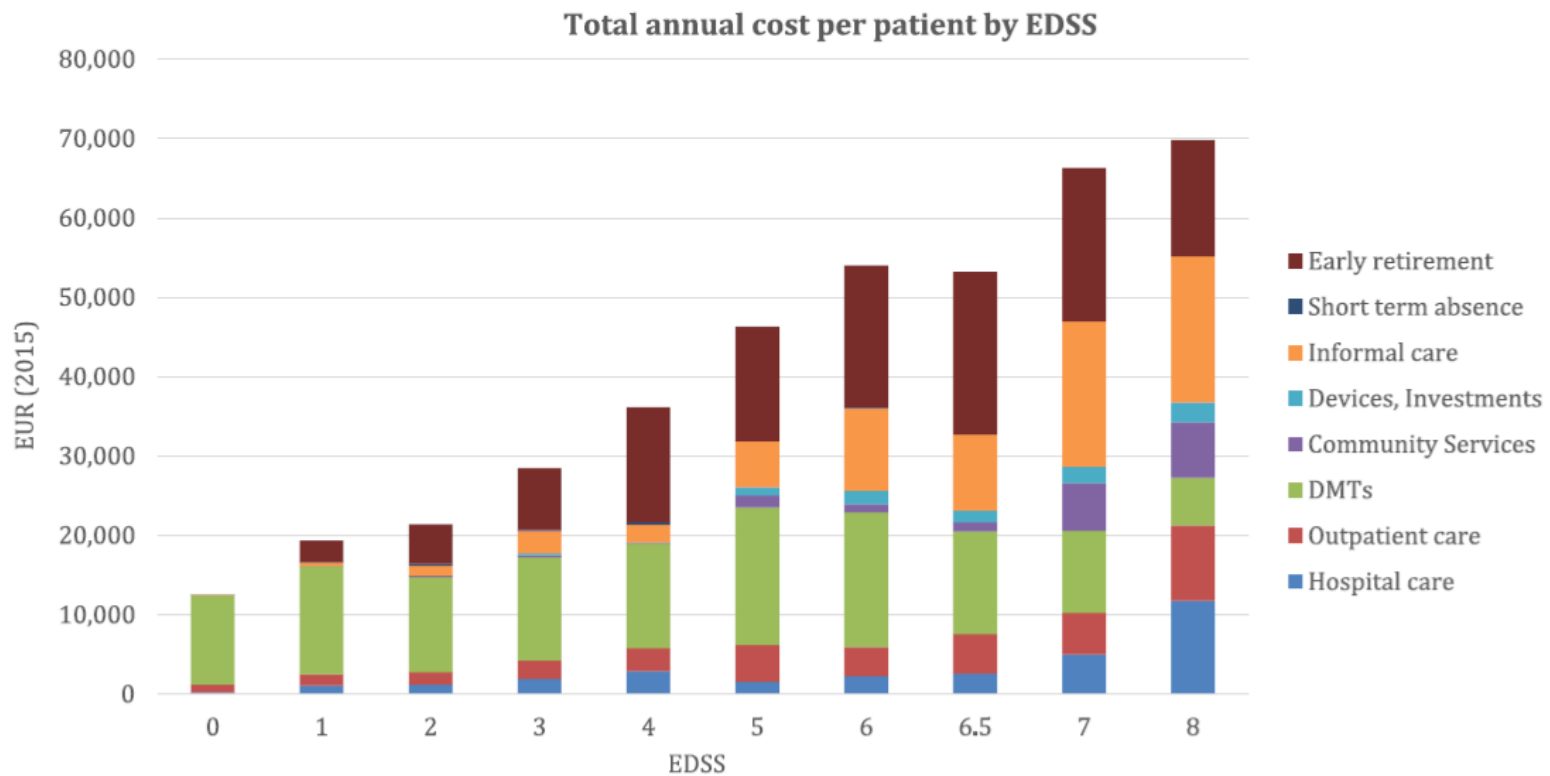
Effect of disease progression





Kobelt G et al. New insights into the burden and costs of multiple sclerosis in Europe. Mult Scler. 2017 Jul;23(8):1123-1136.

Cost structure
SPAIN (N=462)



Oreja-Guevara C, Kobelt G, Berg J, Capsa D, Eriksson J; European Multiple Sclerosis Platform. New insights into the burden and costs of multiple sclerosis in Europe: Results for Spain. Mult Scler. 2017 Aug;23(2_suppl):166-178.

Precipitating and aggravating factors

- The main trigger factors are:
- Fatigue, stress, urinary tract infections, infection of other origins, fever and pain
- Associated therapy should also be considered, as medication for comorbidities might also have an effect on spasticity:
  - Steroid treatment
  - Interferon Beta

Consequences of spasticity

- Restricted movement/mobility
- Reduced range of joint motion
- Altered limb positioning
- Gait disturbances
- Altered bladder and bowel function
- Sleep disturbances
- Contractures
  - Permanent shortening of muscle, leading to deformation
  - Limbs can become fixed in one position
- Pain

Kesselring J, Beer S. Lancet Neurol 2005; 4: 643–652 , Oreja-Guevara C Int J Neurosci. 2013

Spasticity assessment

- Ashworth scale: the most commonly used scale
- Numerical Rating Scale (NRS):symptom severity is estimated by the patient
- Spasm Frequency Scale of Penn: to assess the number of spasms in the last 24 hours in the affected extremity
- Other less common scales are:
    - Multiple Sclerosis Spasticity Scale (MSSS)
    - Daily mean spasm score

de Sá JCC, *et al*. *Ther Adv Neurol Disord* 2011; 4:139–168., biering-Sorensen 2006

Recommendations for treatment

- Effective management of spasticity needs a multidisciplinary approach
- Spasticity requires both pharmacological and non-pharmacological interventions
- Spasticity treatment must only be initiated after rigorous clinical analysis, in order to determine the condition's intensity, true consequences and distribution
- Titration to achieve the optimal dosage is generally required
- When choosing a specific treatment: effectiveness, side-effects and interactions should be considered

Haselkorn 2005, Thompson 2005

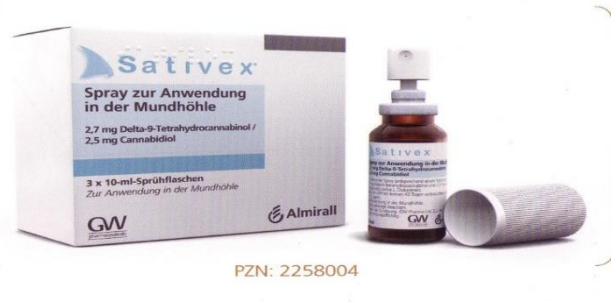
Oral Baclofen (Lioresal)

- Effective in reducing spasms and pain, which can lead to an improvement in gait and overall function
- Side-effects: dry mouth, confusion, drowsiness and nausea
- Starting at a low dose and slowly titrated up

Tizanidine (Sirdalud)

- Effective for painful spasms
- Titration should be very slow until reaching a dose of 36 mg/day
- Side-effects : Drowsiness,Hypotension,Dizziness
- Regular liver function monitoring is required

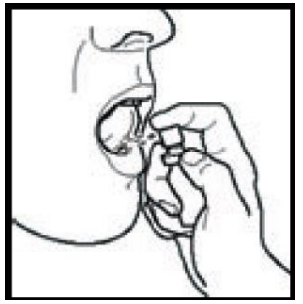
Nabiximol (Sativex)



- Sativex is an endocannabinoid system modulator
- It is a unique cannabinoid-based medicine derived from the active principles of *Cannabis sativa,* THC and CBD
- These 2 cannabinoids account for about 70% of the composition of Sativex; the remaining 30% comprises minor cannabinoids, terpenoids, sterols and triglycerides
- Not recreational cannabis

SmPC Sativex® Oromucosal Spray. February 2014; Oreja-Guevara Expert Rev Neurother 2012; Oreja-Guevara Rev Neurol 2012

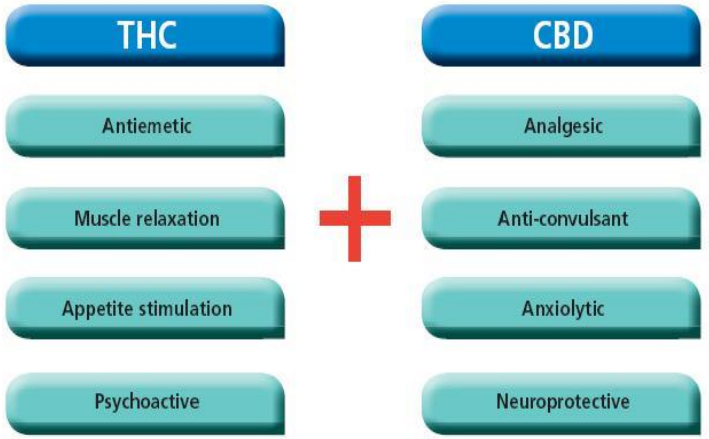
THC:CBD oromucosal spray: Indication



Sativex is indicated as:

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

Second line therapy



EMA SmPC Sativex® Oromucosal Spray March 2015.

Spanish THC:CBD Registry

- 13 MS centres, follow-up at 6 and 12 months between July 2011 and December 2012
- 207 patients, mean age 48.6 years, 62% female
- Mean dose was 6.6 sprays / day
- 35% discontinued treatment (30% until 6 months, 5% between 6 and 12 months)
- Reasons for discontinuation: 1/2 because of lack of effectiveness, 1/2 related to tolerability
- Low rate of adverse events
- No evidence of addiction, abuse or misuse
- More than two-thirds reported driving benefit from THC:CBD spray despite having spasticity resistant to treatment with current antispastic drugs

Oreja-Guevara et al. Clinical Exp Pharmacology 2015

Botulinum toxin A

- Can achieve highly selective blockade of neuronal transmission within individual muscles
- Useful for **focal spasticity**, when spasticity is limiting function
- Achieves reduction in muscle tone, relieving associated stiffness and pain
- Onset of effect is 1–2 weeks post treatment and lasts for about 3 months
- Physiotherapy should be carried out in conjunction with Botulinum toxin A
- Side-effects of treatment are transient and generally related to injection, including muscle pain, bruising and fever. Additionally increased weakness with loss of function can be a problem

Spanish consensus of MS spasticity

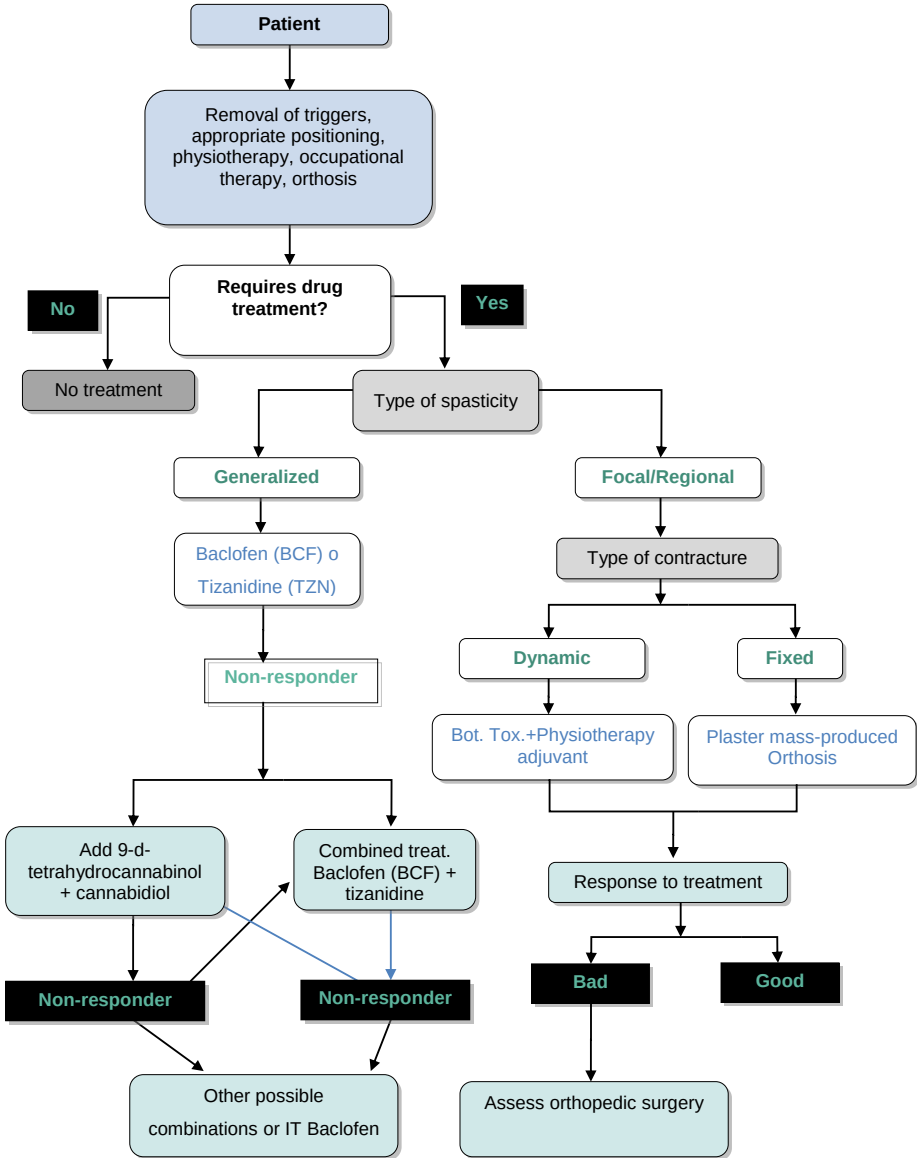
- The Spanish Society of Neurology (SEN) demyelinating diseases working group has developed a consensus document on management of spasticity in patients with MS.

- MS experts from the group used the metaplan method to sum up the most important available information for MS spasticity management to be included it in this guidance document.

- The outcoming recommendations were classified according to the SIGN (Scottish Intercollegiate Guidelines Network) levels of evidence system and approved by members of the group.

Oreja-Guevara, C, Montalban X, de Andres C et al. . Rev Neurol 2013 oct 16;57:359-73

MS spasticity management algorithm



Oreja-Guevara, C, Montalban X, de Andres C et al. . Rev Neurol 2013 oct 16;57:359-73

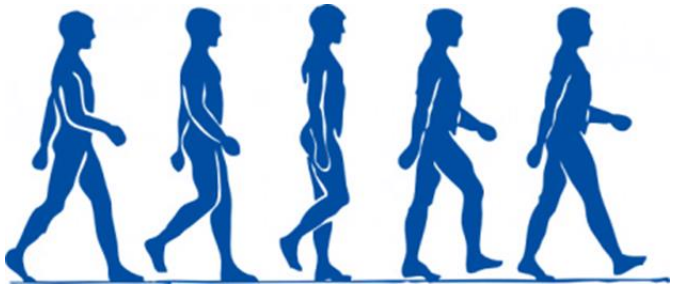
Non-pharmacological treatment

- Physiotherapy represents the mainstay in the management of spasticity.
- The aim of physiotherapy is:
  - to reduce abnormal sensory inputs and decrease alpha-motor neuron activity
  - the most common techniques are: Bobath, Vojta and proprioceptive neuromuscular facilitation; all appear to be of roughly equal efficacy, despite their different rationale
  - other treatment modalities, such as cooling and hydrotherapy are reported to exhibit a transient beneficial effect on elevated muscle tone

Gracies, 2001

Gait disturbances in MS

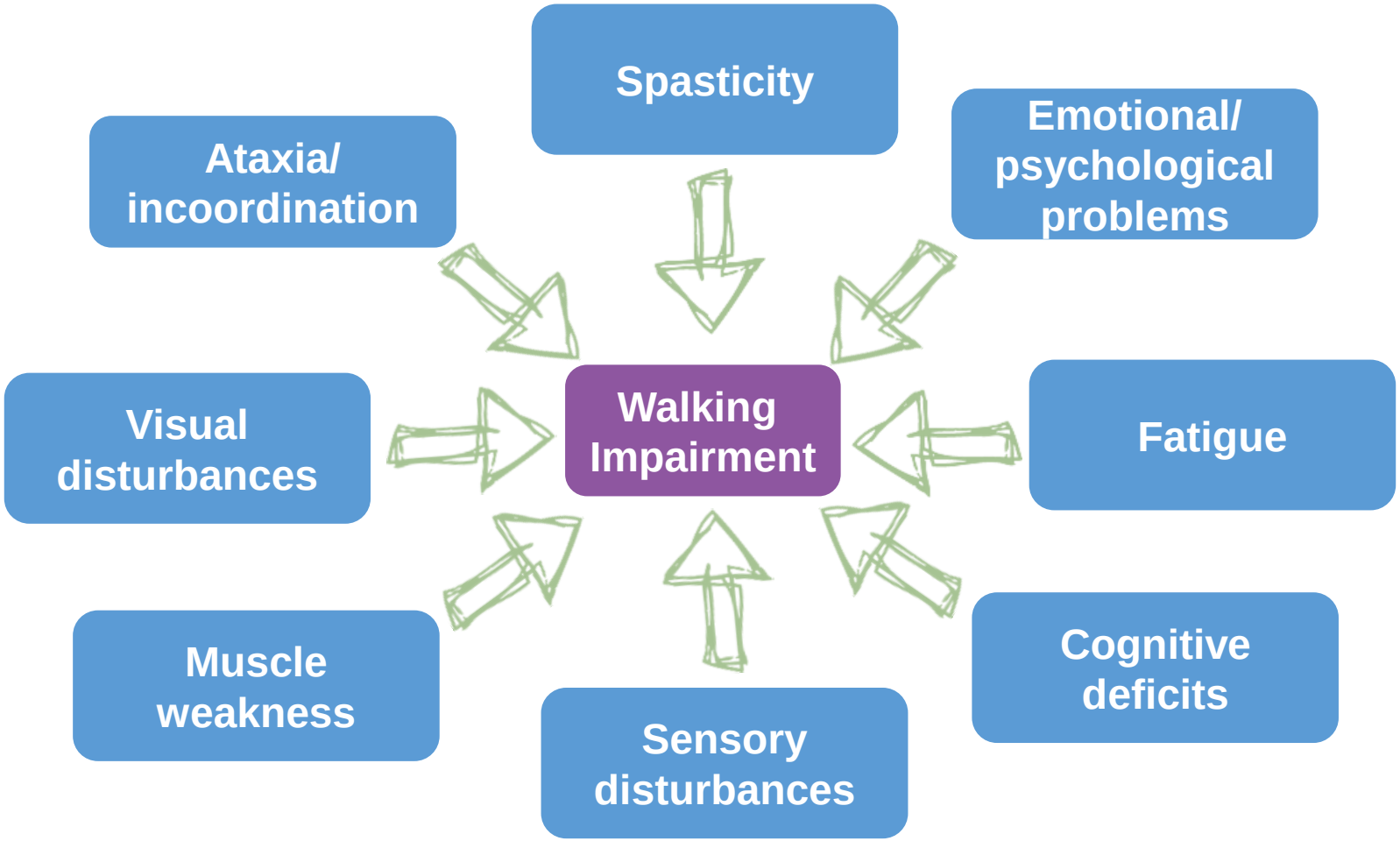
- Walking integrates multiple functional systems, including
  - motor (pyramidal and extra pyramidal)
  - sensory (proprioception)
  - visual
  - cerebellar
  - vestibular



- Up to 58% of patients reported problems with some aspect of mobility in the first year following diagnosis of MS[1]
- Up to 93% of patients reported mobility problems within 10 years of diagnosis[1]
- 70% of patients with walking difficulty state that it is the most challenging aspect of their MS[2]

1. Van Asch P. European Neurol Rev 2011;6:115–120; 2. LaRocca NG. Patient 2011;4:189–201

Multiple factors can cause walking impairment



How to measure walking in MS

Objective walking tests	Patient-reported scales
Short Distance ▪ **Timed 25-Foot Walk Test** ▪ Ambulation Index Dynamic Gait ▪ Six Spot Step Test ▪ Timed Up and Go Test Endurance ▪ Maximum distance ▪ 6-Minute Walk Test ▪ 2-Minute Walk Test ▪ Pedometer/Accelerometer	▪ **MS Walking Scale (MSWS-12)** ▪ Patient-specific goals

The Timed 25-Foot Walk (T25FW)

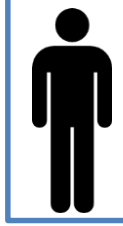
T25FW[1-5]

Standard test **to evaluate severity of MS with respect to ambulatory function irrespective of MS stage or need for ambulation aids**

- Validated
- Known test-retest reliability
- Responsive

- Easily performed in a typical institutional setting
- Sensitive and reproducible, requiring relatively little training and showing little practice effect[6]
- Normal healthy mean T25FW times are approximately:[7]

5.5 seconds for women, age 40



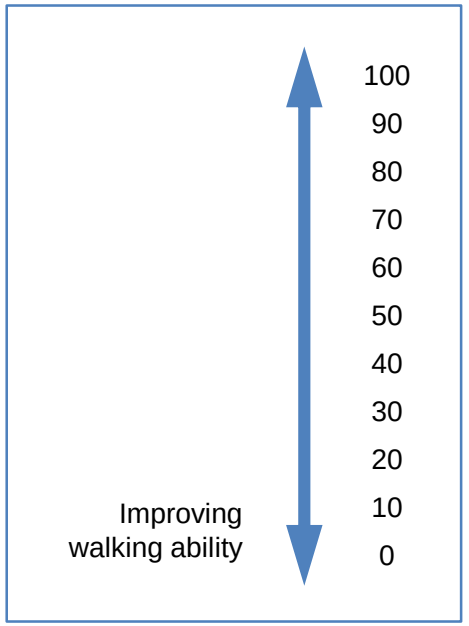
5.2 seconds for men, age 40

1. Schwid SR, et al. *Neurology* 2002;58:1294–1296; 2. Kaufman MD, et al. *Mult Scler* 2000;6:286–290;
3. Hoogervorst EL, et al. *Mult Scler* 2004;10:55–60; 4. Kragt JJ, et al. *Mult Scler* 2006;12:594–598; 5. van Winsen LM, et al. *Mult Scler*

The MS walking scale (MSWS-12)

MSWS-12

A validated, patient-reported outcome measure reflecting the impact of MS impairments on walking ability



- This 12 item scale assesses:

1. Walking
2. Standing
3. Effort
4. Smoothness
5. Running
6. Maintaining balance
7. Need for support indoors
8. Need for support outdoors
9. Climbing stairs
10. Distance
11. Speed
12. Mental concentration

Patients rate limitations of their walking ability due to MS during the preceding two weeks

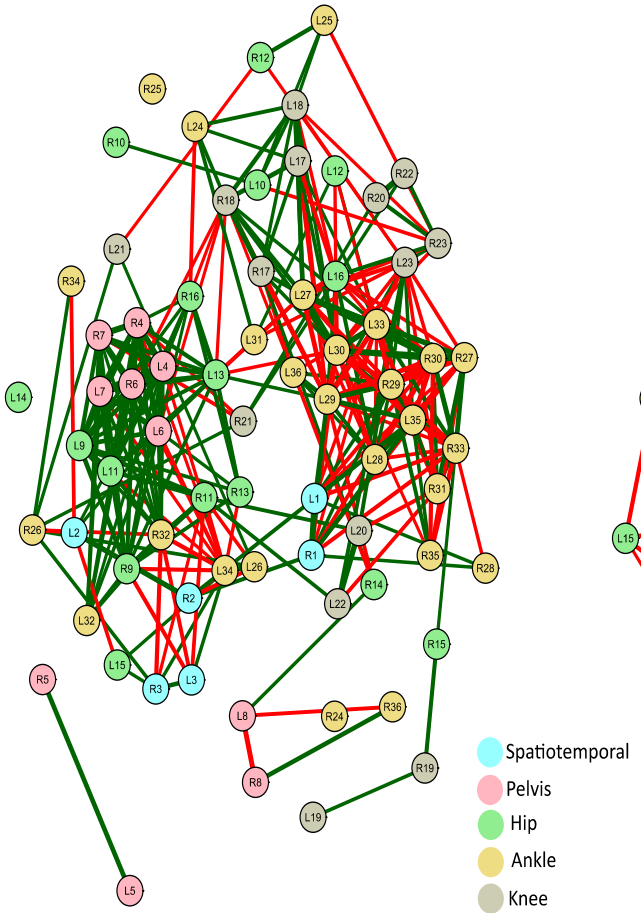
.

A reduction of four to six points on the MSWS-12 is clinically meaningful

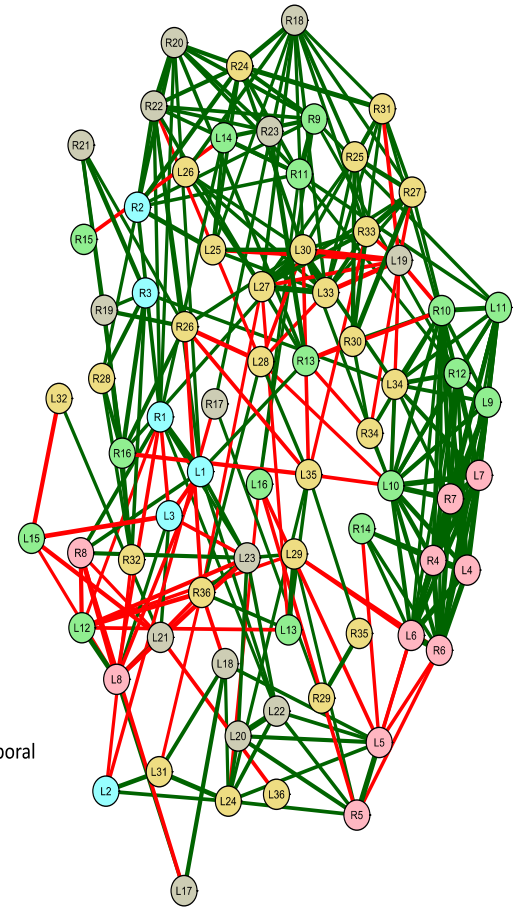
Hobart JC, et al. *Neurology* 2003;60:31–36

SOCIAL NETWORK EN EMPP

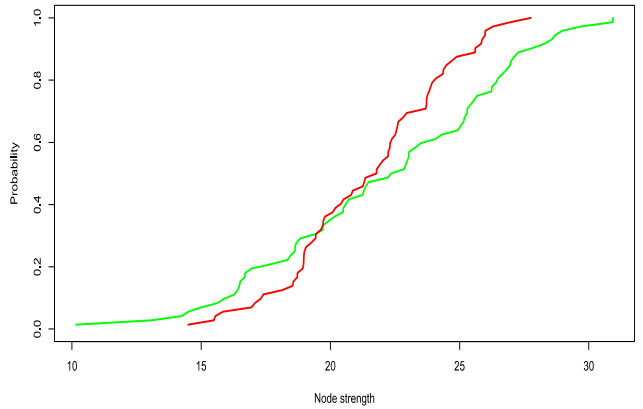
Healthy volunteers



PPMS



Cumulative degree distribution

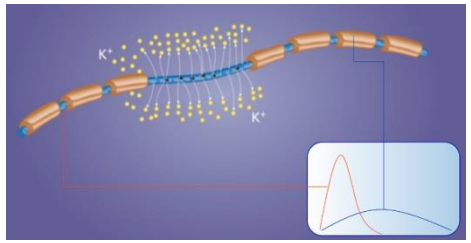


1	Normalized walking speed	19	Time to minimum knee flexion in stance
2	Cadence	20	Maximum knee flexion
3	Stance time	21	Time to peak knee flexion
4	Mean pelvic tilt	22	Maximum knee flexion in swing
5	Range of pelvic tilt	23	Range of knee flexion
6	Minimum pelvic tilt	24	Dorsiflexion at initial contact
7	Maximum pelvic tilt	25	Maximum ankle dorsiflexion in stance
8	Mean pelvic rotation	26	Time to maximum ankle dorsiflexion in stance
9	Hip flexion at initial contact	27	Minimum ankle dorsiflexion in stance
10	Minimum hip flexion	28	Time to minimum ankle dorsiflexion in stance
11	Maximum hip flexion in swing	29	Range of ankle dorsiflexion in stance
12	Time to maximum hip flexion in swing	30	Ankle dorsiflexion at toe off
13	Range of hip flexion	31	Maximum ankle dorsiflexion in swing
14	Maximum hip abduction in swing	32	Time to maximum ankle dorsiflexion in swing
15	Time to maximum hip abduction in swing	33	Minimum ankle dorsiflexion in swing
16	Mean hip rotation in stance	34	Time to minimum ankle dorsiflexion in swing
17	Knee flexion at initial contact	35	Range of ankle dorsiflexion in swing
18	Minimum knee flexion in stance	36	Mean foot progression in stance

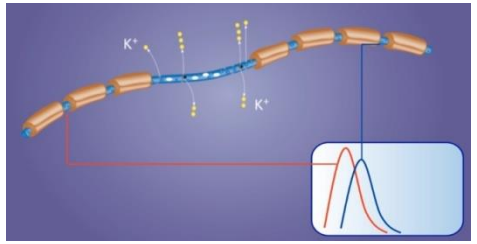
González I, Oreja-Guevara, Ectrims 2015

Fampridine: first treatment to improve the walking impairment

Molecule	• PR-fampridine (4-aminopyridine) is a voltage-dependent potassium channel blocker*
Formulation	• Twice daily, every 12 hours oral PR 10-mg tablet
Molecular hypothesis	• Blocks voltage-gated K+ channels • Has high affinity for K+ channels that are exposed in demyelinated axons • Blockade of K+ channels prolongs action potentials and overcomes conduction failure in demyelinated neurons



Without PR-fampridine



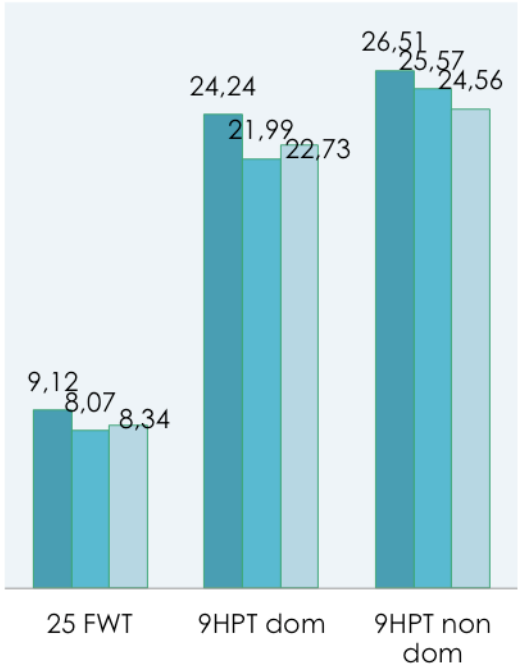
With PR-fampridine

- K+ = potassium; PR = prolonged-release.
- Dunn J, Blight A. Curr Med Res Opin 2011;27(7):1415–1423. FAMPYRA Summary of Product Characteristics, European Medicines Agency. Date of last update: August 4, 2016.

Therapeutic indication

- Fampridine is indicated for the improvement of walking in adult patients with MS with walking disability (EDSS 4–7)
- Initial prescription should be limited to 2 weeks of therapy as clinical benefits should generally be identified within 2 weeks of starting fampridine
- A timed walking test (eg T25FW) is recommended to evaluate improvement after 2 weeks. If no improvement is observed, fampridine should be discontinued
- fampridine should be discontinued if benefit is not reported by patients
- Approximately 38% of patients treated with PR-fampridine showed improvement in walking speed across clinical trials

Fampridine improves manual skills and information processing speed in PPMS patients



	Baseline	15th day	6m	p
EDSS, mean points (SD)	5.72 (0.67)	5.44 (0.63)	5.50 (0.66)	**0.06**
25FWT, mean seconds (SD)	9.12(2.27)	8.07 (1.88)	8.34 (1.85)	**0.06**
AI	3.78 (0.67)	3.00 (1.0)	3.11 (1.05)	**0.039**
MSWS-12, mean points (SD)	44.90 (9.74)	30.22 (11.28)		**0.02**
9HPT dom, mean seconds (SD)	24.24(3.24)	21.99(SD4.14)	22.73(4.97)	**0.04**
9HPT n-do, mean seconds(SD)	26.51(9.18)	25.57 (SD8.87)	24.56(8.89)	**0.02**
SDMT, mean points (SD)	34.71 (7.41)	38.0 (10.44)	40.57 (9.81)	**0.05**

González I, Oreja-Guevara, Ectrims 2015

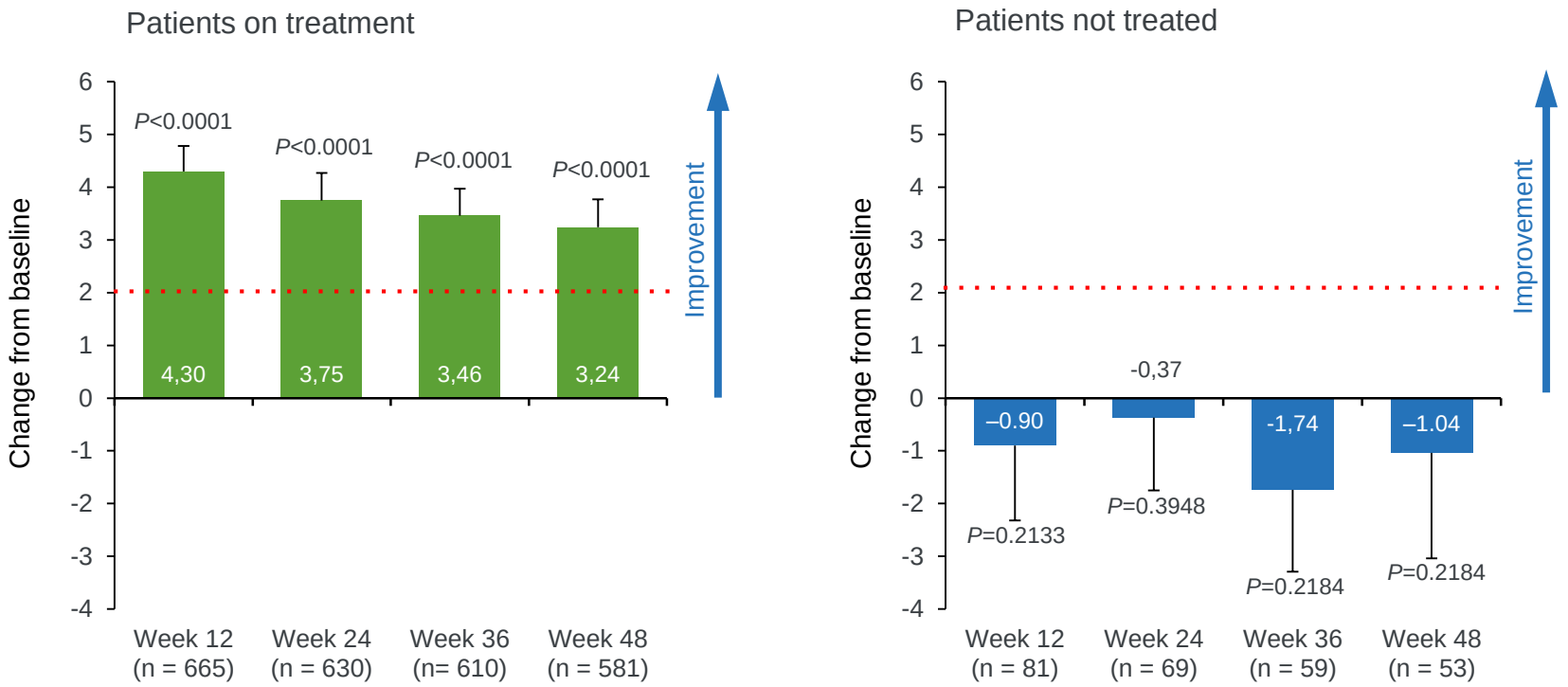
Conclusion

- Spasticity in MS is a chronic and a common symptom which can cause pain, spasms, gait disorders, urinary dysfunction and impairment of activities of daily life
- Early recognition of spasticity allows us to treat the patients at the right timepoint
- An individualised therapeutic plan for spasticity for each patient should be considered; oral treatments are generally prescribed in the early stages of spasticity, whereas invasive treatments are generally reserved for patients with more severe disability
- PR-fampridine has a favourable benefit-risk profile for the treatment of gait disturbances
- By improving spasticity and gait impairment we can greatly improve the quality of life of our patients

MUCHAS GRACIAS

ENABLE: SF-36 PCS

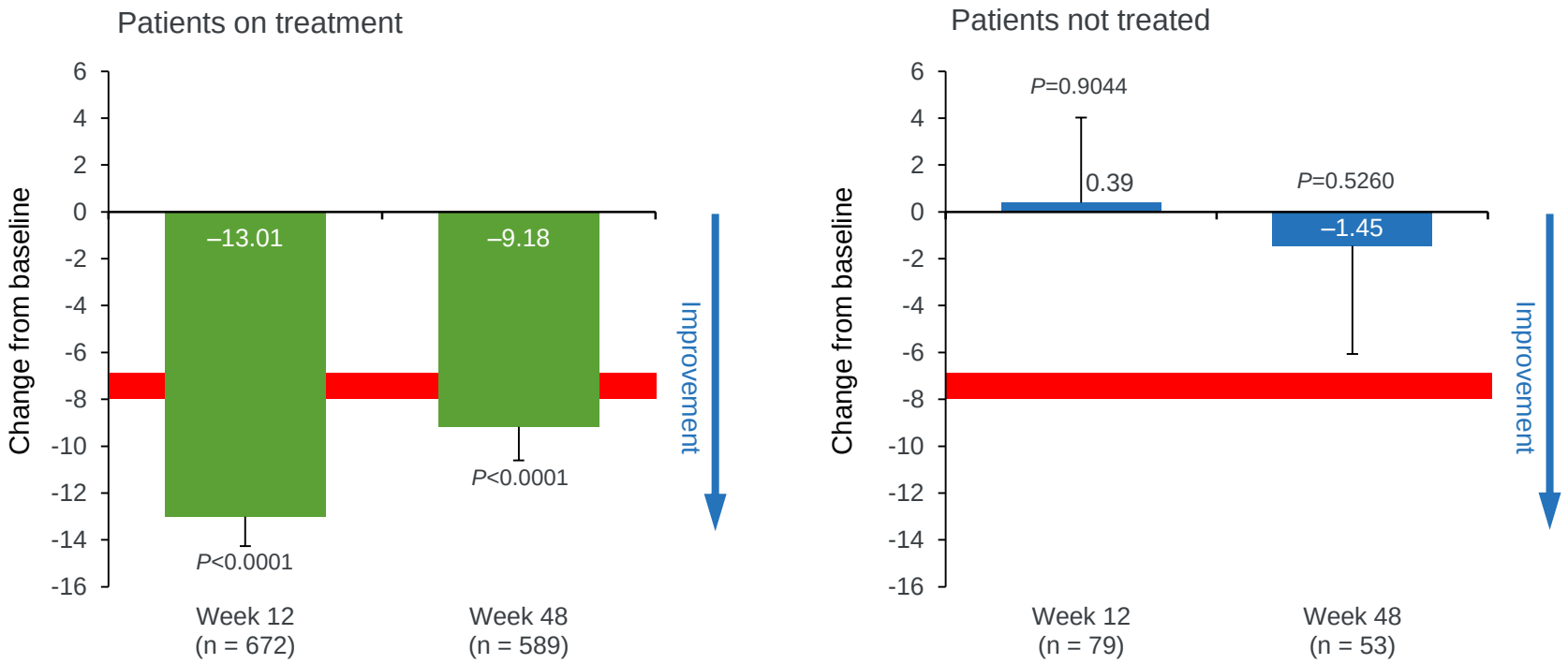
SF-36 PCS



Red dotted line: the change of more than two points indicates a minimal clinically important difference from Weeks 12–48.
PCS = physical component summary; SF-36 = 36-Item Short-Form Health Survey.
Macdonell R et al. Mult Scler 2016;22(7):944–954.

ENABLE: MSIS-29 PHYS

MSIS-29 PHYS



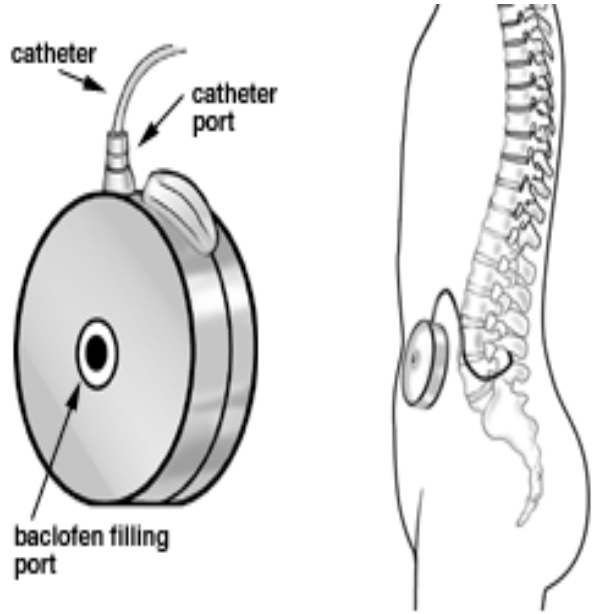
Red line: the change in the range of 7-8 indicates a minimum clinically important difference from Weeks 12–48. Data are mean (95% confidence interval).
MSIS-29 = 29-item Multiple Sclerosis Impact Scale; PHYS = physical impact subscale.
Macdonell R et al. Mult Scler 2016;22(7):944–954.

Intrathecal baclofen

It is useful In MS patients with severe spasticity, with limited mobility, long term evolution and /or generalized, resistant to oral treatments spasticity,.

The baclofen pump works by directly delivering liquid baclofen to the lower cord through the CSF and avoiding the problem of systemic absorption leading to sedation.

Problems with the pump include pump failure, infection, and lead displacement



intrathecal baclofen pump system

The importance of considering MS-related symptoms

- The numerous symptoms and co-morbidities associated with MS can negatively impact patient quality of life (QoL), and places a burden on carers, family, friends and other support networks

- Many MS-related symptoms are frequently ignored in assessments of disease status and often thought not to be associated with the disease

de Sá JCC, *et al*. *Ther Adv Neurol Disord* 2011; 4:139–168.

Fampridine contraindications

- Hypersensitivity to fampridine or to any of the excipients
- Concurrent treatment with other medicinal products containing fampridine (4-aminopyridine)
- Patients with a prior history or current presentation of seizures
- Patients with mild, moderate or severe renal impairment (creatinine clearances <80ml/min)