

SYMPTOM MANAGEMENT: POTASSIUM CHANNEL BLOCKERS



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June 3, 2006



Symptoms of MS

- Ataxia and tremor
- Bladder and bowel dysfunction
- Cognitive Impairment
- Depression
- Fatigue
- Pain
- Sexual dysfunction
- Spasticity
- Weakness
- Visual disturbances

IOM Report, 2001



Symptoms of MS

- Ataxia and tremor
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- Cognitive Impairment
- Depression
- Fatigue
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- Sexual dysfunction
- Spasticity
- **Weakness**
- Visual disturbances

IOM Report, 2001

Veterans Affairs

MS

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Weakness

- One of the most common and disabling symptoms of MS
 - More than 90% of MS patients report motor weakness
 - Leg weakness is much more common than arm weakness
 - In most MS patients, leg weakness is associated with impaired ambulation

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Pathophysiology of Weakness

- Interruption of descending motor pathways
 - Axonal transection
 - Demyelination
 - Rate dependent conduction block
 - Complete conduction block

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Treatment of Weakness

- Corticosteroids
- Physical therapy
 - Strengthening
 - Task specific training
- Adaptive devices
- Environmental modifications

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Pathophysiology of Demyelination

- Reduced sodium channel density in demyelinated areas
- Appearance of abnormal voltage sensitive potassium current on demyelinated fibers
- Reduction in action potential amplitude, duration and velocity leading to defects in conduction.



Use of Potassium Channel Blockers

- Block voltage sensitive potassium channels
- Improve action potential propagation in demyelinated axons
- Increase transmitter release at synaptic endings



Potassium Channel Blockers

- Toxins
 - Mast cell degranulating toxin
 - Scorpion toxin
- Small molecular weight compounds
 - 4 aminopyridine
 - 3,4 diaminopyridine



3,4 Diaminopyridine

- Blocks voltage sensitive potassium channels
- Improves action potential propagation in demyelinated axons
- Increases transmitter release at synaptic endings
- Available for the treatment of Lambert-Eaton Myasthenic Syndrome



Phase II Trial of DAP in MS

- Double-blind, placebo-controlled, crossover design trial
- 22 MS patients with leg weakness
- One month treatment periods with up to 100 mg per day
- Outcome measures:
 - Patient and physician impressions of change
 - Manual motor testing
 - Quantitative motor testing
 - Ambulation index



Results: # Improved

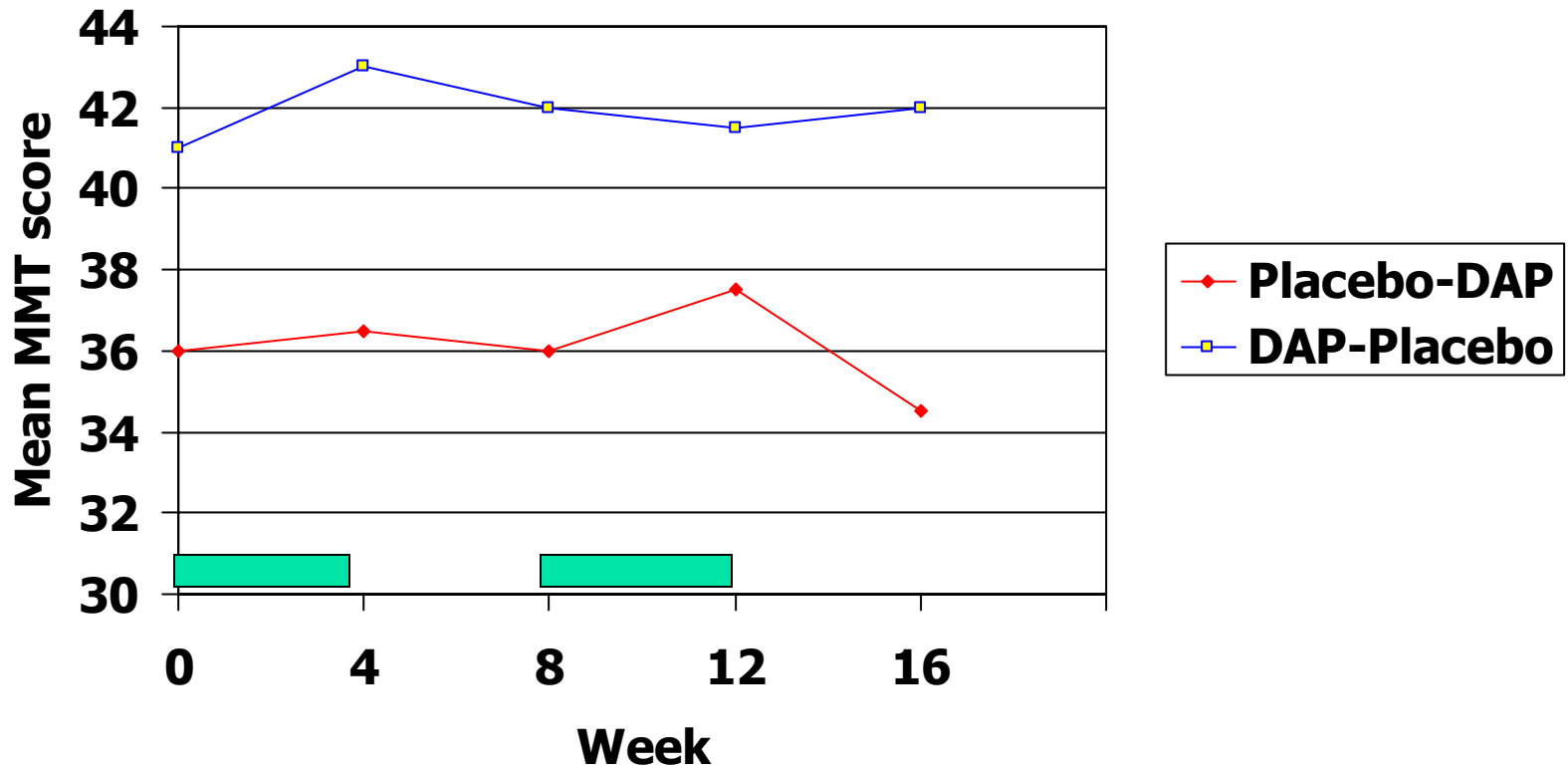
<u>Outcome</u>	<u>DAP</u>	<u>Placebo</u>	<u>p</u>
Physician IC	21	1	0.005
Patient IC	14	2	0.008
MMT	16	3	0.002
QMT-HS	16	9	0.001
QMT-Q	15	8	0.04
AI	5	0	0.02



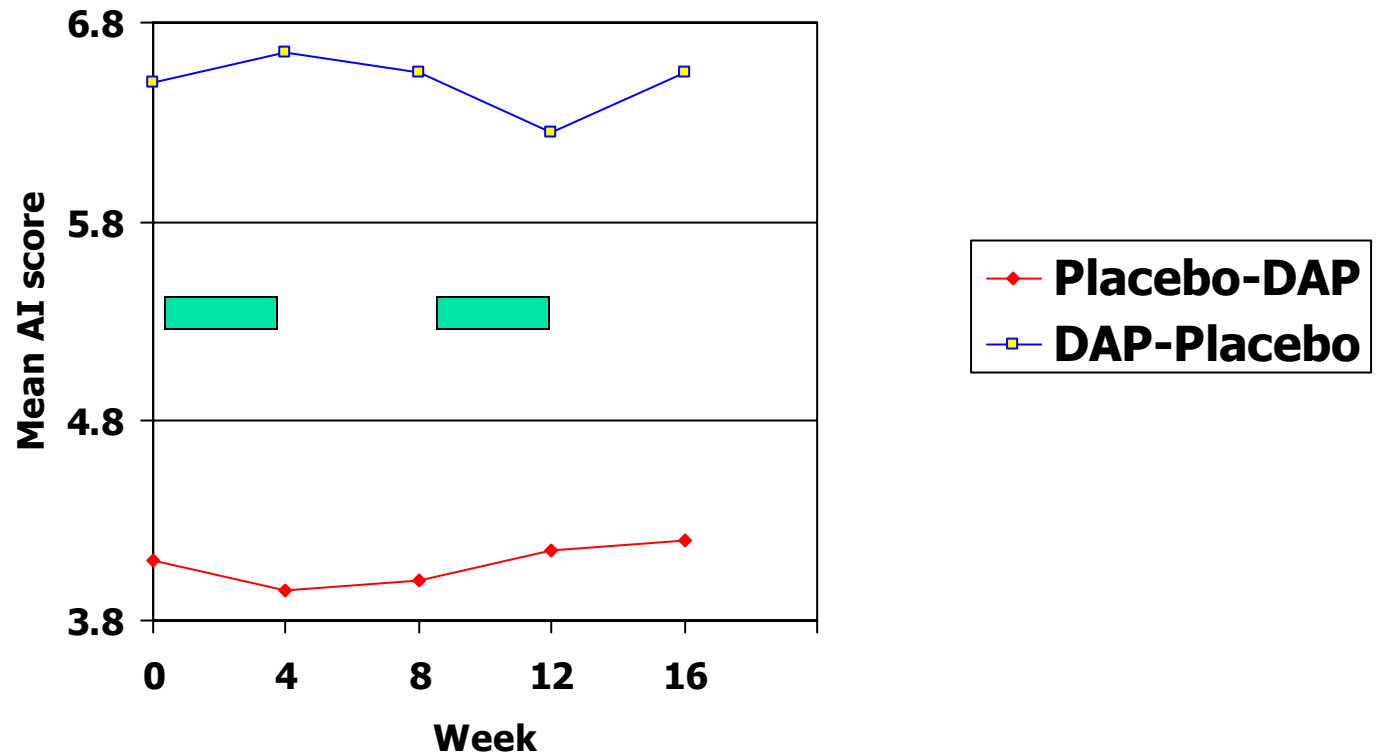
Results: Mean scores

<u>Outcome</u>	<u>DAP</u>	<u>Placebo</u>	<u>p</u>
MMT	41.6	39.9	0.002
QMT-HS	130	123	0.001
QMT-Q	231	206	0.04

Results: Mean Strength Scores



Results: Mean AI Scores





Conclusions

- 3,4 DAP treatment can improve leg strength in selected patients
- 3,4 DAP treatment can improve ambulation times in a subset of patients
- 3,4 DAP treatment causes paresthesias and gastrointestinal adverse events that limit its use
- Rarely 3,4 DAP treatment can cause seizures



4-Aminopyridine

- Blocks voltage sensitive potassium channels
- Improves action potential propagation in demyelinated axons
- Increases transmitter release at synaptic endings
- Used to reverse neuromuscular blockade after surgery



Early Trials of 4-Aminopyridine in MS

- Jones et al: Open label pilot
- Davis & Stefoski: Controlled crossover
- Van Diemen, et al: Randomized, controlled, crossover
- Bever et al: Randomized, controlled, crossover
- Schwid et al: Randomized, controlled, crossover

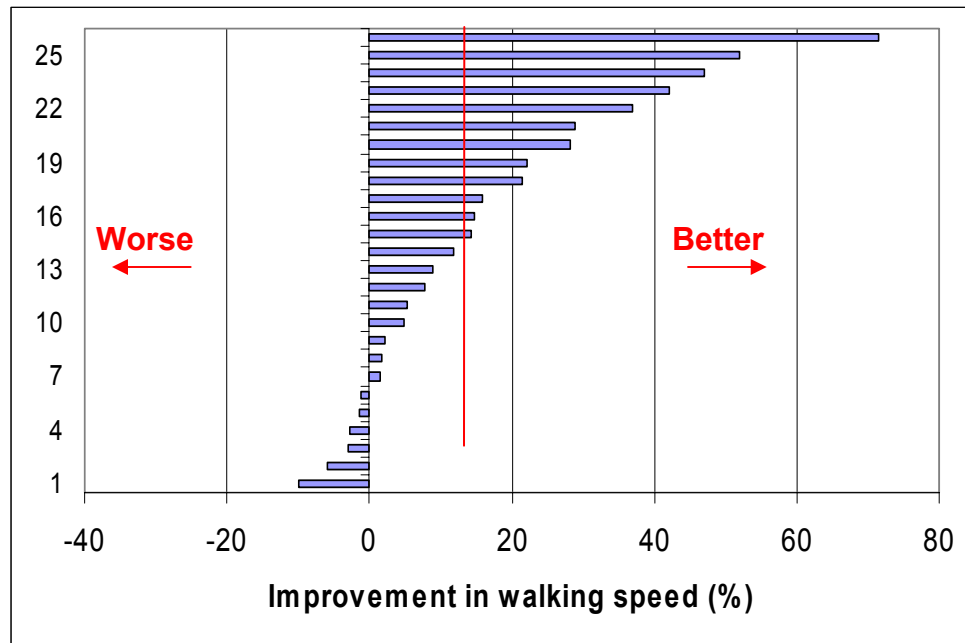


Objectives

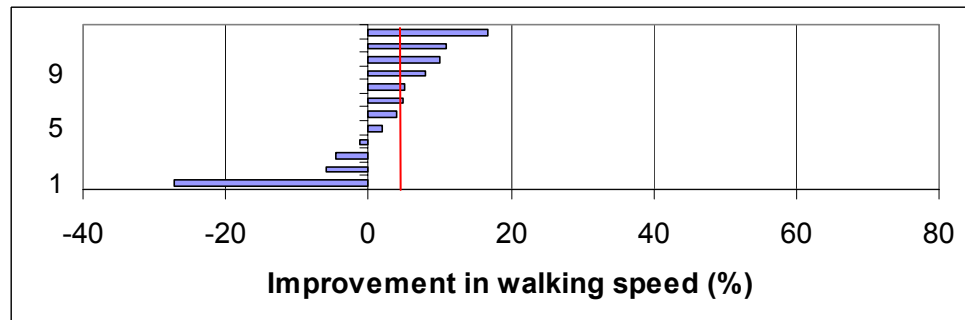
- Primary: Determine safety of multiple doses of fampridine-SR (one week each of 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day and 80 mg/day).
- Secondary: Obtain evidence of efficacy and dose-response using several outcome measures
 - Standard MS measurements, including timed walk, lower extremity muscle strength, PASAT, 9-hole peg test
 - Daily Fatigue Diary – Brief Fatigue Inventory

25-Foot Walk – Change in Speed

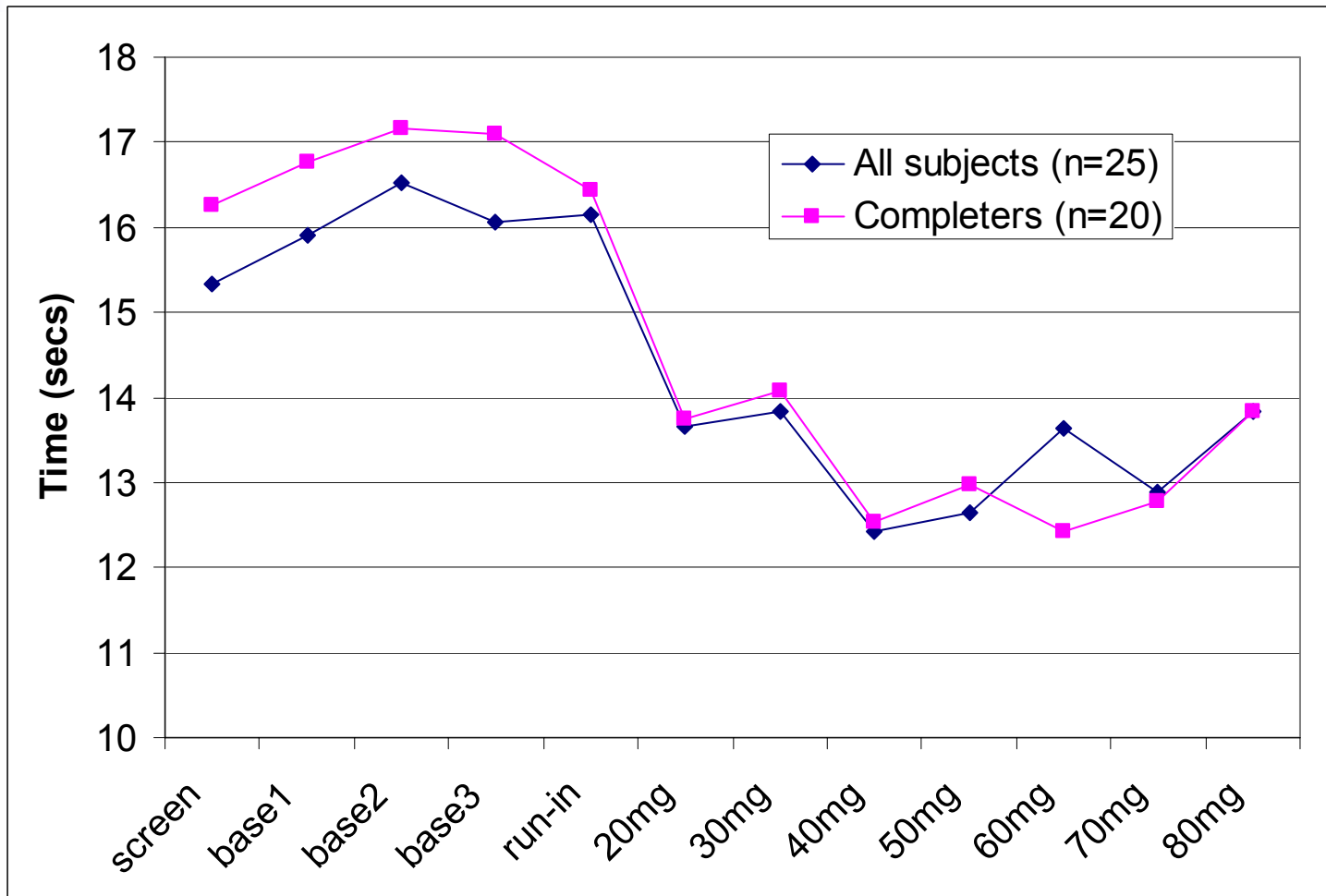
Fampridine-SR
(20-50 mg/day)



Placebo

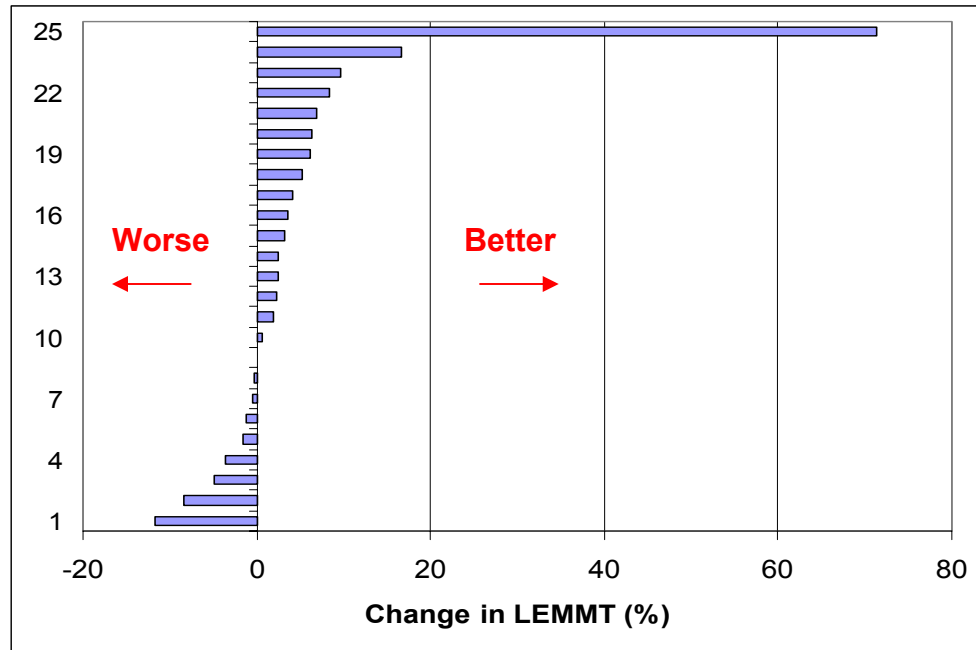


Dose Response- 25 ft Walk

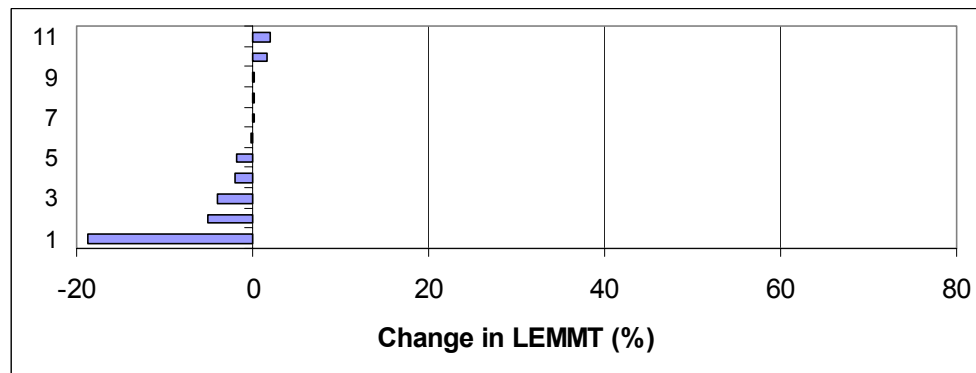


Leg strength

Fampridine-SR
(20-50 mg/day)



Placebo





Treatment emergent adverse events

	Fampridine-SR (N=25)	Placebo (N=11)
<u>No. with AEs</u>		
All AEs	25 (100%)	10 (90.9%)
Most Frequently Reported AEs		
Dizziness	9 (36.0%)	2 (19.2%)
Insomnia	9 (36.0%)	1 (9.1%)
Paresthesia	8 (32.0%)	1 (9.1%)
Nausea	7 (28.0%)	1 (9.1%)
Asthenia	7 (28.0%)	1 (9.1%)
Headache	6 (24.0%)	1 (9.1%)
Tremor	6 (24.0%)	0
Pain	5 (20.0%)	0
Back Pain	5 (20.0%)	0
Anxiety	3 (12.0%)	0
Hypertonia	1 (4.0%)	3 (27.3%)



Safety Summary

- The most common adverse events in the fampridine treated group were consistent with the findings of previous studies
 - Dizziness, Insomnia, Parasthesia, Nausea, Asthenia, Headache, Tremor
- At doses above 40 mg/day, more severe adverse events were reported, including two cases of seizure (at 60 and 70 mg/day)
- As anticipated, the risk of seizure requires further study and characterization particularly in the anticipated dose range

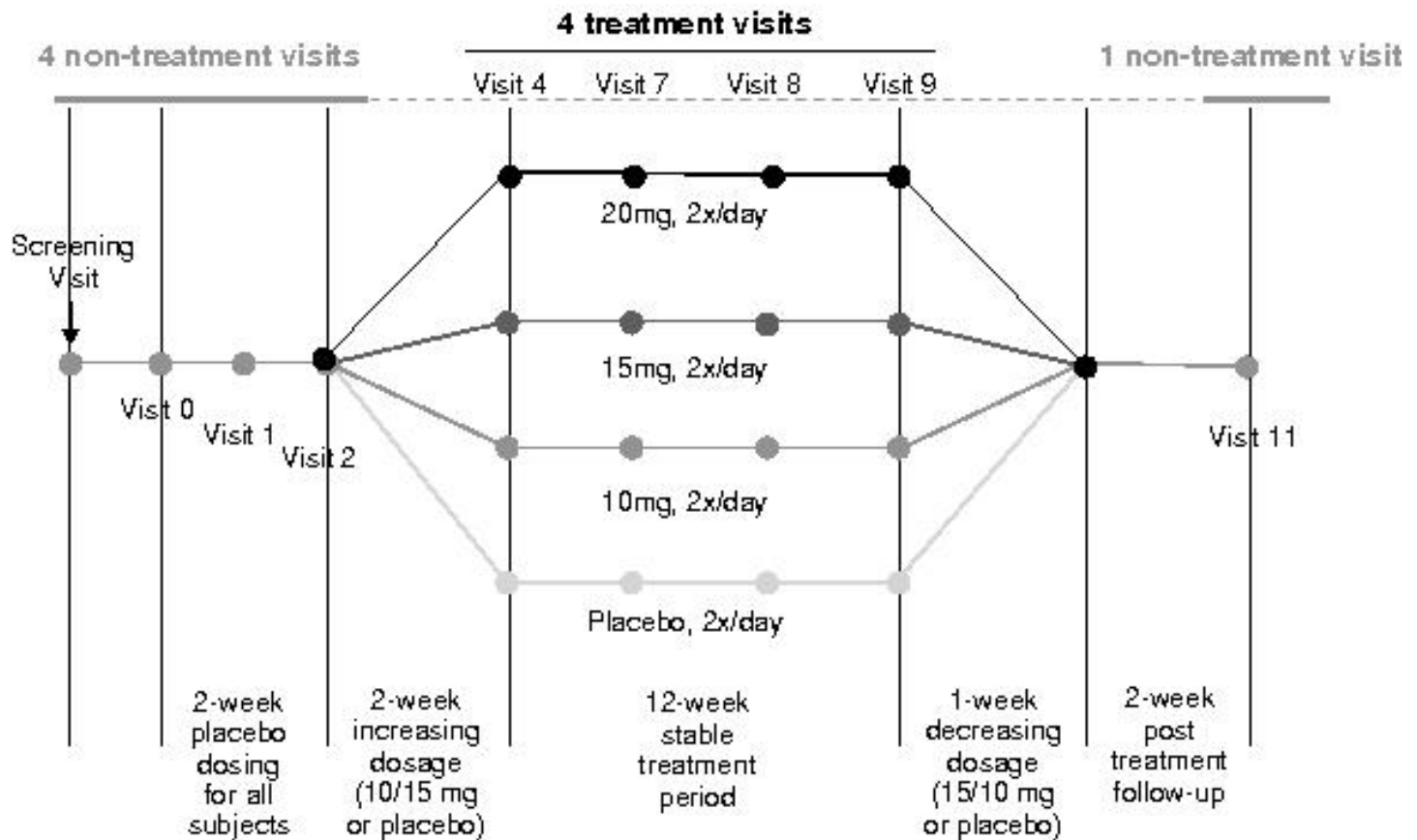


Summary

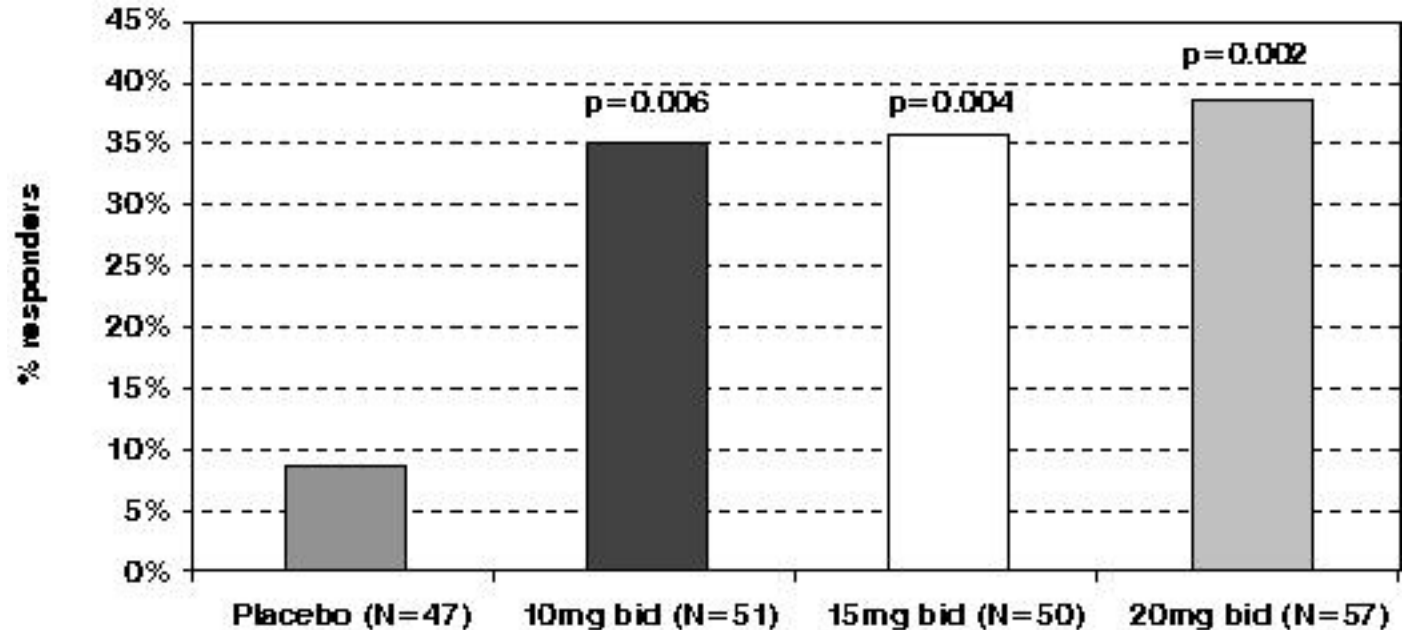
- Safety profile consistent with previous experience
- Significant* benefit on timed walking ($p=0.04$)
- Significant* benefit on lower extremity strength ($p=0.01$)
- Evidence of dose-response in 20-40 mg/day range
- No evidence of benefit on overall fatigue
- Little added benefit, and increased AEs at doses above 50 mg/day

*repeated measure ANOVA (weeks 1-7)

Parallel design trial of 4-AP

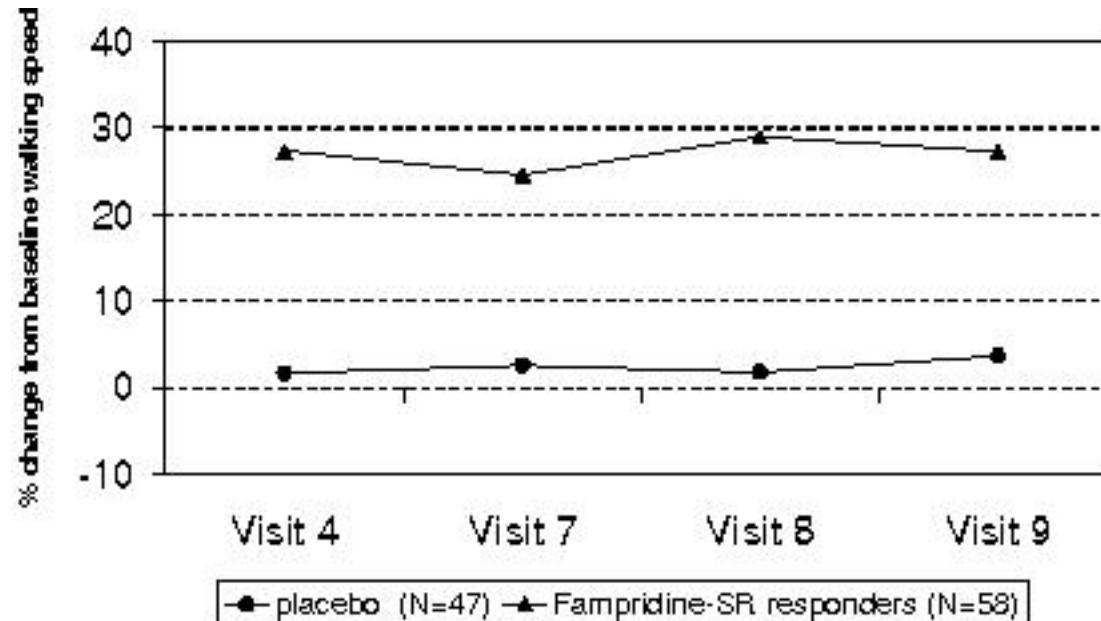


Walking Speeds: Responder Rates

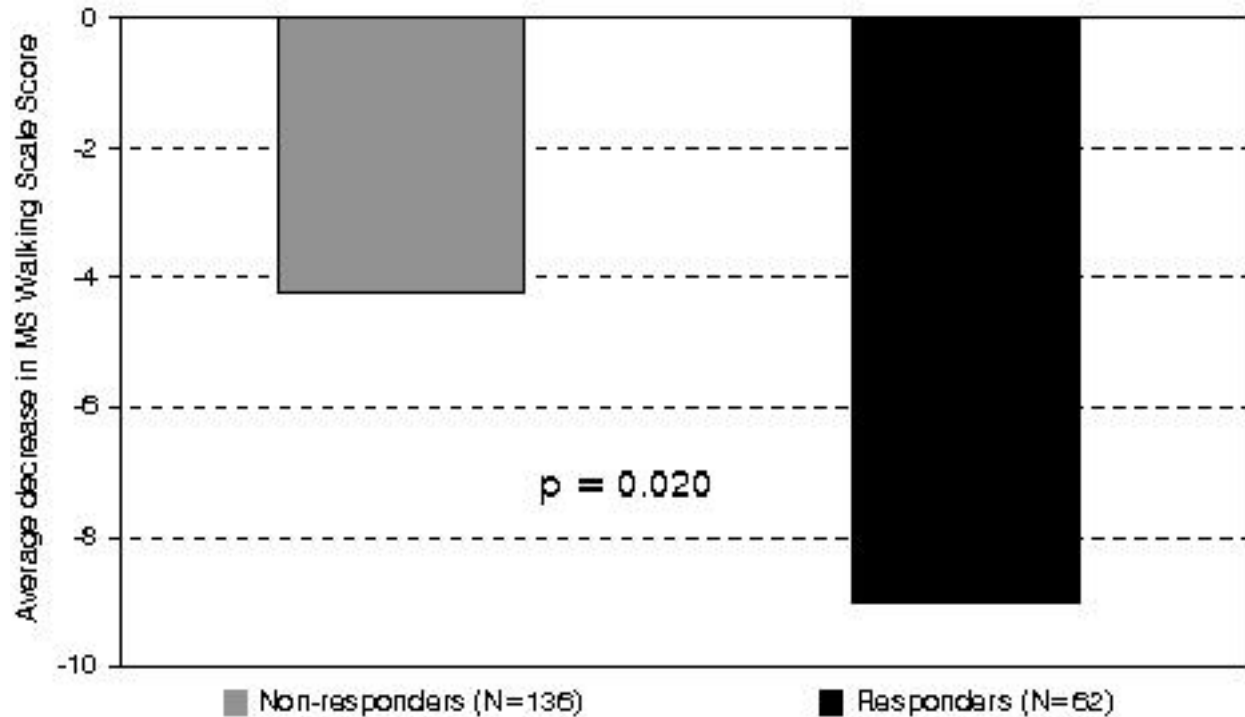


Acorda Therapeutics, 2006

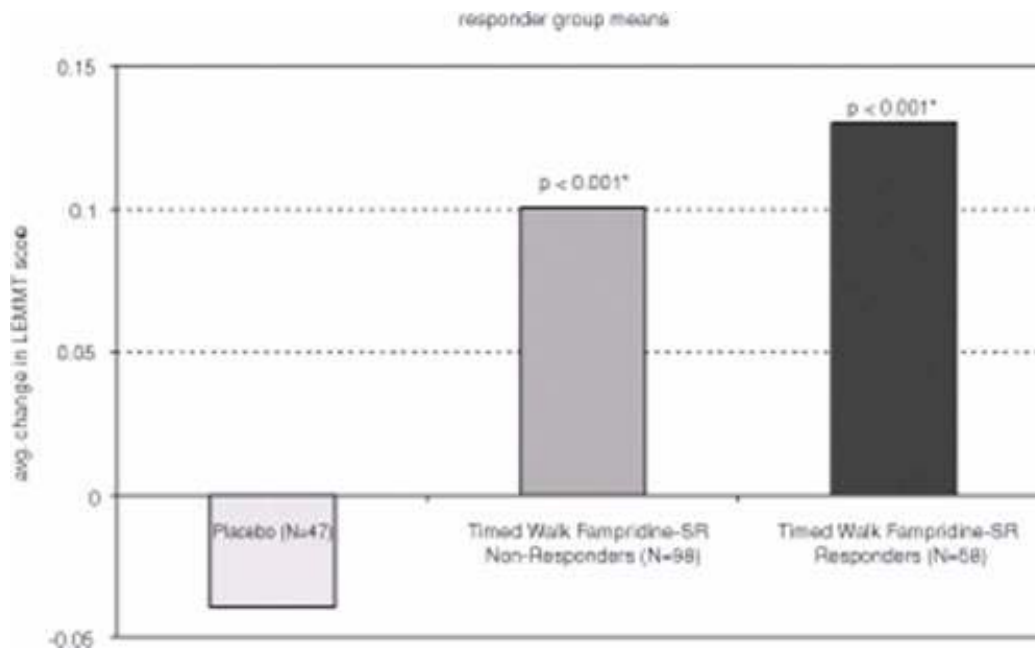
Walking Speeds: Change from Baseline



Patient Subjective: Change in Walking from Baseline



Changes in Leg Strength



Acorda Therapeutics, 2006



Summary

- Improvements in walking speed were seen at a statistically significantly higher rate among patients on AP compared with placebo.
- AP induced improvements in walking were sustained out to 14 weeks and were clinically meaningful to patients.
- Adverse events were similar to previous studies both in types and frequencies.



Conclusions

- AP and DAP treatment can improve leg strength in MS patients
- Treatment can improve walking speed in selected patients
- Seizure induction is dose related and is uncommon at therapeutic doses.