Ecological validity of methods to assess walking ability in Multiple Sclerosis

Mobility is one of the most important bodily functions of persons with Multiple Sclerosis. Cross-sectional data as well as preliminary findings from a short baseline to treatment studies indicate a poor ecological validity of clinical gait tests. Real-life use of accelerometer should be used to assess mobility in MS. Advanced MRI techniques such as probabilistic tractography might help to narrow the gap between structural imaging as a marker of neurodegeneration and real-life performance in Multiple Sclerosis.
Ecological validity of methods to assess walking ability in Multiple Sclerosis

The 2nd Winter Symposium of the Human Motion Project
From Gait Labs to the Real World
March 6, 2015

Jan-Patrick Stellmann, INIMS, Hamburg
• Most frequent inflammatory disease of the central nervous system

• ~2.5 million individuals affected worldwide

• MS usually strikes between puberty and the menopause

• Very disabling disease with ~30% wheel-chair bound after 10 years

• Walking – one of the most valuable bodily functions
Mobility Assessment in MS

- **Real life walking**
- **Clinical tests**
- **Patient reported outcomes**

### Mobility Tests:

<table>
<thead>
<tr>
<th>Test</th>
<th>Distance</th>
<th>Time</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>T25FW</td>
<td>7.5m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T10</td>
<td>10m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T30</td>
<td>30m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T100</td>
<td>100m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2MWT</td>
<td>2 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT</td>
<td>6 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accelerometry</td>
<td>1 week</td>
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</table>
Ecological validity has typically been taken to refer to whether or not one can generalize from observed behaviour in the laboratory to natural behaviour in the world. (Schmuckler 2001)

- behavioural science since the 1950s
- not established in MS
- rare in “biologic” science
- theoretical construct
- denies formal testing
- depends on the entire setting of an experiment
Cross-Sectional Data

- 23 MS patients with mild/moderate impairment
- T25FW/2MWT/6MWT
- Expanded Disability Status Scale
- 7 days accelerometry

Ecological Validity should be high, if...

sequences of uninterrupted 2/6 Minutes walks are common
or
walking tests are correlated with real-life walking speed
6-Minutes Walks in Real-Life

median 0.35 sequences per day

Sequences of uninterrupted walking (Min. Duration: 6 min)

Patient ID

EDSS

# Sequences of uninterrupted walking

0 20 40 60 80

0 2 4 6 8 10

PeerJ PrePrints

Stellmann 2015 PlosOne
2-Minutes Walks in Real-Life

median 2.61 sequences per day

Sequences of uninterrupted walking (Min. Duration: 2 min)
30-seconds Walks in Real-Life

median 22 sequences per day

Sequences of uninterrupted walking (Min. Duration: 15 sec)

# Sequences of uninterrupted walking

EDSS

Patient ID

EDSS

0 2 4 6 8 10

0 10

Sequences of uninterrupted walking (Min. Duration: 15 sec)
# Correlations

<table>
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<tr>
<th>(n=23)</th>
<th>6MWT</th>
<th></th>
<th>2MWT</th>
<th></th>
<th>10mWT</th>
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<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>$R^2$</td>
<td>p-value</td>
<td>$R^2$</td>
<td>p-value</td>
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<tr>
<td>Quantiles of walking speed</td>
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<tr>
<td>10%</td>
<td>0.02</td>
<td>0.47</td>
<td>0.04</td>
<td>0.44</td>
<td>0.01</td>
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<tr>
<td>30%</td>
<td>0.01</td>
<td>0.51</td>
<td>0.02</td>
<td>0.49</td>
<td>0.04</td>
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<td>50%</td>
<td>0.01</td>
<td>0.52</td>
<td>0.01</td>
<td>0.50</td>
<td>0.09</td>
<td>0.36</td>
</tr>
<tr>
<td>70%</td>
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<td>0.52</td>
<td>0.01</td>
<td>0.50</td>
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<tr>
<td>90%</td>
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<td>0.03</td>
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<tr>
<td>Mean distance / day</td>
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<td>0.17</td>
<td>0.08</td>
<td>0.38</td>
<td>0.88</td>
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<tr>
<td>Mean number of steps / hour</td>
<td>0.19</td>
<td>0.28</td>
<td>&lt;0.01</td>
<td>0.69</td>
<td>0.01</td>
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<tr>
<td>Mean walking speed in sequence with at least 50 steps</td>
<td>&lt;0.01</td>
<td>0.68</td>
<td>&lt;0.01</td>
<td>0.79</td>
<td>&lt;0.01</td>
<td>0.61</td>
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<td>Mean walking speed in sequence with at least 100 steps</td>
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<td>0.71</td>
<td>&lt;0.01</td>
<td>0.71</td>
<td>0.09</td>
<td>0.41</td>
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</table>
Improving Walking in MS

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 Schwind*, Ron Cohen, Lawrence N Marinucci, Andrew R Blight, on behalf of the Fampridine MS-F203 Investigators

Summary

Background Clinical studies suggested that fampridine (4-aminopyridine) improves motor function in people with multiple sclerosis. This phase III study assessed efficacy and safety of oral, sustained-release fampridine in people with ambulatory deficits due to multiple sclerosis.

Timed 25-Foot Walk

Direct evidence that improving 20% or greater is clinically meaningful in MS

Jemmy Hobart, MD, PhD
Andrew R. Blight, PhD
Andrew Goodman, MD
Frances Lynn, MSc
Norman Puziki, MD

ABSTRACT

Objective: In this study, we used data from clinical trials of daflampridine (fampridine outside the United States) to re-examine the clinical meaningfulness of Timed 25-Foot Walk (T25FW) changes.

Methods: Pooled data were analyzed from 2 phase III randomized placebo-controlled clinical trials of daflampridine in multiple sclerosis (MS) (n = 533). Walking speed (T25FW) and patient-reported walking ability (MS Walking Scale-12 [MSWS-12]) were measured, concurrently, multiple times before and during treatment. We examined T25FW speed variability within and between visits, correlations of T25FW speed with MSWS-12 score, and changes in MSWS-12 (mean scores, effect sizes) associated with percent T25FW changes.

Results: T25FW speed variability was small (within- and between-visit averages = 7.2%–8.7% and 14.4%–16.3%). Correlations between T25FW and MSWS-12 values were low (−0.20 to −0.30), but relatively 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.

Conclusions: This study builds on existing research and provides direct evidence that improvements in T25FW speed of ≥20% are meaningful to people with MS. The daflampridine data enabled examinations previously not possible, including spontaneous and induced speed changes, speed change anchored to change in self-reported walking ability, and a profile of speed changes. Results support the T25FW as a clinically meaningful outcome measure for MS clinical trials. Neurology

2013:80:1509-1517
- N=28
- EDSS 4.0-6.5 (max: distance 500 m – 20m bilateral walking aid)

**Baseline Day 0–14**

- Day 0
  - Actibelt Week 1
  - T25FW 6MWT
  - HAQUAMS

**Treatment Day 15–28**

- Day 14
  - Actibelt Week 2
  - T25FW 6MWT
  - HAQUAMS
- Day 28
  - Actibelt Week 3
  - T25FW 6MWT
  - HAQUAMS
- Day 28
  - Actibelt Week 4
  - T25FW 6MWT
  - HAQUAMS

**Ecological Validity should be high, if…**

Clinical tests or PROMS agree with real-life response
Defining Real-life Response Criteria

Response Criteria:

Distance Change $\geq 5\%$

&

Speed Change $> 0$
### 20% Improvement and Real-Life

<table>
<thead>
<tr>
<th></th>
<th>ACC</th>
<th>DOC</th>
<th>PAT</th>
<th>MSWS</th>
<th>HAQUAMS</th>
<th>FAI</th>
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</tr>
</tbody>
</table>

**phi**

- **No agreement**
- **Moderate**
Understanding Mobility in MS

- Real life walking
- Patient reported outcomes
- Clinical tests
- Brain structure

Mobility
Real-Life Mobility and Cortical Thickness

N=35, PPMS, Stellmann in preparation
Real-Life Mobility and White Matter Tracks

N=35, PPMS, Stellmann in preparation
Summary

- Ecological validity of clinical walking test is poor
- 6/2-MWT slightly better than T25FW
- Real-life accelerometry correlates with brain structure
- Use accelerometry as outcome
• RCT
• Training vs. Waiting
• Cognition
• Connectivity
• Accelerometry