

The Effects of Dalfampridine Extended Release on Motor Function Beyond Walking in Multiple Sclerosis

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Disclosures

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 - Acorda Therapeutics, Inc., and
 - Mount Sinai Rehabilitation Hospital, Hartford, Connecticut
- Albert Lo has served on prior advisory boards for Acorda Therapeutics, Inc.

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* Brown University & Mandell Multiple Sclerosis Center

Background

- Dalfampridine Extended Release (D-ER; Amypra Extended Release Tablets, Acorda Therapeutics, Inc.)
 - FDA approved in January 2010
 - Indication: to improve walking in patients with multiple sclerosis
 - Demonstrated through increased walking speed, Timed 25 foot-walk
 - Thought to block K⁺ channels exposed through demyelination to improve conduction

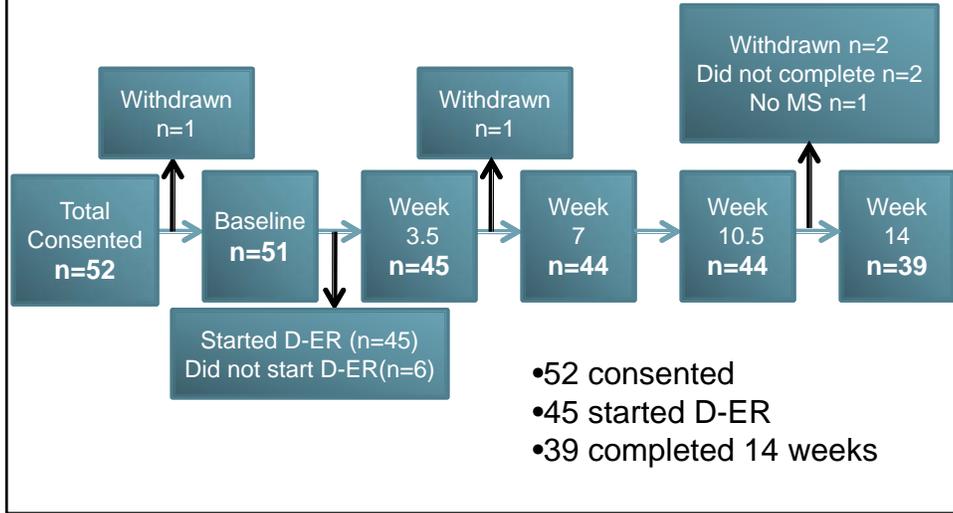
Purpose

- Examine “responsiveness” to dalfampridine-ER in a clinical setting for outcomes beyond walking speed
 - To address anecdotal patient comments
- Goal: To identify potential alternative outcomes **despite** categorization of **responder status** based on **walking speed**.

Design

- Observational, prospective study
- Patients newly prescribed dalfampridine-ER for routine MS clinical care
- 14 weeks

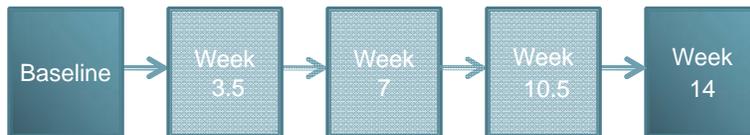
Enrollment



Outcomes, (motor)

Assessment	Test	Abbreviation
Gait Speed	Timed 25 Ft Walk	T25FW
Gait Endurance	6 Minute Walk Test	6MW
Dynamic Gait	Six Spot Step Test	SSST
Self Perceived Walking Ability	12-Item MS Walking Scale	MSWS-12
Upper Extremity – Fine Motor	9 Hole Peg Test	9HPT
Upper Extremity – Gross Motor	Box and Blocks Test	BBT

Data in this presentation were analyzed as baseline vs. week 14 comparisons. All time points were used to define responder status.



Demographics

mean \pm SD (range)	Present Study (n=39)	Goodman 2009 (n=228)	Goodman 2010 (n=120)
Age, years	54.1 \pm 9.9 (21-67)	51.5 \pm 8.8 (26-70)	51.8 \pm 9.6 (25-73)
Gender: n (%) Female	31 (79.5%)	162 (71%)	88 (73%)
Subtype, n (%)			
Primary Progressive/ Progressive Relapsing	9 (23%)	41 (18%)	15 (12.5%)
Relapse Remitting/ Secondary Progressive	30 (77%)	187 (82%)	105 (87.5%)
Disease Duration	12.9 \pm 8.8 (0.0-34.0)	13.4 \pm 8.29 (0.4-41.7)	14.4 \pm 9.5 (0.5-45.6)

Demographics (Con't)

mean \pm SD	Present Study (n=39)	Goodman 2009* (n=228)	Goodman 2010** (n=119)
EDSS Score	5.1 \pm 1.6	5.8 \pm 1.0	5.8 \pm 1.0
T25FW, ft/sec	2.9 \pm 1.5	2.1 \pm 0.7	2.1 \pm 0.8

*Goodman AD et al., (2009) Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet 373(9665): 732-738.

**Goodman AD et al., (2010) A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. Ann Neurol 68(4): 494-502.

Timed Walk Responder (TWR) Definitions

- Current Study
 - TWR:** persons with a faster walking speed for at least **3 of the 4** visits during the treatment period as compared with the **single off-drug baseline** visit.



- Goodman et al. 2009
 - TWR:** persons with a faster walking speed for at least **3 of the 4** treatment visits compared with the maximum speed for any of the **5 off-drug visits**.

Off Drug visits
 On Drug Visits

Statistical Methods

- Change from Baseline to Week 14:
 - Paired-sample T tests for normally-distributed
 - Wilcoxon signed-rank test for non-normally distributed
- Categorization of Groups:

Observational group (OG; n=39) – All participants that started D-ER for the study

Timed Walk Responders (TWR; n=20)
– Ambulatory participants that showed improvement in T25FW

Timed Walk Non-Responders (TWNr; n=8)
– Ambulatory participants that did not show an improvement in T25FW

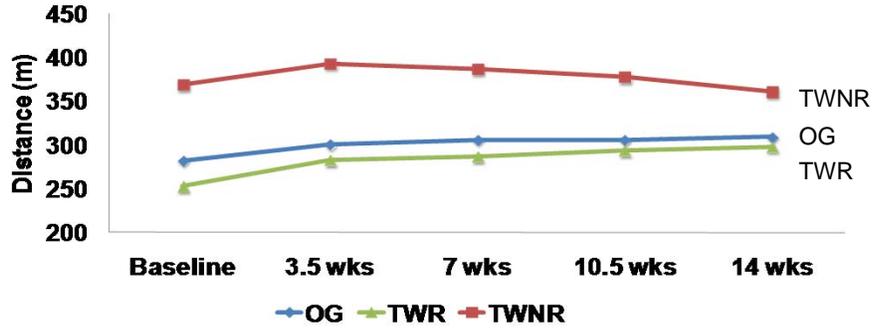
Lower Extremity Function

Results: T25FW



Baseline vs. 14 week
OG (n=36), p<.001*
TWR (n=20), p<.001*
TWNR (n=8), p=.13

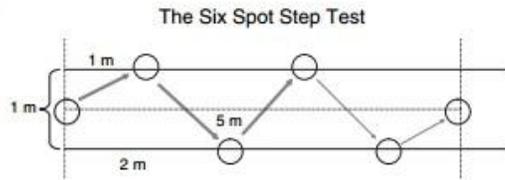
Results: 6MW



Baseline vs. 14 week
OG (n=34), p=.021*
TWR (n=19), p=.001*
TWNR (n=7), p=.764

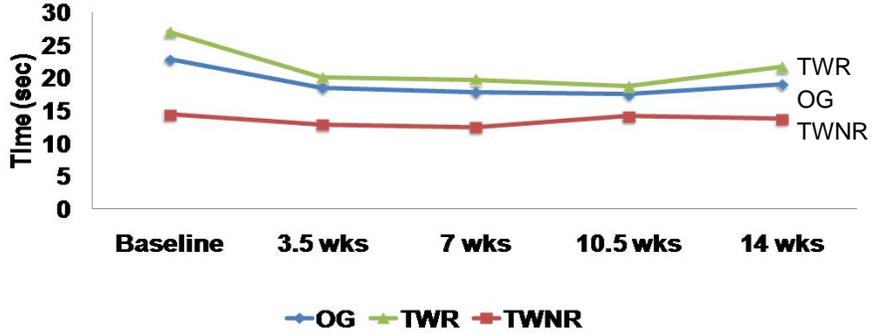
Six Spot Step Test (SSST)

- Navigate 1 x 5 meter course as quickly as possible.
- Participant uses dominant foot to kick a wooden block off of a marked position.
- Repeat with non-dominant side.
- The total time to complete each task is recorded.



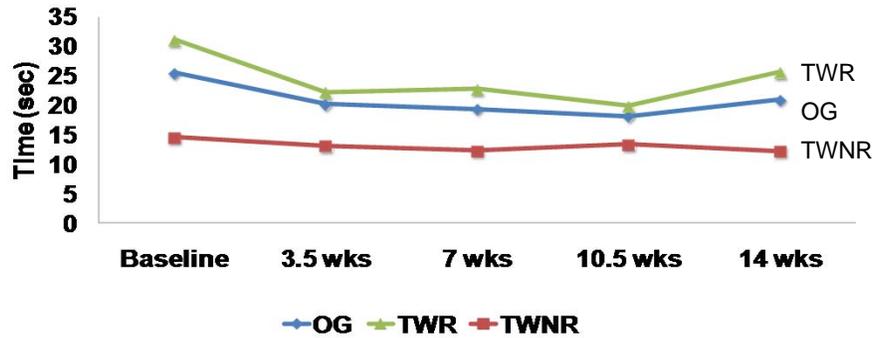
Nieuwenhuis et al., 2006

SSST: Dominant Leg



Baseline vs. 14 week
OG (n=35), $p < .001^*$
TWR (n=20), $p = .003^*$
TWNR (n=7), $p = .310$

SSST: Non-Dominant Leg



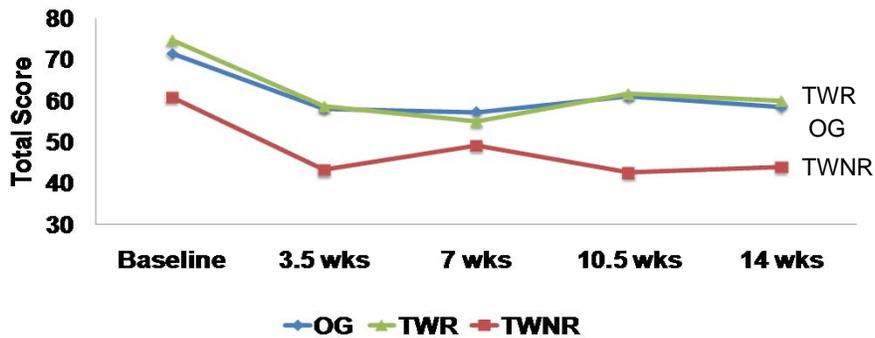
Baseline vs. 14 week
OG (n=35), $p < .001^*$
TWR (n=20), $p = .023^*$
TWNR (n=7), $p = .028^*$

MS Walking Scale-12

In the past two weeks, how much has your MS:	Not at all	A little	Moderately	Quite a bit	Extremely
1. Limited your ability to walk?	1	2	3	4	5
2. Limited your ability to run?	1	2	3	4	5
3. Limited your ability to climb up and down stairs?	1	2	3	4	5
4. Made standing when doing things more difficult?	1	2	3	4	5
5. Limited your balance when standing or walking?	1	2	3	4	5
6. Limited how far you are able to walk?	1	2	3	4	5
7. Increased the effort needed for you to walk?	1	2	3	4	5
8. Made it necessary for you to use support when walking indoors (e.g., using a stick, a frame, etc)?	1	2	3	4	5
9. Made it necessary for you to use support when walking outdoors (e.g., using a stick, a frame, etc)?	1	2	3	4	5
10. Slowed down your walking?	1	2	3	4	5
11. Affected how smoothly you walk?	1	2	3	4	5
12. Made you concentrate on your walking?	1	2	3	4	5

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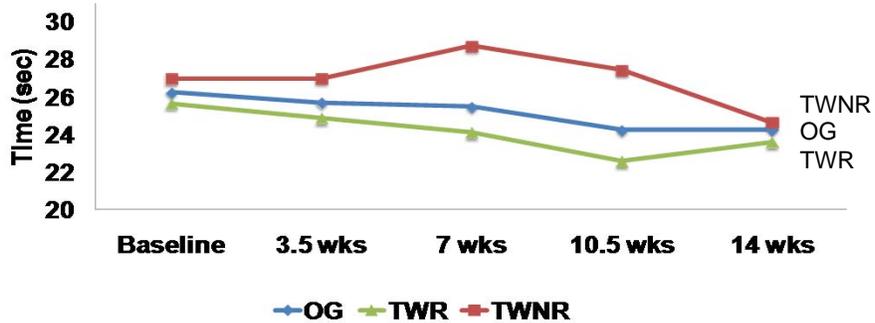
MSWS-12 Total Score



Baseline vs. 14 week
 OG (n=38), p<.001*
 TWR (n=20) p=.001*
 TWNR (n=8) p=.004*

Upper Extremity Function

9HPT: Dominant Hand



Baseline vs. 14 week
OG (n=36), p<.001*
TWR (n=19), p<.001*
TWNR (n=8), p=.017*

9HPT: Non-Dominant Hand



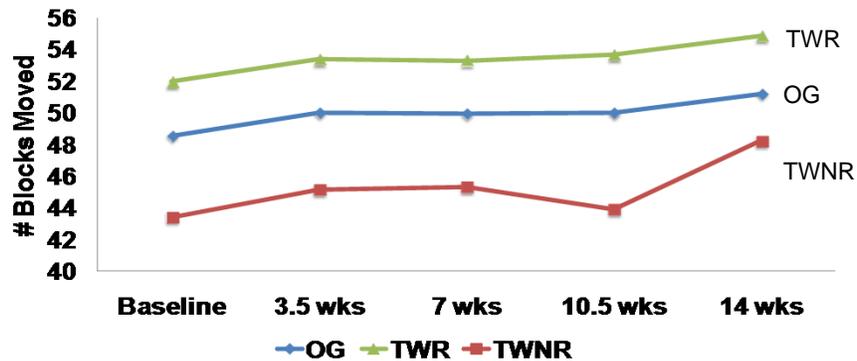
Baseline vs. 14 week

OG (n=36), p<.001*

TWR (n=19), p=.020*

TWNR (n=8) p=.025*

BBT: Dominant Hand



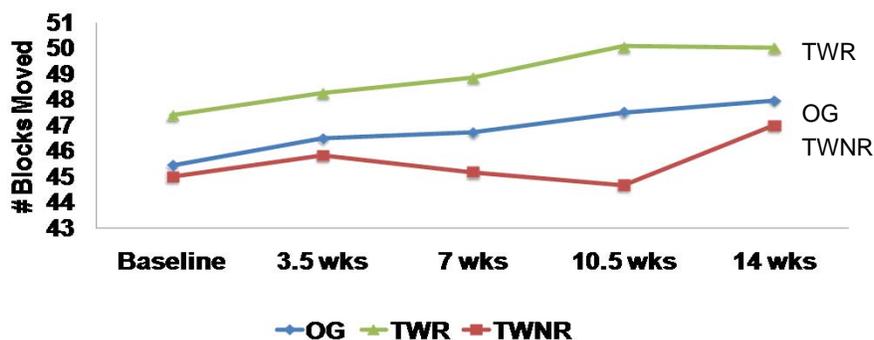
Baseline vs. 14 week

OG (n=27), p=.005*

TWR (n=15), p=.026*

TWNR (n=6), p=.001*

BBT: Non-Dominant Hand



Baseline vs. 14 week

OG (n=27), p=.001*

TWR (n=15), p=.009*

TWNR (n=6), p=.084

Summary Table: Baseline to Week 14 Lower Extremity

	OG (n=39)	TWR ^a (n=20)	TWNR ^a (n=8)
	<i>p</i>	<i>p</i>	<i>p</i>
6 Minute Walk Test (m)^b	.021	.001	.764
MS Walking Scale: Total Score^b	< .001	.001	.004
Timed 25 Ft Walk (sec)^c	< .001	< .001	.484
Six Spot Step Test: (sec)			
Dominant Side ^c	< .001	.003	.310
Non-Dominant Side ^c	< .001	.023	.028

^a On drug 100% of the time ^b Parametric analyses ^c Non-parametric analyses

Summary Table: Baseline to Week 14 Upper Extremity

	OG (n=39)	TWR ^a (n=20)	TWNR ^a (n=8)
	<i>p</i>	<i>p</i>	<i>p</i>
Box & Block Test: (# Blocks)			
Dominant Side ^b	.005	.026	.001
Non-Dominant Side ^b	.001	.009	.084*
9 Hole Peg Test: (sec)			
Dominant Side ^c	< .001	.003	.017
Non-Dominant Side ^c	< .001	.020	.025

^a On drug 100% of the time ^b Parametric analyses ^c Non-parametric analyses
* Trend towards a significant difference $p < .10$

% Improvement Summary

6MW

- OG: 10.61%*
- TWR: 15.70%*
- TWNR: 0.63%

SSST: Dominant Side

- OG: 14.90%*
- TWR: 16.74%*
- TWNR: 11.19%

SSST: Non-Dominant Side

- OG: 14.73%*
- TWR: 14.36%*
- TWNR: 13.50%*

MSWS-12

- OG: 19.63%*
- TWR: 19.97%*
- TWNR: 30.69%*

T25FW

- OG: 11.54%*
- TWR: 16.37%*
- TWNR: 2.61%

* Significant difference between baseline and week 14 data, $p < .05$

% Improvement Summary

BBT: Dominant Side

- OG: 6.05%*
- TWR: 6.18%*
- TWNR: 11.74%*

9HPT: Dominant Side

- OG: 7.02%*
- TWR: 7.25%*
- TWNR: 7.70%*

BBT: Non-Dominant Side

- OG: 6.41%*
- TWR: 6.01%*
- TWNR: 4.58%**

9HPT: Non-Dominant Side

- OG: 7.60%*
- TWR: 5.46%*
- TWNR: 6.44%*

*Significant difference between baseline and week 14 data, $p < .05$

** Trend towards a significant difference between baseline and week 14 data, $p < .10$

Conclusion

- Among traditional **TWRs**
 - All outcomes (6MW, SSST, MSWS-12, BBT, 9HPT) showed significant improvement.
- Even those who did not meet traditional timed walk response definition, **TWNR**, improved on
 - MSWS-12, SSST*, BBT* and 9HPT.
- Potential alternative or additional outcomes identified were:
 - 6MW, MSWS-12, SSST, BBT, 9HPT.

*improved on either dominant or non-dominant side

Thank You

Questions?

Future Analysis Areas

Cognitive Function
Mood
Fatigue
Vision
Pain
Physical Fitness
Overall Disability and Function
Biomarkers of Disease Progression
MRI Lesion Location