Exoskeletal-Assisted Walking in MS: Can this Technology be Integrated into the Rehabilitation Setting?

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Disclosures

1. The authors have no past or current affiliation with ReWalk Robotics
2. ReWalk Robotics has invited Dr. Kozlowski to sit on an advisory board; this request is under review of the ISMMS Conflict of Interest Officer.
3. The study was approved by the Icahn School of Medicine at Mount Sinai Clinical Institutional Review Board.
4. All participants provided signed informed consent.

Acknowledgements

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2. Co-investigators:

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Outline

1. Background
   1. Rationale for exoskeleton use by persons with multiple sclerosis (MS)
   2. Exercise and MS
   3. Body-weight supported treadmill walking and MS
   4. Mobility and MS
2. Pilot study – Safety and feasibility of ReWalk™ with MS.
   1. Objectives
   2. Methods
   3. Outcomes
   4. Early results
3. Future of exoskeletons in rehabilitation (Discussion)
   1. Clinical intervention
   2. Fitness and wellness
   3. Community mobility

Background – Overview of SCI experience

- Powered exoskeletons provide persons with spinal cord injury (SCI) with opportunity to walk.
- Two devices currently available for clinical use: ReWalk™ and Ekso™
- Indego® clinical trials for FDA approval under way
- Evidence for feasibility and safety for persons with paraplegia:

Device (Author Year)	N	SCI & Study Characteristics	Results
ReWalk (Zeilig 2012)	6	T1-L1, AIS A-B 13-14 sessions	Walk 100 m; no adverse events
ReWalk (Esquenazi 2012)	12	T3-T12, AIS A-B 13-25 sessions	Walk 50-100 m in 5-10 min (0.03 – 0.45 m/s); some reported improved pain, spasticity, bowel & bladder function
ReWalk (Spungen 2013)	7	T1-T11, AIS A-B 15-70 sessions	Walk (0.14-0.50 m/s); RPE 15±2 (1-5 sessions), 8±1 (>40 sessions. Stairs (n=4) mod assist. Mild skin abrasions with early sessions.
Ekso (Kolakowsky-Hayner 2013)	8	T4-T11, AIS A 6 weekly sessions	Walk 28-60 min (0.14-0.42m/s). Minor skin redness anterior tibia, greater trochanter

Background – SCI trajectories

Spinal Cord (2014), 1–6

www.nature.com/sc

ORIGINAL ARTICLE

Using rasch motor FIM individual growth curves to inform clinical decisions for persons with paraplegia

CR Pretz[1,2], AJ Kozlowski[3], S Charlifue[1], Y Chen[4] and AW Heinemann[5]

Patterns of recovery

- Individual variability
- Pattern of rapid recovery to plateau in +/- one year

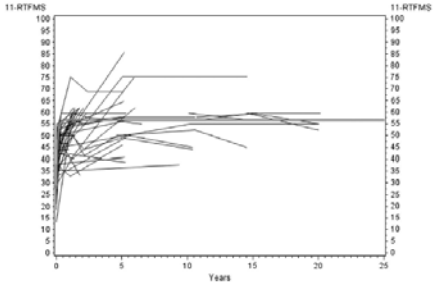


Figure 1 Group trajectory and random sample of individual patterns.

Background – SCI trajectories

ACRM
AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2013;94(4 Suppl 2):S154-64

ORIGINAL ARTICLE

Using Individual Growth Curve Models to Predict Recovery and Activities of Daily Living After Spinal Cord Injury: An SCIRehab Project Study

Allan J. Kozlowski, PhD,[a,b] Allen W. Heinemann, PhD

Patterns of recovery

- Varies in magnitude and rate
- Similar regardless of
  - Neurological level
  - SCI completeness

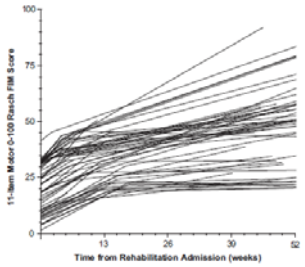


Fig 1 Five percent random sample of SCIRehab project motor FIM individual responses.

Background – MS trajectories

Recent reclassification

- Clinically Isolated Syndrome
- Relapsing-Remitting
  - Active
  - Not Active
- Secondary Progressive
- Primary Progressive
  - Active with progression
  - Active without progression
  - Not Active with progression
  - Not active without progression (stable)
- Radiologically Isolated Syndrome
  - Potential for earlier Dx

European Neurology

Extended Abstract

Eur Neurol 2014;72(suppl 1):1–5
DOI: 10.1159/000367614

New Multiple Sclerosis Phenotypic Classification

Fred D. Lublin

Icahn School of Medicine, Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Mount Sinai, New York, N.Y., USA

Background – MS trajectories

New perspectives in the natural history of multiple sclerosis

Helen Tremlett, PhD, Yinshan Zhao, PhD, Peter Rieckmann, MD and Michael Hutchinson, MD

+ SHOW AFFILIATIONS
Address correspondence and reprint requests to Dr. Helen Tremlett, Department of Medicine (Neurology), Room S178, 2211 Wesbrook Mall, University of British Columbia, Vancouver, BC V6T 2B5, Canada tremlett@interchange.ubc.ca

doi: 10.1212/WNL.0b013e3181e3973f
Neurology June 15, 2010 vol. 74 no. 24 2004-2015

- Variations in natural history for MS
  - Relapsing-Remitting: 20-year disease course
  - Secondary Progressive: onset Dx/EDSS variable – difficult to characterize
  - Primary Progressive: onset to EDSS 6 – 6 to 21 years (and slowing?)
- Wide variation in trajectories of progression within types

Background – Rationale for persons with MS

- Mobility: wheelchair alternative?
- Fitness/wellness: slow disability regardless of MS progression?
  - Physical: weight gain, cardiovascular disease, diabetes
  - Psychological: depression, fatigue
  - Social wellbeing
- Clinical Intervention
  - Disease modification?
  - Mechanism?
- Time line
  - Potential value increases with progression of disability due to MS
  - Easier to learn to use with lower EDSS
  - Capability to safely use exoskeleton may decline with higher EDSS

Background – Rationale for persons with MS

ClinicalEvidence

Multiple sclerosis

Search date June 2008

Richard Nicholas and Jeremy Chataway

- Don't know whether exercise reduces fatigue.
- Exercise may help to maintain
  - Strength
  - Fitness
  - Mobility
- Exercise may improve quality of life
- BUT study comparisons were difficult to make

Background – Rationale for persons with MS

ORIGINAL RESEARCH ARTICLE

Patient 2011; 4 (3): 189-201
1178-1653/11/0003-0189/$49.95/0

Impact of Walking Impairment in Multiple Sclerosis

Perspectives of Patients and Care Partners

Nicholas G. LaRocca

National Multiple Sclerosis Society, New York, NY, USA

- 41% of people with MS reported difficulty with walking
- 13% unable to walk at least twice per week
- 70% report as the most challenging aspect of MS
- 74% report walking difficulty disrupted their daily lives

Background – Rationale for persons with MS

Journal of the Neurological Sciences
Volume 328, Issues 1–2, 15 May 2013, Pages 70–76

Physical fitness, walking performance, and gait in multiple sclerosis

Brian M. Sandroff, Jacob J. Sosnoff, Robert W. Motl

- Physiological deconditioning may contribute to walking impairments in MS
- Aerobic capacity and balance were associated with walking performance on 25 Foot Walk Test (25FWT) and 6 Minute Walk Test (6MWT)
- Multimodal exercise training interventions might improving mobility outcomes

Background – Rationale for persons with MS

Archives of Physical Medicine and Rehabilitation
journal homepage: www.archives-pmr.org
Archives of Physical Medicine and Rehabilitation 2013;94:1800-28

REVIEW ARTICLE (META-ANALYSIS)

Effects of Exercise Training on Fitness, Mobility, Fatigue, and Health-Related Quality of Life Among Adults With Multiple Sclerosis: A Systematic Review to Inform Guideline Development

Amy E. Latimer-Cheung, PhD,[a] Lara A. Pilutti, PhD,[b,c] Audrey L. Hicks, PhD,[b] Kathleen A. Martin Ginis, PhD,[b] Alyssa M. Fenuta, HBSc,[b] K. Ann MacKibbon, PhD,[b] Robert W. Motl, PhD[c]

- Systematic review of 54 studies
- Strong evidence that moderate-intensity exercise twice per week increases aerobic capacity and muscular strength for persons with mild to moderate disability
- Exercise may improve mobility, fatigue, and health-related quality of life

Background – BWSTT and MS

NRC Research Press

ABSTRACT

Adapted exercise interventions for persons with progressive multiple sclerosis

Lara A. Pilutti

- Exercise benefits have been established for ambulatory MS patients with a relapsing-remitting disease course
- Investigated the exercise benefits for patients with progressive MS and greater impairment.
- 24 weeks of Body-weight supported treadmill training (BWSTT)
- 12 weeks of total-body recumbent stepper training
- Both training modalities improved fatigue and quality of life outcomes but neither improved physical function
- Benefits of long-term BWSTT were not maintained when exercise was discontinued

Background – BWSTT and MS

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Robot-assisted gait training in multiple sclerosis patients: a randomized trial

Multiple Sclerosis Journal
18(6) 881–890

DOI: 10.1177/1352458511431075
msj.sagepub.com
SAGE

Isabella Schwartz[1], Anna Sajin[1], Elior Moreh[1], Iris Fisher[2], Martin Neeb[2], Adina Forest[2], Adi Vaknin-Dembinsky[3], Dimitrios Karusis[3] and Zeev Meiner[1,3]

- Compared effectiveness of robot-assisted BWSTT with conventional walking on gait, functional independence, and quality of life in 15 and 17 MS patients, respectively
- Some gait parameters, FIM scores, and EDSS scores improved following the treatment with no difference between the groups.
- At 6 months, most gait and functional parameters had returned to baseline.

Questions

- Can exoskeletons facilitate accessibility to walking
  - For persons with greater disability?
  - For community settings?
  - In dosages that are manageable to people with
    - Moderate disability (too easy?)
    - More severe disability (too hard?)
  - For clinical applications?

Pilot Study - Objectives

- **Aim 1:** To determine the feasibility of a powered exoskeleton walking program (EWP) for persons with MS. Sub-aims are
  - accessibility
  - safety
  - tolerability of dosing parameters
  - patient acceptability
  - learnability
- **Aim 2:** To generate pilot data on secondary benefits of a powered exoskeleton exercise program on walking ability, and symptom management. Sub-aims are
  - Walking ability
  - Secondary benefits: spasticity, pain, sleep, depression and fatigue

Pilot Study - Design

- Prospective preliminary study
  - 8-week baseline
    - Weekly patient-reported outcomes
    - Timed walk and spasticity tests at 0, 4, and 8 weeks
  - 8-week walking phase
    - 3 sessions per week
    - 30 to 120 minutes per session
    - Weekly patient-reported outcomes phase
    - Timed walk and spasticity tests at 12, and 16 weeks
  - 4-week follow-up phase
    - Weekly patient-reported outcomes
    - Timed walk and spasticity tests at week 20

Pilot Study: Outcomes - Aim 1

- Accessibility:
  - Eligibility and enrollment (count/%)
  - Attendance: late/missed sessions, study drop out (count/%)
- Safety: adverse events
  - count/type
- Tolerability of dosing:
  - Session frequency and duration
  - Session intensity (BP, HR, RPE)
  - Energy expenditure in last week
- Acceptability
  - QUEST 2.0 (Quebec User Evaluation of Assistive Technology)
  - Weekly during walking phase
  - Attendance: late or missed sessions, and study drop out
- Learnability (in ReWalk)
  - Level of assistance for stand/sit and walking
  - 6MWT distance
  - 10MWT
  - Timed Up and Go test

Pilot Study: Outcomes - Aim 2 Walking ability

- 6 Minute Walk Test (6MWT)
- 25 Foot Walk Test (25FWT)
- Scored as '0' if not able to perform

- Baseline Phase: mean of three trials at Weeks 0, 4, and 8

- Walking Phase: Weeks 12 and 16
  - Change and trend from baseline
  - Energy expenditure in Week 16
    - 2 trials of 6MWT
    - Mean VO_2 relative to resting VO_2

- Follow-up at Week 20

Pilot Study: Outcomes - Aim 2 Secondary Benefits

- Spasticity:
  - Modified Ashworth Scale (MAS) by physical therapist
  - Baseline Phase mean of Weeks 0, 4, 8
  - Walking Phase at Weeks 12, 16,
  - Follow-up Phase at Week 20

- Pain
  - Numeric Rating Scale (NRS) for up to three pre-existing pain locations
  - Baseline Phase weekly by NIH Assessment Center
  - Walking Phase before and after each session
  - Follow-up Phase weekly by NIH Assessment Center
  - New pains will be documented as adverse events)

Pilot Study: Outcomes - Aim 2 Secondary Benefits

Patient-Reported Outcomes via NIH Assessment Center

- Sleep disturbance (PROMIS 10-item short form)
- Depression (Neuro-QoL 8-item short form)
- Positive affect and well-being (Neuro-QoL 8-item short form)
- Fatigue
  - Neuro-QOL 8-item short form
  - Neurologic Fatigue Index for MS (NFIMS)
- Baseline Phase mean (SD) of weekly assessments Weeks 0 through 8
- Walking Phase change and trend for weekly assessments Weeks 9 through 16
- Follow-up Phase change and trend for weekly assessments Weeks 17 through 20

Study Methods: Eligibility - Inclusion

- Definitive MS diagnosis
  - relapsing-remitting
  - primary progressive
  - secondary progressive
- EDSS score 5.0 to 7.5
- Age 18 - 65
- Height 1.57 m – 1.88m
- Weight <100 kg
- Tolerate standing 30 minutes
- No weight-bearing limitations
- No medical contraindications

Study Methods: Eligibility - Exclusion

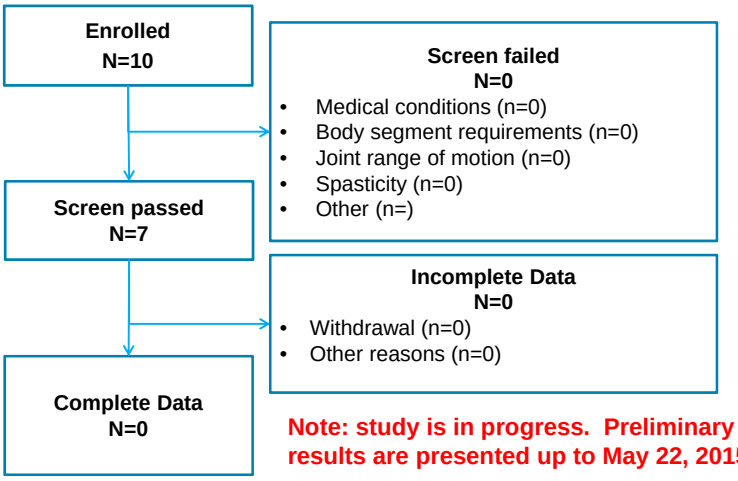
- Walking limitations attributable to another condition age, or both
- Uncontrolled cardiovascular conditions (e.g., heart failure, angina, hypertension)
- Osteoporosis or other risk of bone fracture from weight bearing
- Pregnancy
- Competing inflammatory or autoimmune diagnosis
- Alternate neurologic diagnosis
- Joint contractures
  - Hip 5° extension
  - Knee 5° extension flexion
  - Ankle: neutral dorsiflexion
- Severe spasticity: Modified Ashworth Scale 4
- Body segment length
  - Hip width >42 cm
  - Thigh >61.5 cm
  - Leg >63.5
- Limb length discrepancy
  - Thigh >1.3 cm
  - Leg >1.9 cm

Participant Characteristics

Subject ID	Age (years)	EDSS score	Height (m)	Weight (kg)	BMI (kg/m^2)
1					
2					
3					
4					
5					
6					
Median					

Age = age at enrollment; EDSS = Expanded Disability Status Scale score; m = meters; kg = kilograms; BMI = body mass index

Outcomes: Accessibility - Enrollment (target n=12)



Note: study is in progress. Preliminary results are presented up to May 22, 2015

Outcomes: Accessibility - Attendance

Subject ID	Sessions			Sessions Missed	
	Scheduled	Attended	Late	n	Reasons
1	9	8		1	transportation
2	5	6		1	transportation
3	In baseline				
4	In baseline				
5	In baseline				
6	In baseline				
7	In baseline				

Outcomes: Safety

- Serious Adverse Events: none to date
- Minor Adverse Events: none to date

Outcomes: Tolerability - Dosing

Subject ID	Sessions			
	Weeks	Frequency	Duration (mean/SD)	Duration (min/max)
1	4	3	80	60 – 90
2	3	2.5	70	60 – 90
3				
4				
5				
6				
7				

Outcomes: Tolerability - Best Efforts

ID	Sessions (n)	Longest Walk			6MWT	25FWT
		Time (min)	Distance (m)	Steps	Distance (m)	Speed (m/s)
1	8	90	136.4	311	26.7	0.16
2	5	90	121.2	275	33.0	0.18
3						
4						
5						
6						
7						

6MWT = 6 Minute Walk test; m = meters); m/s = meters per second

Outcomes: Tolerability - Intensity

ID	Sn	Heart Rate			Blood Pressure			Borg RPE		
		Pre	Mid	Post	Pre	Mid	Post	Pre	Mid	Post
1										
2										
3										
4										
5										
6										
7										

Sn = Session number
RPE = rating of perceived exertion

Outcomes: Learnability – Level of Assistance

ID	Sn	Stand	Walk	Sit	6MWT	TUG
1	8	Mod	Mod	Mod	Mod	NT
2	5	Mod	Min	Mod	Min	NT
3						
4						
5						
6						
7						

Sn = Session number; 6MWT = Six Minute Walk Test; TUG = Timed Up and Go
Levels of Assistance: C.S. = Close Supervision; G.C. = Contact Guard;
Min = Minimal; Mod = Moderate; Max = Maximal

Outcomes: Walking ability

Subject ID	6MWT (m)		25FWT (m/s)	
	Baseline (mean/SD)	Walking (mean/SD)	Baseline (mean/SD)	Walking (mean/SD)
1	36.5 (4.5)		0.08 (0.02)	
2	0		0	
3	60.0 (9.9)		0.21 (0.04)	
4	10.9		0.15	
5	68.5		0.22	
6	0		0	
7	36.1		0.19	

6MWT = Six Minute Walk Test; 25FWT = 25 Foot Walk Test

Outcomes: Secondary Benefits

Subject ID	Spasticity (MAS)		Pain (NRS)	
	Baseline (mean/SD)	Walking (mean/SD)	Baseline (mean/SD)	Walking (mean/SD)
1	-	-	3.3 (2.4)	NR
2	-		1.1 (0.4)	
3	-		1.0 (0.0)	
4	-		3.0 (0.0)	
5	-		4.0 (1.4)	
6	-		6.0	
7				

MAS = Modified Ashworth Scale; NRS = Numeric Rating Scale

Outcomes: Secondary Benefits

Subject ID	Sleep Quality (PROMIS)		Depression (Neuro-QoL)	
	Baseline (mean/SD)	Walking (mean/SD)	Baseline (mean/SD)	Walking (mean/SD)
1	46.4 (3.0)	46.0 (0.8)	50.4 (2.6)	45.1 (3.0)
2	39.2 (3.4)		37.8 (2.4)	
3	38.8 (3.8)		40.0 (3.5)	
4	52.2 (2.1		50.2 (2.1)	
5	47.6 (5.9)		36.9 (0.0)	
6	36.6		36.6	
7				

PROMIS = Patient Reported Outcomes Measurement and Information System; Neuro-QoL = Neurological Quality of Life
(T-score mean=50, SD=10)

Outcomes: Secondary Benefits

Subject ID	Positive Affect and Well-Being (Neuro-QoL)	
	Baseline (mean/SD)	Walking (mean/SD)
1	43.9 (4.8)	51.1 (1.3)
2	65.7 (3.2)	
3	60.1 (2.3)	
4	49.9 (2.7)	
5	56.1 (4.3)	
6	68.0	
7		

Neuro-QoL = Neurological Quality of Life
(T-score mean=50, SD=10)

Outcomes: Secondary Benefits

Subject ID	Fatigue (NFIMS)		Fatigue (Neuro-QoL)	
	Baseline (mean/SD)	Walking (mean/SD)	Baseline (mean/SD)	Walking (mean/SD)
1	-	-	50.6 (4.3)	42.3 (0.4)
2	-		45.3 (5.1)	
3	-		31.8 (2.6)	
4	-		45.2 (2.1)	
5	-		51.3 (0.1)	
6	-		36.6	
7				

NFIMS = Neurologic Fatigue Index for MS (Raw score 0-30)
Neuro-QoL = Neurological Quality of Life (T-score mean=50, SD=10)

Video Clips

- Participant A
- Participant B

Future of Exoskeletons in Rehabilitation: Assisted walking for small sample of persons with MS

- Accessibility:
  - n=2
  - Age: 30-45
  - EDSS scores: 6-7
- Learnability: walk 121-136 m, moderate to minimal assistance, 5-8 sessions
- Tolerability: Borg RPE range from 10-16/20
- Potential for exercise effects: not yet walking for endurance
  - BP response
  - HR
  - RPE
- Secondary benefits: Reports for
  - Pain, spasticity, posture, sleep, fatigue
  - Psychosocial aspect: ability to walk

Future of Exoskeletons in Rehabilitation

- Accessibility: Are different devices suited to different levels of mobility disability?
  - ReWalk for lower EDSS?
  - Ekso for higher EDSS?
- Mobility: Will the technology evolve to function as a replacement for wheelchairs or scooters?
- Potential for exercise effects: Can the technology provide titrated dosage to match the frequency, intensity, and duration parameters to individual levels of ability for endurance exercise?
- Potential for secondary benefits: Will device users experience improvements to MS symptoms including pain, spasticity, sleep disturbance, and fatigue?
- Modification of MS progression: If exercise can influence systemic changes to the central nervous system, will exoskeletons facilitate such changes?

Questions and Discussion