Improving the Management of Walking Impairment and Foot Drop in Multiple Sclerosis

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Gait Assessment and Nonpharmacologic Management

Common MS Symptoms

- Fatigue
- Motor impairment − spasticity, weakness
- Gait difficulty
- Cognitive impairment
- Depression
- Pain
- Tremor
- Bladder symptoms
- Bowel symptoms
- Sexual dysfunction

Prevalence of Gait Impairment

- Survey commissioned by the National MS Society
  - 1011 people with MS
- 64% experienced trouble walking at least twice weekly
- Of these, 70% reported it to be the most challenging aspect of their MS

National MS Society. News Detail. March 25, 2008. Accessed 11/11/13 at: http://www.nationalmssociety.org/research/research-news/news-detail/index.aspx?nid=199.

Underreporting of Gait Impairment

- A significant proportion of patients with MS and their caregivers rarely or never discuss mobility issues with a physician
  - 39% of surveyed MS patients (n = 1100)
  - 49% of surveyed caregivers (n = 317)
- Indicates need for neurologists and other MS care providers to initiate conversations about mobility

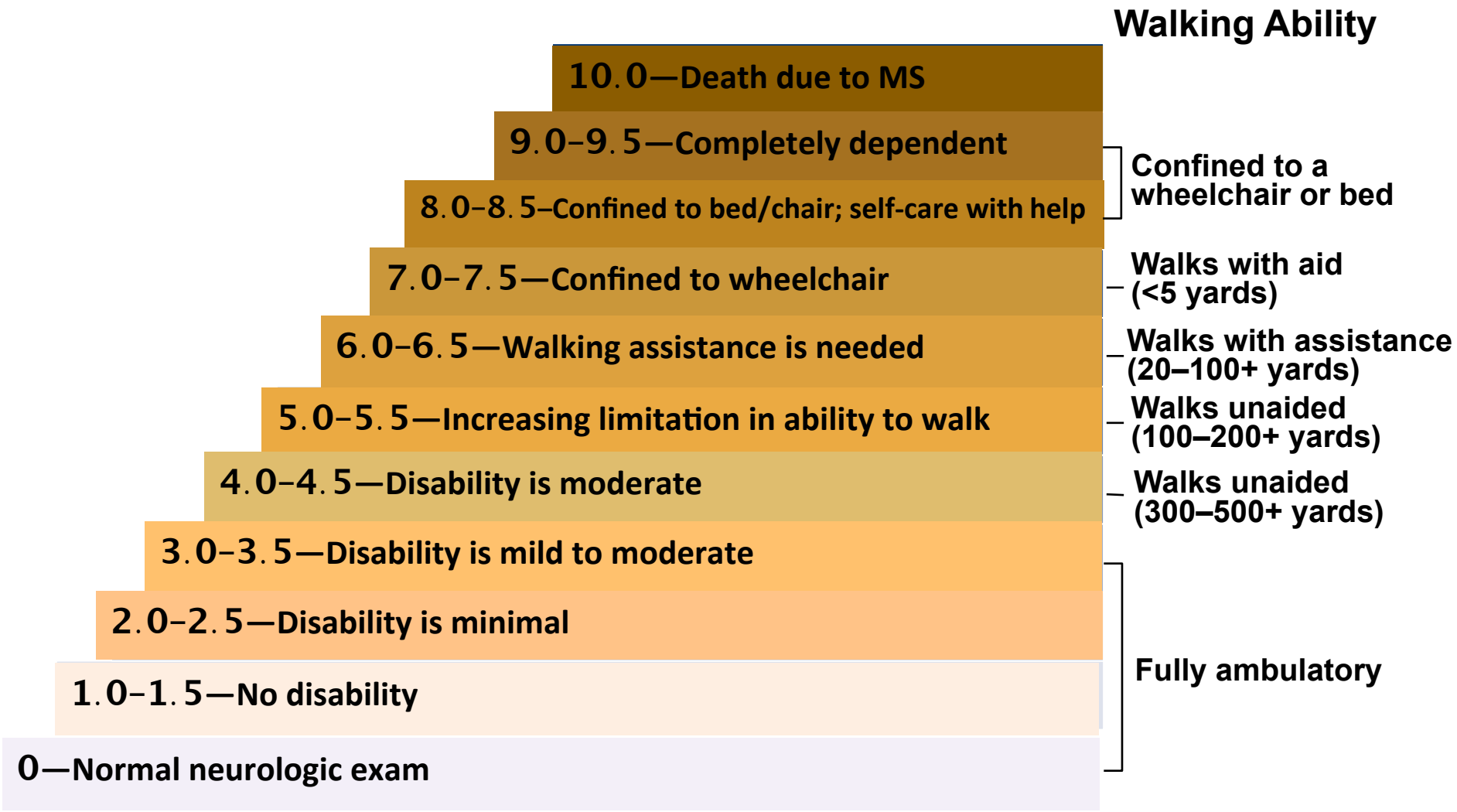
National MS Society. News Detail. March 25, 2008. Accessed 11/11/13 at: http://www.nationalmssociety.org/research/research-news/news-detail/index.aspx?nid=199.

Gait Impairment's Impact on Quality of Life

- Loss of independence
- Physical appearance of disability
- Increased unemployment

Sutliff MH. *Curr Med Res Opin*. 2010;26:109-119.

EDSS—Progression to Disability



Kurtzke JF. *Neurology.* 1983;33:1444-1452. Graphic courtesy of Dr. Andrew D. Goodman.

Ambulation
Definition

- The goal of ambulation is to move from point A to point B safely
- Ambulation not only encompasses typical bi-pedal walking, but also includes locomotion via other means such as with a manual or power wheelchair

Normal Gait
Basic Requirements

- Sufficient antigravity strength to clear the foot during the swing phase of each step
- Stability across the ankle, knee, and hip joints

Common Tools to Measure Gait Impairment

- Clinical assessment of casual gait
  - Spasticity
  - Ataxia
  - Foot drop
- Validated instruments[1]
  - Timed 25-foot walk
  - EDSS (distance walked up to 500 m)
  - 12-Item Multiple Sclerosis Walking Scale (MSWS-12)

1. Bethoux F, et al. *Int J MS Care*. 2011;13:4-14.

Common Gait Abnormalities

- Foot slap due to mild ankle dorsiflexion weakness
- Knee instability with buckling leading to a fall
- Trendelenburg's sign secondary to hip abduction weakness
- Steppage gait with moderate to severe ankle dorsiflexion weakness

Foot Drop in MS

- Mild ADF weakness – Foot slap pattern
  - Initial ground contact will usually occur with the heel, and a loud sound will be heard as the rest of the foot comes down
- Severe ADF weakness – Steppage gait pattern (assuming sufficient hip flexor strength)
  - Knees will raise as if marching and initial contact will be quiet and occur with the front of the foot

Foot Drop in MS

- ADF weakness may not fully manifest on manual motor testing
- Some patients with full strength on manual motor testing may exhibit a foot slap only after walking for some distance or walking quickly
- Detection of such weakness is of paramount importance as insufficient foot clearance puts the patient at risk for further injury

Principles of Management

- Multidisciplinary approaches
  - Rehabilitation
    - Physiatry, physical therapy, occupational therapy
  - Exercise
  - Stretching
  - Assistive devices
- Individualized pharmacotherapy

Assistive Devices for Ambulation

- Single-point canes
- Quad cane
- Forearm crutches
- 4-point folding walker
- Front-wheeled walker
- 4-wheeled walker with seat and active braking system
- 4-wheeled walker with seat and passive braking system (U-Step walker)

Ankle Foot Orthoses

- Posterior leaf spring
- Double metal upright
- Ground reaction force
- Carbon fiber

Functional Electrical Stimulation Devices

- Commercially available
  - Ness L300™
  - WalkAide®
  - Odstock® Dropped Foot Stimulator
- Geared toward assisting foot drop through stimulation of the common fibular nerve

National MS Society. Functional Electrical Stimulation (FES). Accessed 11/12/13 at: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/rehabilitation/functional-electrical-stimulation/index.aspx.

Functional Electrical Stimulation Devices
Contraindications

- Individuals with pacemakers
- Uncontrolled epilepsy
- Skin breakdown in the area of stimulation
- Peripheral nerve injury in the area of stimulation

Fall Prevention Strategies

- Change the environment
  - Install heavy-duty grab bars in showers and tubs and beside toilets
  - Avoid “obstacle courses” in the home
  - Maintain clear pathways inside and out
- Assistive devices

Pharmacologic Management—Dalfampridine-ER, Part 1

Historic Rationale for 4-Aminopyridine in MS

- 4-aminopyridine (4-AP) is a broad spectrum potassium channel blocker
- In animal studies, it was shown to restore conduction of action potentials in focally demyelinated axons through inhibition of potassium channels
- It had been seen as a promising candidate to reverse the underlying neurologic deficits associated with MS demyelination, hopefully restoring neurological function in these patients

Hayes KC. *CNS Drug Rev*. 2004;10:295-316. Hayes KC. *Neuropsychiatric Disease Treatment*. 2011;7:229-239.

4-Aminopyridine (4-AP)

- Fampridine
  - Name used in published studies in clinical development of 4-AP
- Dalfampridine
  - US Adopted Name (USAN) to eliminate confusion with other drugs
- FDA-approved as a treatment to improve walking in patients with MS

4-AP—Clinical Research in MS

- 1992: crossover study (N = 70)[1,2]
  - Broad effects on disability (EDSS)[1]
  - Dose and serum level related to efficacy and safety[2]
  - Plasma levels difficult to control with immediate-release formulation; need for extended-release formulation[2]
- 1994: concentration-controlled, crossover study (N = 8)[3]
  - Improvements in contrast sensitivity, limb strength, neurologic exam
  - No benefit on EDSS
  - Seizure, acute confusional episode at serum levels >100 ng/mL

1. van Diemen HA, et al. *Ann Neurol*. 1992;32:123-130. 2. van Diemen HA, et al. *Clin Neuropharmacol.* 1993;16:195-204. 3. Bever CT Jr, et al. *Neurology.* 1994;44:1054-1059.

Rationale for Extended-Release (ER) Formulation

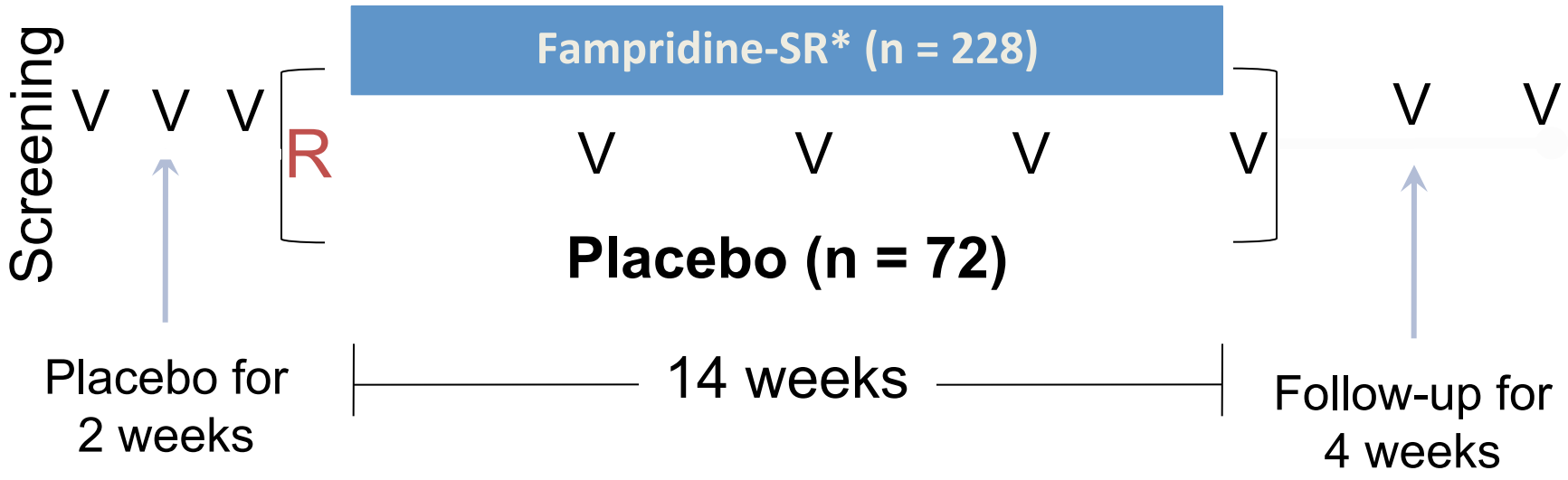
- Immediate-release formulations are limited by
  - Rapid rise in plasma level associated with adverse effects
    - Dizziness, nausea, paresthesias
  - Short half-life, requiring frequent dosing
  - Substantial effect of food on pharmacokinetics
- "Extended release (ER)" = "sustained release (SR)"
  - SR – term used in phase IIIa trial publication
  - ER – term used in phase IIIb trial publication and product label

“Sustained-Release Oral Fampridine in Multiple Sclerosis: A Randomised, Double-Blind, Controlled Trial”

Andrew D. Goodman, Theodore R. Brown, Lauren B. Krupp, Randall T. Schapiro, Steven R. Schwid, Ron Cohen, Lawrence N. Marinucci, Andrew R. Blight; on behalf of the Fampridine MS-F203 Investigators

Goodman AD, et al. *Lancet.* 2009;373:732-738.

Dalfampridine-ER—Phase IIIa Study Design



*10 mg BID.

Abbreviations: R, randomization; V, clinic visit.

Goodman AD, et al. *Lancet.* 2009;373:732-738.

Dalfampridine Phase III Trials
Responder Analysis

- Phase IIIa[1] and IIIb[2] trials
  - Blinded placebo-controlled randomized trials
  - Class I evidence
- Typical data analysis in MS clinical trials
  - Compare mean differences between the placebo and active treatment groups
- "Responder analysis" in dalfampridine phase III trials
  - Compare percentage of patients in each group who responded
  - Used to evaluate primary outcome

1. Goodman AD, et al. *Lancet.* 2009;373:732-738. 2. Goodman AD, et al. *Ann Neurol.* 2010;68:494-502.

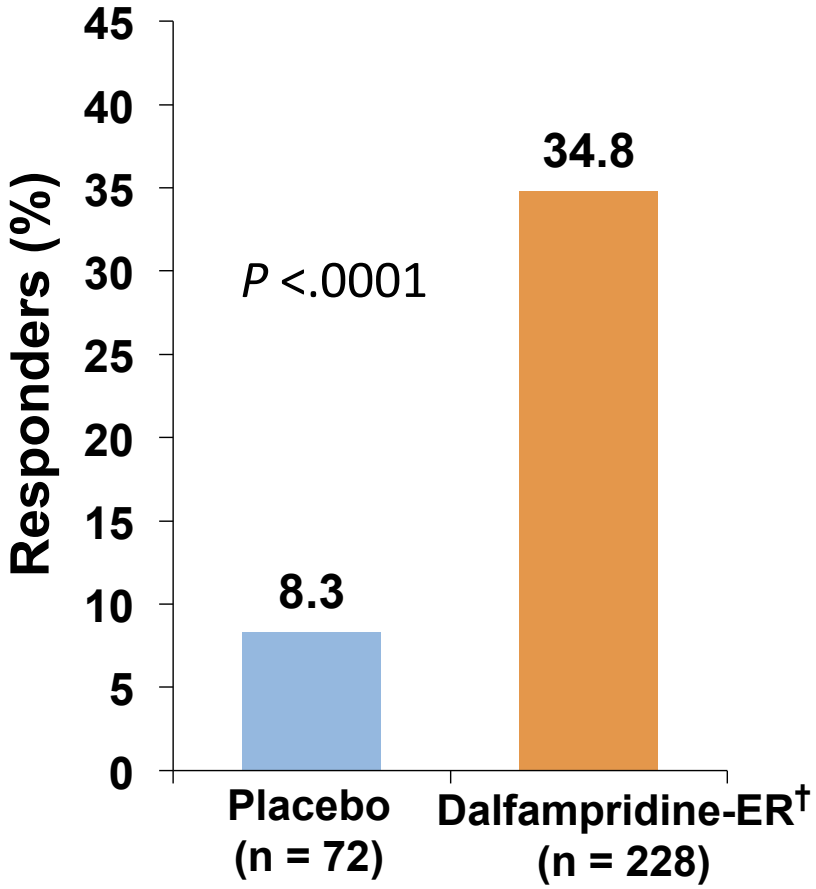
Dalfampridine Phase III Trials
Responder Analysis

- Responder analysis = % of patients in each group who respond, not mean differences between groups
- A method of capturing highly variable response – ie, when some individuals have a high level of response, while others have little or no response
  - Intrapatient variability of MS patients
  - Interpatient variability
    - Some patients responded briefly or not at all
    - Other patients responded very well
- Responder analysis allows assessment on individual basis
  - Consistent with individualized approach to patient care
- Facilitates assessing patient-perceived value of response

Dalfampridine- ER
Phase IIIa Primary Outcome

- Primary outcome = proportion of “timed walk responders”
- Measured by change in walking speed as measured by timed 25-foot walk
- Timed walk responder = a subject whose walking speed on at least 3 of the 4 “on-drug” visits is faster than the fastest speed during any of the 5 “off-drug” visits

Dalfampridine-ER
Timed Walk Responders, Phase IIIa

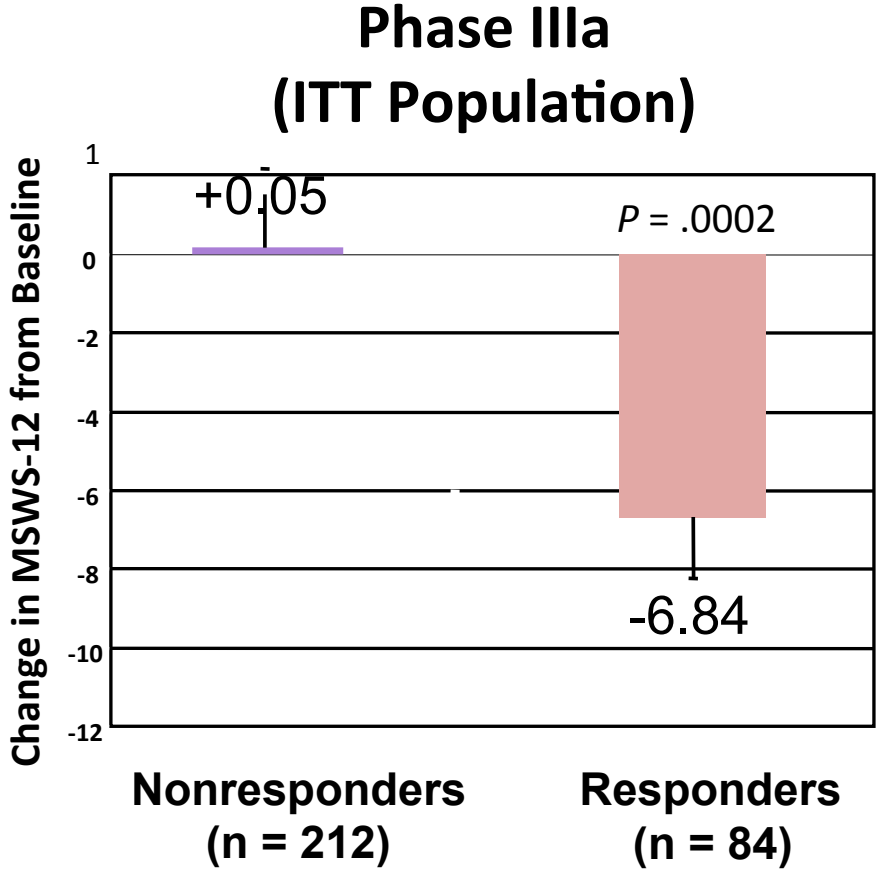


†10 mg BID.

Goodman AD, et al. *Lancet.* 2009;373:732-738.

Dalfampridine-ER

Change in MSWS-12 Score, Phase IIIa



Abbreviations: MSWS, multiple sclerosis walking scale.

Goodman AD, et al. *Lancet.* 2009;373:732-738. Graphic courtesy of Dr. Andrew D. Goodman.

Dalfampridine
First Phase III Trial

- 14-wk study in 301 patients with RRMS, SPMS, PPMS, PRMS
  - 229: Dalfampridine 10 mg BID
  - 72: Placebo
- Proportion of TWRs: Dalfampridine (35%) vs placebo (8%) (*P* <.0001)
- Change from baseline TW: Dalfampridine TWRs (25.2%) vs placebo (4.7%)
- MSWS-12: TWRs* had significantly greater improvement compared to non-TWRs (*P* = .0002)
- Leg strength: Dalfampridine TWRs and non-TWRs had significantly greater improvement compared to placebo patients (.18 and .11 vs .04) (*P* = .0002 and *P* = .046, respectively)

*Independent of treatment group

Abbreviations: MSWS-12, 12-item MS Walking Scale; PPMS, primary progressive MS; PRMS, progressive relapsing MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; TW, Timed 25-foot walk; TWRs, Timed 25-foot walk responders.

Goodman AD, et al. *Lancet*. 2009;373:732-738.

Dalfampridine-ER

Consistent Improvement in Walking Speed, Phase IIIa

- Consistent improvement in walking speed among dalfampridine responders
- Over the course of 14 weeks
  - Difference in magnitude of change in walking speed from baseline
  - Change in walking speed was sustained

Goodman AD, et al. *Lancet.* 2009;373:732-738.

Phase IIIa—Most Frequent Adverse Events

- Serious adverse events
  - Fampridine 7%, placebo 0%
- Most frequent adverse events
  - Falls: Fampridine 16%, placebo 15%
  - UTI: Fampridine 14%, placebo 14%
  - Dizziness: Fampridine 8%, placebo 6%
  - Insomnia: Fampridine 8%, placebo 4%
- Other frequent adverse events
  - URTI: Fampridine 6%, placebo 10%
  - Fatigue, nausea, asthenia, back pain, balance disorder, headache
    - All 6% for fampridine, 6% or less for placebo

Abbreviations: URTI, upper respiratory tract infection; UTI, urinary tract infection.
Goodman AD, et al. *Lancet.* 2009;373:732-738.

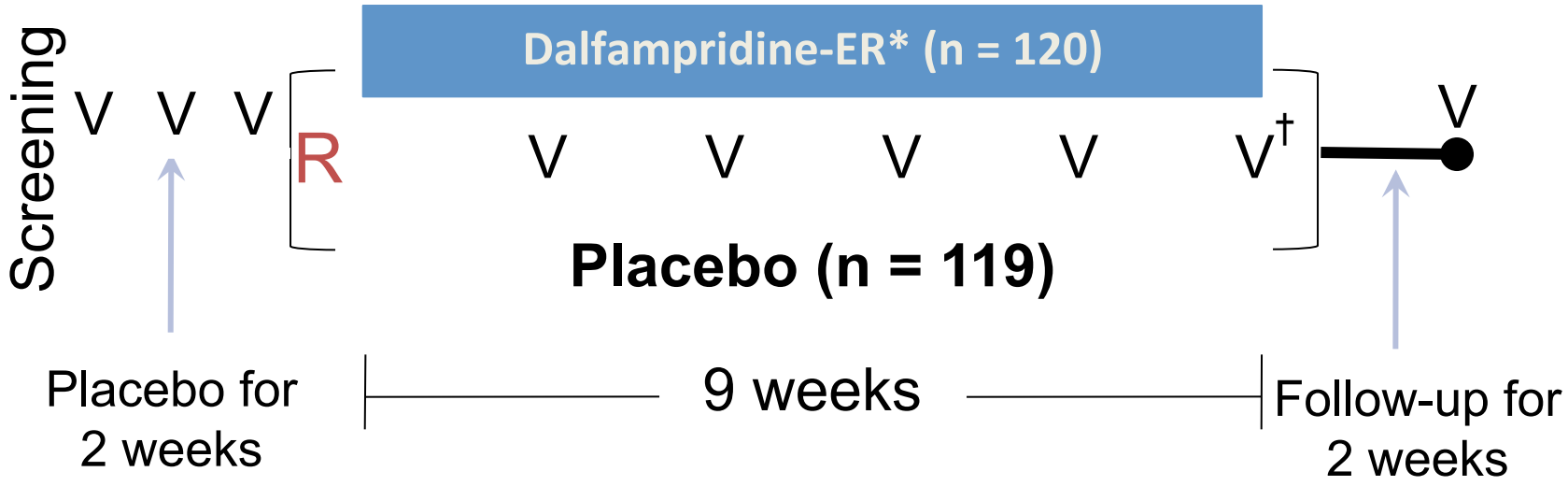
Pharmacologic Management—Dalfampridine-ER, Part 2

“A Phase 3 Trial of Extended Release Oral Dalfampridine in Multiple Sclerosis”

Andrew D. Goodman, Theodore R. Brown,
Keith R. Edwards, Lauren B. Krupp,
Randall T. Schapiro, Ron Cohen,
Lawrence N. Marinucci, Andrew R. Blight;
on behalf of the
MSF204 Investigators

Goodman AD, et al. *Ann Neurol.* 2010;68:494-502.

Dalfampridine-ER
Phase IIIb Study Design



Primary outcome = proportion of "timed walk responders"

Timed walk responder = subject whose walking speed on at least 3 of the 4 "on-drug" visits is faster than the fastest speed during any of the 5 "off-drug" visits

*10 mg BID. †Pharmacodynamics visit

Abbreviations: R, randomization; V, clinic visit.

Goodman AD, et al. *Ann Neurol.* 2010;68:494-502.

Dalfampridine
Second Phase III Trial

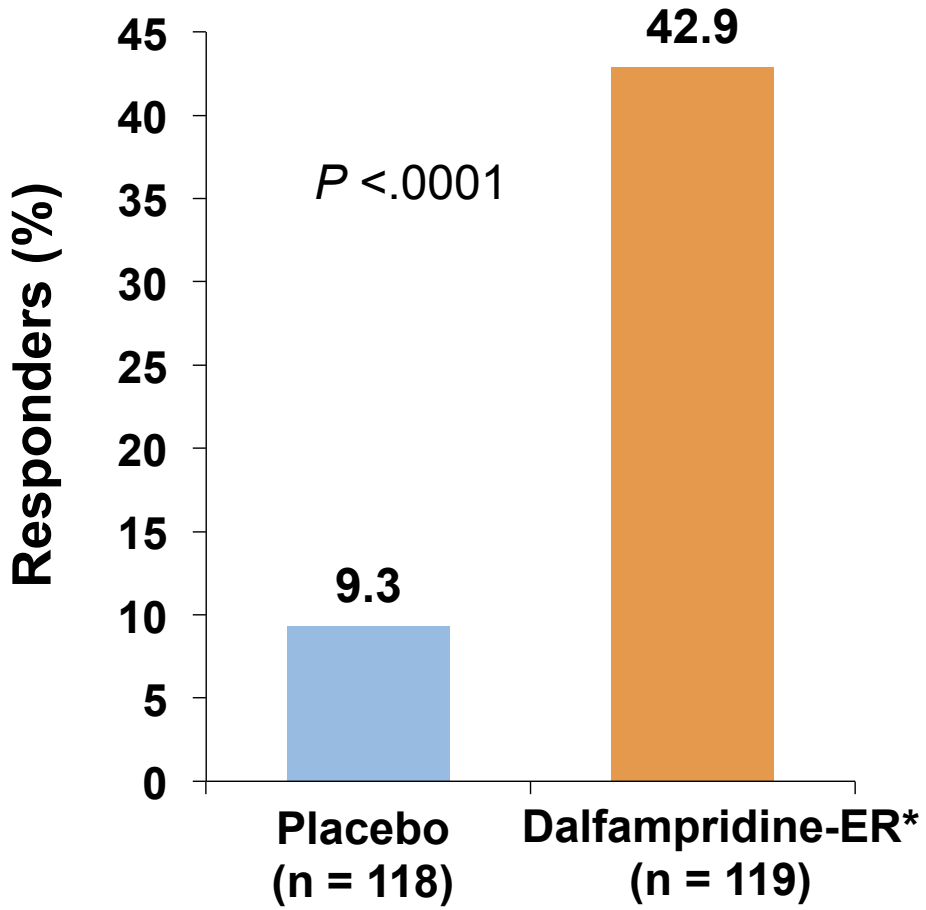
- 9-week study in 237 patients with RRMS, SPMS, PPMS, PRMS
  - 119: Dalfampridine 10 mg twice daily
  - 118: Placebo
- Proportion of TWRs: Dalfampridine (42.9%) vs placebo (9.3%) (*P* <.0001)
- Change from baseline TW: Dalfampridine TWRs (24.7%) vs placebo (7.7%)
- MSWS-12: TWRs* had significantly greater improvement than did non-TWRs (*P* <.001)
- Leg strength: Dalfampridine TWRs had significantly greater improvement (.145 U) compared to placebo patients (.042 U) (*P* = .028)

*Independent of treatment group

Abbreviations: MSWS-12, 12-item MS Walking Scale; PPMS, primary progressive MS; PRMS, progressive relapsing MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; TW, Timed 25-foot walk; TWR, Timed 25-foot walk responder.

Goodman AD, et al. *Ann Neurol*. 2010;68:494-502.

Dalfampridine-ER
Timed Walk Responders, Phase IIIb

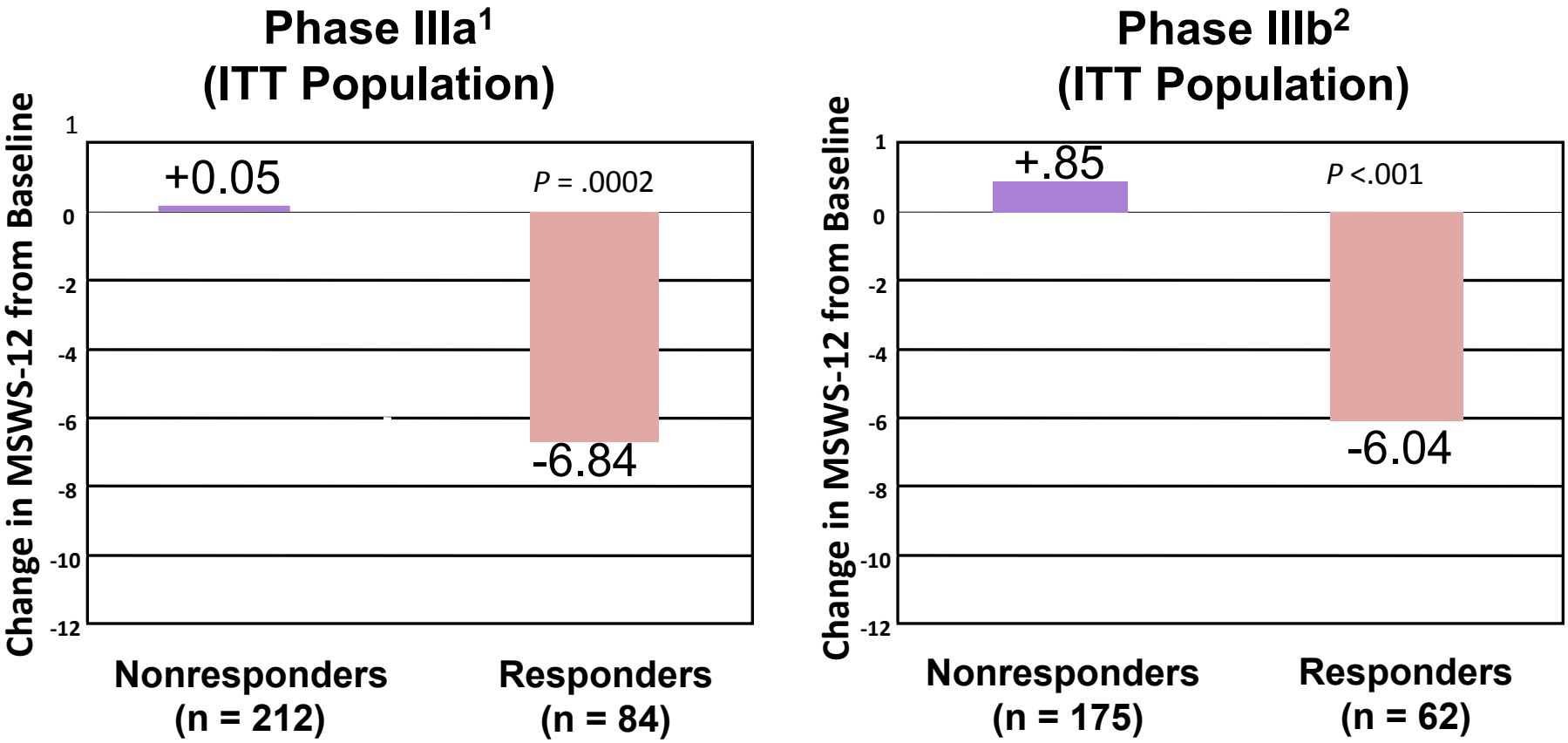


*10 mg BID.

Goodman AD, et al. *Ann Neurol.* 2010;68:494-502.

Dalfampridine-ER

Change in MSWS-12 Score, Phase IIIa and IIIb

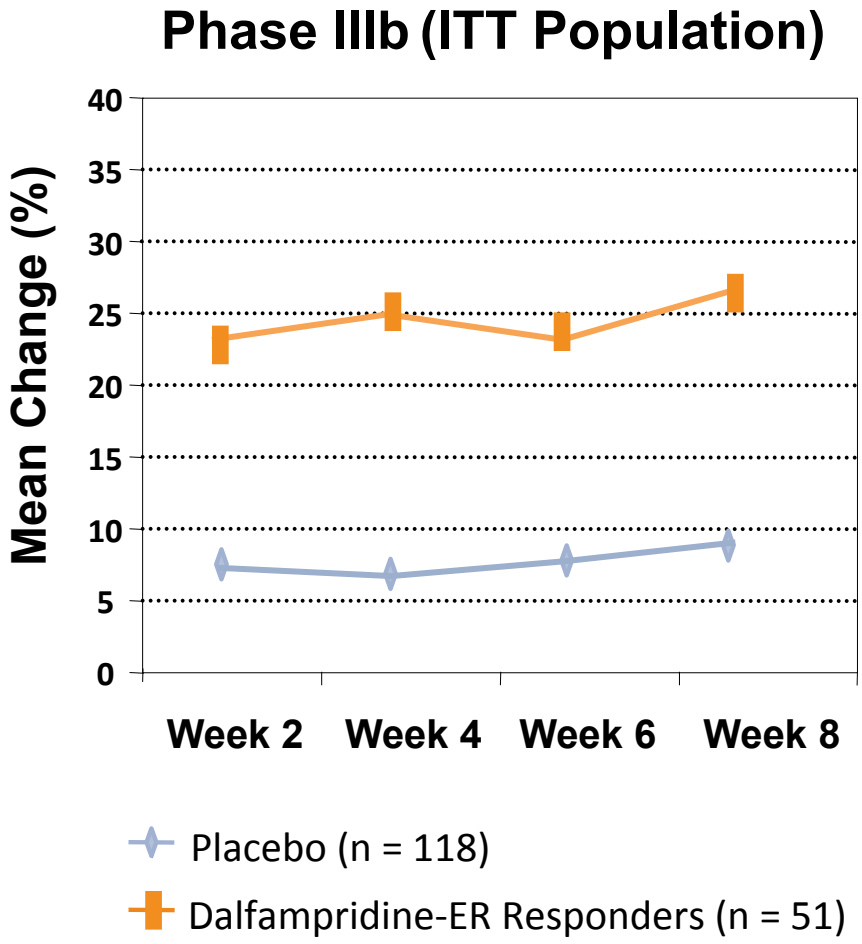


Abbreviations: MSWS, multiple sclerosis walking scale.

1. Goodman AD, et al. *Lancet.* 2009;373:732-738. 2. Goodman AD, et al. *Ann Neurol.* 2010;68:494-502. Graphics courtesy of Dr. Andrew D. Goodman.

Dalfampridine-ER

Efficacy in Walking Speed Over Time, Phase IIIb



With permission from Goodman AD, et al. *Ann Neurol.* 2010;68:494-502.

U.S. Food and Drug Administration

FDA NEWS RELEASE

January 22, 2010

FDA Approves Dalfampridine to Improve Walking in Adults with Multiple Sclerosis

"In clinical trials, patients treated with [dalfampridine extended release] had faster walking speeds than those treated with an inactive pill (placebo). This is the first drug approved for this use."

FDA. News Release. January 22, 2010. Accessed 11/12/13 at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm198463.htm.

Postmarketing Update on Patient Outcomes

Clinical Meaningfulness of 20% Improvement in T25FW
Study Design

- Pooled data from 2 phase III clinical trials of dalfampridine in multiple sclerosis (MS) (N = 533)
- T25FW and MSWS-12 measured concurrently before and during treatment
- Outcomes
  - T25FW speed variability within and between visits
  - Correlations of T25FW speed with MSWS-12 score
  - Changes in MSWS-12 (mean scores, effect sizes) associated with percent T25FW changes

Abbreviations: MSWS-12, 12-item Multiple Sclerosis Walking Scale; T25FW, Timed 25-Foot Walk

Hobart J, et al. *Neurology.* 2013;80:1509-1517.

Clinical Meaningfulness of 20% Improvement in T25FW
Results

- T25FW speed variability was small
  - Averages: Within- (7.2%-8.7%) and between- (14.4%-16.3%) visits
- Correlations between T25FW and MSWS-12 values were low (-0.20 to -0.30), but stronger between their change values (-0.33 to -0.41).
- Speed improvements of >20%, and possibly 15%, were associated with clinically meaningful changes in self-reported walking ability using MSWS-12 change score and effect size criteria

Hobart J, et al. *Neurology.* 2013;80:1509-1517.

Long-Term Clinical Benefit of Dalfampridine in Real-World Setting (N=67)

- 67 consecutive MS patients with walking impairment deemed suitable for dalfampridine treatment
  - 75% had primary or secondary progressive MS
- Dalfampridine-ER 10 mg BID
- Assessed at baseline, week 4, 3 months, and 6 months
- Clinical benefit = any improvement on Timed 25-Foot Walk (T25FW) or 12-item Multiple Sclerosis Walking Scale (MSWS-12)

Prugger M, Berger T. *Patient Related Outcome Measures* 2013:4:75-85.

Long-Term Clinical Benefit of Dalfampridine in Real-World Setting (N=67)

Duration of Treatment	Walked ≥10% Faster (T25FW)	Walked ≥20% Faster (T25FW)	MSWS-12 Scores Improved
4 Weeks	50.7%	36.8%	65.7%
3 Mo	52.2%	29.9%	64.2%
6 Mo	38.8%	16.4%	59.7%

- Among patients who demonstrated clinical benefit at 6 months, Fatigue Severity Scale scores improved on average by 1 point and MSWS-12 scores by 10 points.
- Defined improvements in walking ability should not be limited to a single clinical assessment, but should also include patient-reported assessment of benefit.

Prugger M, Berger T. *Patient Related Outcome Measures* 2013:4:75-85.

Longitudinal Cohort Study in Veterans with MS

- Patients: 39 veterans prescribed dalfampridine-ER over one year
- Objective: Determining change from baseline at initial follow-up (at ~6-8 weeks) and one year
- Efficacy outcome measures
  - Timed 25 Foot Walk (T25FW)
  - Multiple Sclerosis Walking Scale-12 (MSWS-12)
  - 2 Minute Timed Walk (2MTW)
  - Community Integration Questionnaire (CIQ)

Cameron MH, et al. *Mult Scler.* 2013 Nov 7. Epub ahead of print.

Longitudinal Cohort Study in Veterans with MS

- First follow-up: All measures improved significantly from baseline
  - T25FW: -2.7s, *P* = .004
  - 2MTW: 41 feet, *P* = .002
  - MSWS-12: -11, *P* <.001
  - CIQ: 1.2, *P* = .003
- One year follow-up: Walking endurance and self-perceived walking remained significantly improved
  - 2MTW: 33 ft, *P* = .03
  - MSWS-12: -5.9, *P* = .007

Cameron MH, et al. *Mult Scler.* 2013 Nov 7. Epub ahead of print.

Dalfampridine-ER—Post-Hoc Analyses
Abstracts

"Response…Is Independent of Baseline Patient Characteristics and Concomitant Immunomodulator Therapy"[1]

"Dalfampridine Extended Release Tablets Improve Walking Speed Across A Wide Range of Baseline Deficits"[2]

"Patients With Progressive Forms of Multiple Sclerosis Benefit From Treatment With Dalfampridine Extended Release Tablets"[3]

1. Brown T, et al. 62nd AAN; April 10–17, 2010; Toronto, Ontario, Canada. Abstract P06.136.
2. Edwards K, et al. 62nd AAN; April 10–17, 2010; Toronto, Ontario, Canada. Abstract P06.223.
3. Pozzilli C, et al. *Neurology.* 2011;76(suppl 4):A73.

Dalfampridine-ER + Walking Aids

- Dalfampridine improved walking speeds in phase III trials in patients already requiring walking aids (EDSS 6.0+)[1-3]
- Clinical experience suggests synergy between physical therapy, exercise, walking devices, and pharmacotherapy with dalfampridine

1. Goodman AD, et al. *Lancet.* 2009;373:732-738. 2. Goodman AD, et al. *Ann Neurol.* 2010;68:494-502. 3. Brown T, et al. 62nd AAN; April 10–17, 2010; Toronto, Ontario, Canada. Abstract P07.164.

Future Research

- Can we improve responsiveness?
  - Better understanding of distribution and pharmacology of channelopathy
- Can we use similar trial methodology for novel restorative or regenerative experimental therapeutics?
  - eg, Anti-LINGO, cell-based therapy

Practical Application

My Clinical Experience

- Trial of 10-mg dalfampridine-ER tablets BID for 2−4 weeks
- Exclude patients with
  - History of seizure, or
  - Renal insufficiency (creatinine clearance <50 mL/min)
- Clinical evaluation
  - Timed 25-foot walk
  - Symptom assessment, including gait quality and fatigability, stair climbing, distance
- Adverse effect assessment: Insomnia, nausea, tingling, etc
- Continue on therapy with favorable benefit/risk assessment

Dalfampridine-ER
Individual Benefit:Risk Ratio

- Objective measures
  - 20% improvement in timed 25-foot walk considered clinically meaningful change[1,2,3]
- Subjective measures
  - Patient-reported functional improvements in distance, stair climbing, and dependence on walking aids

1. van Winsen LM, et al. *Mult Scler.* 2010;16:604-610.
2. Coleman CI, et al. *Curr Med Res Opin.* 2012;28:49-56.
3. Hobart J, et al. *Neurology*. 2013;90:1509-1517.

Conclusions

- Gait problems are common in MS and not always addressed
- Optimal individualized approach includes
  - Physical therapy
  - Walking aids when appropriate
  - Pharmacotherapy for spasticity
  - Consideration of dalfampridine

Conclusions

- Dalfampridine – the first FDA-approved drug to specifically address gait disability in patients with MS
- Dalfampridine may improve speed by 20% or more, which has been shown to be clinically meaningful
- Benefit is seen in patients with progressive MS, as well as relapsing-remitting disease
- Not all patients benefit from treatment. To date, there are no predictive factors that permit the identification of those in whom the drug will be effective
- In those patients who benefit, dalfampridine results in a significant improvement in walking and quality of life.

Conclusions

- Care must be taken in administering dalfampridine as indicated in the prescribing information
- Benefit:risk easily assessed with patient input
- 2013 patient-centric studies demonstrate the value of treatment in improving patient functioning and quality of life