Responsiveness of walking-based outcome measures after multiple sclerosis relapses following steroid pulses

Petar Filipović Grčić1, Meri Matijaca1, Ivo Lušić1, Vesna Čapkun2

1 Department of Neurology, University Hospital Center Split, Split, Croatia
2 Department of Nuclear Medicine, University Hospital Center Split, Split, Croatia

Source of support: Departmental sources

Summary

Background:
The aim of this study was to examine the impact of intravenous methylprednisolone therapy (IVMP) on the recovery of walking ability in patients experiencing multiple sclerosis (MS) relapses, to compare the responsiveness of walking-based measures, and to estimate the impact of different walking-based measures responsiveness on clinical trials.

Material/Methods:
The study included 49 consecutive patients with relapsing-remitting MS who received Solu-Medrol 1000 mg/day over 3 days for relapse with difficulties in walking. The following walking-based measures were administered before and a month after IVMP: the Multiple Sclerosis Walking Scale-12 (MSWS-12), the Expanded Disability Status Scale (EDSS), the 2-minute timed walk (2-minTW), the 25-foot walk test (25FWT), the Six Spot Step Test (SSST). All patients had worn the step activity monitor accelerometer (SAM) 1 week prior to IVMP was applied and wore it again the fourth week upon the corticosteroid therapy was completed. The SAM analysis utilized the average daily step count and data regarding frequency and intensity of walking over a continuous time interval.

We examined: (1) the impact of IVMP on the recovery of walking ability; (2) the responsiveness of each walking-based measure; (3) the relative responsiveness of competing walking-based measures; and (4) the impact of different walking-based measures responsiveness on clinical trials.

Results:
All walking-based measures showed significant improvement of walking ability 1 month after the IVMP. The most responsive were MSWS-12 and EDSS. Different responsiveness implied a greater than 6-fold impact on sample size estimates.

Conclusions:
All applied walking-based measures showed significant improvement of walking ability 1 month after the IVMP. Responsiveness of various walking-based measures notably differ, thus affecting sample size calculations.

key words: intravenous methylprednisolone • multiple sclerosis • relapses • responsiveness • walking-based measures

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=882130

Word count: 3062

Tables: 6

Figures: –

References: 37

Author’s address: Petar Filipović Grčić, Department of Neurology, University Hospital Center Split, Spinčićeva 1, 21000 Split, Croatia, e-mail: pfg@hi.t-com.hr
BACKGROUND

The selection of outcome measures to be applied is one of the most important factors in designing a clinical trial. The outcome measures present a major factor influencing the duration of a trial, likelihood of detecting a therapeutic effect, size of the sample and acceptance of study results [1]. Selection of outcome measures is particularly difficult for multiple sclerosis (MS) trials because MS affects patients in many different ways. Among many difficulties, walking problems are very common and important for MS patients; about three-quarters of them experience mobility problems [2,3] and they consider walking as the most valuable bodily function [4]. Also, new developments in the pharmacotherapy to improve walking in MS patients have occurred [5,6]. Therefore, the assessment of walking ability in MS patients is of a great importance for clinical research and practice.

Assessment of walking ability in MS patients began in 1955 with the first measure of disease severity, the Kurtzke Disability Status Scale [7]. Since that time, there has been a proliferation of numerous generic and genuine walking-based measures for MS patients. They are either clinician-based, patient-based, timed over fixed distance, measure the maximum distance a person can walk over a specific time interval, or use motion sensors such as accelerometers [8]. There is a considerable body of literature on the reliability and validity of walking-based measures but, regardless of their clinical importance, the studies of their responsiveness are either deficient or mostly related to rating scales [9–12].

Responsiveness is a measure to detect clinically important change or change over time, and is evaluated by various responsiveness statistics. Typically, responsiveness is determined by comparing before and after scores of interventions expected to produce a change in health. As the interpretation of P values is somewhat binary and sample size-dependent [13], it has become common to report responsiveness as an effect size, or standardized change score, by converting change scores into standard deviation units. Effect size and P values are limited indicators of responsiveness because they are inseparably linked to the magnitude of change induced by the intervention [14]. This can be partly overcome by comparing measures head-to-head in the same sample, which keeps sample and treatment effect constant and enables researchers to compare the relative responsiveness of competing measures [15].

The aims of this study were: to examine the effects of IVMP on the recovery of walking ability in patients experiencing MS relapse; to compare, head-to-head, the responsiveness of some walking-based measures applied for MS trials; and to consider their potential implications for clinical trials.

MATERIAL AND METHODS

Patients

The patients involved in this study were recruited from the Department of Neurology, University Hospital Center Split, from July 2008 to December 2010. The research was approved by local Ethics Committee and all participants gave their informed consent. A total of 54 consecutive patients who were selected for IVMP (1000 mg/day over 3 days) due to MS relapse and who met the inclusion criteria were asked to participate in the study. Three patients refused to take part, 1 patient did not appear for control testing, and 1 patient was found to be noncompliant with wearing the accelerometer; therefore 49 patients were included in the statistical analyses. During the study, 6 patients experienced more than 1 relapse meeting the inclusion criteria. Due to minimizing the potential impact of practice effects on the results, only their first relapse was considered. A relapse was defined as either new nervous system deficits or worsening of previous ones lasting at least 24 hours [16]. All patients complained of walking difficulties caused by MS relapse and had clinical involvement, individually or combined, of the corticospinal tract (paresis, hyperreflexia, spasticity, extensor plantar response), posterior columns or medial lemniscus tract ( proprioception) and cerebellum (cerebellar ataxia) affecting 1 or both lower limbs. The new nervous system deficits or worsening of previous ones were assessed strictly by clinical examination. MRI studies for documenting location and size of the MS lesions responsible for the relapses were not included. The inclusion criteria were: 1) age 18 years or over; 2) definite diagnosis of relapsing-remitting MS (RRMS) [17]; 3) EDSS [18] ≤6.5 at the time of the inclusion; 4) relapse with onset of symptoms within 2 weeks prior to IVMP; 5) no spontaneous improvement prior to IVMP; 6) relapse involvement of gait with deterioration of at least 1 step in the relevant functional system (FS) (pyramidal, sensory or cerebellar) or an increase in EDSS of 1 point or more; and 7) ability to perform walking tests. Exclusion criteria were: 1) treatment with corticosteroids in the previous 3 months; 2) cognitive impairment; 3) vision impairment; 4) orthopedic disease; and 5) cardiac disease. Pre-attack EDSS and FS were well known because the patients were routinely seen in our outpatient facility every 3 to 6 months by a trained neurologist with experience in multicentre clinical trials (M.M.) [19].

Outcome measures

The following walking-based measures were administered before and after IVMP: the Expanded Disability Status Scale (EDSS) [18]; the Multiple Sclerosis Walking Scale-12 (MSWS-12) [20]; the 25-foot walk test (25FWT) [21]; the Six Spot Step Test (SSST) [22] and the StepWatch Activity Monitor (SAM, OrthoCare Innovations, Washington DC, USA). The 2-minute timed walk (2-minTW) was administered as a shorter (reduced) version of the 6-minute timed walk (6-minTW) [23]. The 2-minTW was chosen as a more appropriate walk test for patients suffering from MS relapse than the 6-minTW. The 25FWT and the SSST were repeated twice, and the average number of seconds was used in the analysis. Since test-retest reliability of the 2-minTW for the first 10 participants in both tests (before and after IVMP) was high (Cronbach α=0.981 and 0.992, respectively), subsequent participants were tested once. Comparison was undertaken using the first 2-minTW in those who had repeated testing. The translation of the MSWS-12 into Croatian was undertaken for the first 100 steps. Evaluation of the output
data confirmed compliance with wearing the accelerometer for all patients except for 1. The analysis utilized the average daily step count, the percentage of time spent inactive, the percentage of time spent in low step activity (1–15 steps/min), the percentage of time spent in medium step activity (16–30 steps/min), the percentage of time spent in high step activity (>31 steps/min), the average peak activity index (average steps/min of the highest 30 minutes of the day regardless of when they occurred) and the average steps in 1, 5, 30 and 60 minutes (average steps/min of the highest continuous period of 1-min, 5-min, 30-min and 60-min periods). No significant difference was found in SAM output data between the first and the seventh day of monitoring before and after IVMP. Other tests were administered between 1 and 3 p.m. before IVMP and 31 days later at the same time of day. All walk tests, (25FWT, SSST and 2-minTW) participants performed in the same type of footwear and clothes. To reduce patients’ bias, the walking-based tests were conducted without fixed order, with the exception of continuous long-term walk monitoring. To reduce the clinicians’ bias, the indication for IVMP was established independently of the study and different parts of research were also performed independently by different authors (clinical examination – M.M.; MSWS-12 and walk tests – P.F.G.; SAM instructions and analyses of outputs – I.L.; statistics – V.C.).

Statistical analysis

All statistical analyses were done using Statistica 7.0 software. Wilcoxon signed rank test was used to assess the significance of changes of walking-based measures after IVMP. Differences were considered significant at P<0.05. Responsiveness was determined from Time 1 and 2 data by calculating both effect size (ES: mean change score divided by SD of admission scores) [24] and standardized response means (SRM: mean change score divided by SD of change scores) [25], since they can produce different values [26]. They were interpreted using Cohen’s criteria (values of 0.2–0.49 were defined as small, those of 0.5–0.79 as moderate and that of 0.8 and greater as large) [27]. The relative responsiveness of competing walking-based measures (EDSS, MSWS-12, 2-minTW, SSST, 25FWT and SAM parameters) was determined by computing their relative efficiency (RE) [28]. RE estimates the extent to which 1 measure is more or less efficient at detecting change relative to another measure. We computed RE as pair-wise squared Z values from Wilcoxon signed ranks test. The walking-based measure with the largest Z value was chosen as the denominator for the pair-wise calculation. This measure has a measurement precision of 100%. The 2-minTW, MSWS-12 and 25FWT had measurement precision of 95.1%, 82.4%, 75% and 68.3%, respectively. SAM parameters had RE between 60% for average steps in 1 minute and 15.5% for percentage of time spent in low step activity.

Different responsiveness between applied walking-based measures is showed in Table 3. Both the patient-rated (MSWS-12) and clinician-rated (EDSS) scales showed large degrees of responsiveness as determined by SRM (1.05 and 1.29, respectively) and large or moderate responsiveness as determined by ES (1.02 and 0.69, respectively). Walk tests (2-minTW, SSST and 25-FTW) showed large and moderate responsiveness as determined by SRM (0.89, 0.69 or 0.55, respectively) and moderate or small responsiveness as determined by ES (0.54, 0.31 and 0.27, respectively). The real-world ambulation measured by SAM had small responsiveness of all parameters except for average steps in 1 minute and average peak activity index, which had moderate responsiveness as determined by SRM (0.70 and 0.53, respectively).

Table 4 presents slightly different results regarding RE. The EDSS had the largest Z value and was chosen as the denominator for the pair-wise calculation. This scale had measurement precision of 100%. The 2-minTW, MSWS-12, SSST and 25FWT had measurement precision of 95.1%, 82.4%, 75% and 68.3%, respectively. SAM parameters had RE between 60% for average steps in 1 minute and 15.5% for percentage of time spent in slow step activity.

Table 5 displays RE of SAM parameters, which were obtained by proprietary software. The average steps in 1 minute had

### Table 1. Demographic and clinical characteristics of patients.

| Sample size | 49 |
|-------------|----|
| Age, y, median; range | 35; 18–56 |
| No. female (%) | 39 (79.6) |
| Y since MS onset, median; range | 8; 1.3–27 |
| EDSS prior IVMP, median; range | 3.0; 1.5–6.0 |
| BMI, median; range | 22.7; 16.7–32.3 |

| Education (y): |
|----------------|
| Elementary (1–8) | 4 |
| High school (9–13) | 35 |
| College, master (14+) | 10 |

| Current employment status: |
|---------------------------|
| Employed | 19 |
| Unemployed | 9 |
| Retired owing to MS | 21 |

MS – Multiple Sclerosis; EDSS – Expanded Disability Status Scale; BMI – Body Mass Index.
### Table 2. Walking-based measures.

| Measures, median; range | Time 1 | Time 2 | p value |
|------------------------|--------|--------|---------|
| EDSS                   | 3.0; 1.5–6.0 | 2.0; 0–6.5 | <0.001  |
| 25FWT                  | 6.8; 4.1–23.5 | 5.9; 3.2–23.3 | <0.001  |
| SSST                   | 10.9; 6.3–47.4 | 8.7; 5.7–48.4 | <0.001  |
| 2-min TW               | 127; 30–215.5 | 156; 36.7–248.4 | <0.001  |
| MSWS-12                | 64.6; 9–97.9 | 31.3; 2.1–95.8 | <0.001  |
| Average daily step count | 2607; 690–8411 | 3856; 640–7208 | <0.001  |
| % inactive             | 79; 57.6–92 | 75.3; 58.3–90.3 | 0.006   |
| % low activity         | 16.8; 6.9–32.2 | 19.3; 8.1–29.1 | 0.028   |
| % medium activity      | 2.8; 0.01–9.3 | 3.7; 0.04–10.5 | 0.009   |
| % high activity        | 0.7; 0–5.5 | 1.4; 0–6 | 0.003   |
| Average peak activity index | 28.4; 9.3–53.2 | 34.8; 9–56.4 | <0.001  |
| Average steps in 1 minute | 43.8; 14.1–64.6 | 48.3; 14.1–66 | <0.001  |
| Average steps in 5 minutes | 30.7; 6.8–89.9 | 34.5; 7.4–60.1 | <0.001  |
| Average steps in 30 minutes | 14; 2–34.8 | 18; 2.8–45 | <0.001  |
| Average steps in 60 minutes | 10.1; 1.9–24.9 | 13.1; 1.9–35.9 | 0.006   |

EDSS – Expanded Disability Status Scale; 25FWT – 25 foot Walk Test; SSST – Six Spot Step Test; 2-minTW – 2-minute Timed Walk; MSWS-12 – 12-item Multiple Sclerosis Walking Scale; % inactive — percentage of time spent inactive; % low activity — percentage of time spent in low step activity (1–15 steps/min); % medium activity — percentage of time spent in medium step activity (16–30 steps/min); % high activity — percentage of time spent in high step activity (>31 steps/min); Average peak activity index — average steps/min of the highest 30 minutes of the day regardless of when they occurred; Average steps in 1, 5, 30 and 60 minutes — average steps/min of the highest continuous period of 1, 5, 30 and 60 minutes of the day.

### Table 3. Responsiveness of walking-based measures.

| Outcome measures | Mean score (SD) | Change | EF* | SRM** |
|------------------|-----------------|--------|-----|-------|
|                  | Time 1          | Time 2 |     |       |
| MSWS-12          | 62.7 (24.0)     | 38.2 (25.3) | −24.5 (23.4) | 1.02 | 1.05 |
| EDSS             | 3.4 (1.3)       | 2.5 (1.6) | −0.9 (0.7) | 0.69 | 1.29 |
| 2-min TW         | 123.4 (48.0)    | 149.1 (48.8) | 25.7 (28.9) | 0.54 | 0.89 |
| SSST             | 14.1 (7.8)      | 11.7 (8.0) | −2.4 (3.5) | 0.31 | 0.69 |
| 25FWT            | 8.1 (4.1)       | 7.0 (3.9) | −1.1 (2.0) | 0.27 | 0.55 |
| Average daily step count | 3090.5 (1664.9) | 3684.6 (1614.5) | 594.1 (1546.5) | 0.36 | 0.38 |
| % inactive       | 78.1 (7.8)      | 76.0 (7.0) | −2.1 (5.8) | 0.27 | 0.36 |
| % low activity   | 17.5 (6.1)      | 18.7 (5.0) | 1.2 (4.4) | 0.20 | 0.27 |
| % medium activity| 3.3 (2.0)       | 3.8 (2.1) | 0.5 (1.7) | 0.25 | 0.29 |
| % high activity  | 1.1 (1.2)       | 1.5 (1.3) | 0.4 (1.0) | 0.33 | 0.40 |
| Average peak activity index | 29.5 (10.8) | 33.6 (11.3) | 4.1 (7.8) | 0.38 | 0.53 |
| Average steps in 1 minute | 42.4 (11.3) | 47.0 (11.0) | 4.6 (6.6) | 0.41 | 0.70 |
| Average steps in 5 minutes | 31.7 (14.8) | 35.8 (13.0) | 4.1 (11.1) | 0.28 | 0.37 |
| Average steps in 30 minutes | 15.1 (7.4) | 18.2 (8.8) | 3.1 (6.6) | 0.42 | 0.47 |
| Average steps in 60 minutes | 11.1 (5.6) | 13.2 (6.3) | 2.1 (5.3) | 0.38 | 0.40 |

* effect size (mean change score/SD of Time 1 scores); ** standardized response mean (mean change score/SD of change scores).

MSWS-12 — 12-item Multiple Sclerosis Walking Scale; EDSS — Expanded Disability Status Scale; 2-minTW — 2-minute Timed Walk; SSST — Six Spot Step Test; 25FWT — 25 foot Walk Test; % inactive — percentage of time spent inactive; % low activity — percentage of time spent in low step activity (1–15 steps/min); % medium activity — percentage of time spent in medium step activity (16–30 steps/min); % high activity — percentage of time spent in high step activity (>31 steps/min); Average peak activity index — average steps/min of the highest 30 minutes of the day regardless of when they occurred; Average steps in 1, 5, 30 and 60 minutes — average steps/min of the highest continuous period of 1, 5, 30 and 60 minutes of the day.
the largest Z value; this was chosen as the denominator for pair-wise calculation and had measurement precision of 100%. Average steps in 5 minutes, average peak activity index and average daily step count had measurement precision of 77.5%, 70% and 68.4%, respectively. The worst RE had percentage of time spent inactive;% low activity – percentage of time spent in low step activity (1–15 steps/min);% medium activity – percentage of time spent in medium step activity (16–30 steps/min);% high activity – percentage of time spent in high step activity (>31 steps/min); Average peak activity index – average steps/min of the highest 30 minutes of the day regardless of when they occurred; Average steps in 1, 5, 30, 60 minutes – average steps/min of the highest continuous period of 1, 5, 30 and 60 minutes of the day.

**Discussion**

Walking difficulties are very common for MS patients [2,3]; therefore the selection of appropriate walking-based outcome measures is essential to evaluate response to treatment, as well as disease progression sensitivity. The aim of this study was to examine the effects of IVMP on the recovery of walking ability in patients experiencing MS relapses and to compare the responsiveness of walking-based measures that might be used in MS clinical trials. As the importance of responsiveness lies in the balance between statistical power and sample size [28], the next step taken was to examine the potential implications for clinical trials of using walking-based measures with different levels of responsiveness.

In this study all applied methods of walking assessment indicated significant improvement of walking ability in patients with walking difficulties caused by MS relapse 1 month after IVMP. Two previous randomized, double-blind and placebo-controlled studies [29,30] convincingly demonstrated, by EDSS scoring, that IVMP accelerates clinical recovery from relapse of RRMS 1 month after treatment. As the EDSS is strongly biased toward walking, our finding is not surprising.

However, the responsiveness of different walking-based measures varied markedly in terms of effect sizes, relative efficiency and implication for sample size estimation. The highest responsiveness was obtained by MSWS-12, EDSS and 2-minTW. Regarding the RE, the most successful measures were EDSS, 2-minTW and MSWS-12. The potential impact of different responsiveness on sample size estimation showed that the number of patients required to detect the same improvement of walking ability obtained by IVMP ranged from 1 (EDDS) to 6.5 (percentage of time spent in low step activity).
Several of walking-based measures have been criticized on some disadvantages (single activity execution within a limited time frame, non-familiar environment, and unquantifiable impact of the observer). The 25FWT reflects only the ability to walk a given distance and walking speed. In our study, the responsiveness of the 25FWT is small and is very similar to the responsiveness of 25FWT in Hobart et al. [20]. The responsiveness of the SSST has never been studied, and we suppose it is higher than the responsiveness of the 25FWT. The SSST also reflects the ability to walk a given distance and walking speed, but it depends more on coordination, balance, and ease of abdication in the hip than does the 25FWT. The range of measurement of SSST is much wider and its floor effect is less pronounced than that of the 25FWT [22]. We confirmed the higher responsiveness of the SSST according to the 25FWT in this sample of patients. However, the responsiveness of SSST determined by SRM is moderate and that determined by EF is small. Responsiveness of 2-minTW in MS patients with relapse has never been studied. The results reveal that out of all applied walking tests, the 2-minTW has the best responsiveness (large responsiveness determined by SRM and moderate responsiveness determined by EF).

In recent years, accelerometer-based technology has enabled reliable and valid data recording of frequency and intensity of walking over continuous time intervals [31,32]. Continuous walking monitoring provides a direct and objective measure of mobility in a community setting. In this study, the SAM outputs have small responsiveness. Exceptions are the 2 parameters reflecting burst walking activity (average steps in 1 minute and average peak activity index), which have moderate responsiveness determined by SRM. The obtained result indicating that SAM parameters show relatively small responsiveness was actually expected, because numerous personal and environmental factors affect everyday walking [33,34].

This study has some limitations concerning the generalizability and direct applicability of our results to clinical trials in MS. Firstly, the data were not collected within the context of a randomized controlled trial. Secondly, we compared several walking-based measures in a small sample from 1 clinical site. Thirdly, we examined walking-based measures only in a sample of MS patients who were selected for steroid therapy and with the single restriction of having MS relapse with walking difficulties. Fourthly, the relatively short period between the 2 tests involves the potential practice effects of all walking-based tests, not just the MSWS-12. Another limitation is that we studied only "positive" responsiveness of walking-based measures. Nevertheless, showing that the

### Table 6. Implications of different responsiveness for sample size calculations.

| Parameters       | Sample size |
|------------------|-------------|
| EDSS             | 100         |
| 2-min TW         | 105         |
| MSWS-12          | 121         |
| SSST             | 133         |
| 25FWT            | 146         |
| Average daily step count | 244 |
| % inactive       | 413         |
| % low activity   | 647         |
| % medium activity| 453         |
| % high activity  | 343         |
| Average peak activity index | 238 |
| Average steps in 1 minute | 167 |
| Average steps in 5 minutes | 215 |
| Average steps in 30 minutes | 296 |
| Average steps in 60 minutes | 418 |

Sample size requirements computed as 100×(z value measure with largest z value/z value this measure)². EDSS – Expanded Disability Status Scale; 2-min TW – 2-minute Timed Walk; MSWS-12 – 12-item Multiple Sclerosis Walking Scale; SSST – Six Spot Step Test; 25FWT – 25 foot Walk Test; % inactive – percentage of time spent inactive; % low activity – percentage of time spent in low step activity (1–15 steps/min); % medium activity – percentage of time spent in medium step activity (16–30 steps/min); % high activity – percentage of time spent in high step activity (>31 steps/min); Average peak activity index – average steps/min of the highest 30 minutes of the day regardless of when they occurred; Average steps in 1, 5, 30 and 60 minutes – average steps/min in continuous period of 1, 5, 30 and 60 minutes.
variable responsiveness of walking-based measures has substantial implications for clinical trials, we hope this study will contribute to creation of a body of knowledge for evidence-based selection of outcome measures [15].

CONCLUSIONS

Further evaluations of responsiveness of walking-based measures for a more modest treatment [5, 35–37] of walking difficulties in MS patients are suggested. The “negative” responsiveness of walking-based measures for evaluation of walking ability worsening that may occur over time might be the topic of another research study. Finally, the impact of practice effects on responsiveness of walking-based measures in MS patients should be quantified.

Acknowledgments

We wish to thank the patients who participated in this study.

REFERENCES:

1. Schwid SR, Goodman AD, Apatoff BR et al: Are quantitative functional measures more sensitive to worsening MS than are traditional measures? Neurology, 2000; 55: 1901–3
2. Swingler R, Compston DAS: The morbidity of multiple sclerosis. Q J Med, 1992; 83: 325–37
3. Hobart JC, Lamping DL, Fitzpatrick R et al: The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain, 2001; 124: 962–75
4. Heesen C, Bohm J, Reich C et al: Patient perception of bodily function in multiple sclerosis: gait and visual function are the most valuable. Mult Scler, 2008; 14: 988–91
5. Goodman AD, Brown TR, Krupp LB et al: Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet, 2009; 373: 732–38
6. Sanofi-Aventis. Efficacy, safety and tolerability of nerispiridine in patients with multiple sclerosis. Last updated 2010 Mar 22. ClinicalTrials.gov Web site. Available from: http://clinicaltrials.gov/ct2/show/NCT00811902. Accessed Apr 9 2010
7. Kurtzke JF: A new scale for evaluating disability in multiple sclerosis. Neurology, 1955; 5: 580–83
8. Pearson OR, Buse ME, van Deursen RWM, Wiles CM: Quantification of walking ability worsening that may occur over time might be the topic of another research study. Finally, the impact of practice effects on responsiveness of walking-based measures in MS patients should be quantified.
9. Hobart JC, Lamping DL, Fitzpatrick R et al: The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain, 2001; 124: 962–75
10. Mcguigan C, Hutchinson M: Confirming the validity and responsiveness of the Multiple Sclerosis Walking Scale-12 (MSWS-12). Neurology, 2004; 62: 2105–5
11. Hobart JC, Riazi A, Lamping DL et al: How responsive is the Multiple Sclerosis Impact Scale (MSIS-29)? A comparison with some other self-report scales. J Neurol Neurosurg Psychiatry, 2005; 76: 1539–43
12. Giordano A, Pucci E, Naldi P et al: Responsiveness of patient reported outcome measures in multiple sclerosis relapses: the REMS study. J Neurol Neurosurg Psychiatry, 2009; 80: 1025–28
13. Cohen J: The earth is round (p<.05). Am Psychol, 1994; 49: 997–1003
14. O’Connor RJ, Cano SJ, Thompson AJ, Hobart JC: Exploring rating scale responsiveness: does the total score reflect the sum of its parts? Neurology, 2004; 62: 1842–44
15. Hobart JC, Lamping DL, Freeman JA et al: Evidence-based measurement: which disability scale for neurological rehabilitation? Neurology, 2001; 57: 639–44
16. McDonald WI, Compston A, Edan G et al: Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol, 2001; 50: 121–27
17. Goraj B: Multiple sclerosis diagnostic criteria – an update. Pol Przegl Radiol, 2010; 75(Suppl.1): 110–10
18. Kurtzke JF: Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology, 1983; 33: 1444–52
19. Liepert B, Lechner-Scott J, Müller U, Kappos L: Reliability of EDSS and FS-score rating can be improved by standardised training. Mult Scler, 2002; 8: S33
20. Hobart JC, Riazi A, Lamping DL et al: Measuring the impact of MS on walking ability: the 12-item MS Walking Scale (MSWS-12). Neurology, 2005; 65: 31–36
21. Cutter GR, Baier ML, Rudick RA et al: Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain, 1999; 122: 871–82
22. Nieuwenhuis MM, Van Tongeren H, Sorensen PS, Ravnborg M: The Six Spot Step Test: a new measurement for walking ability in multiple sclerosis. Mult Scler, 2006; 12: 495–500
23. American Thoracic Society Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med, 2002; 166: 111–17
24. Kissel JT, Anderson JJJ, Meenan RF: Effect size for interpreting changes in health status. Med Care, 1989; 27: 178–89
25. Kremer M, Wolters EF, van der Werken CH et al: Accelerometry in persons with multiple sclerosis: measurement of physical activity or walking mobility? J Neurol Sci, 2010; 290: 6–11
26. Molloy LW, Snook EM, Agorvalis S: Does an accelerometer accurately measure steps taken under controlled conditions in adults with mild multiple sclerosis? Disabil Health J, 2011; 4: 52–57
27. Molloy LW, Snook EM, Mc Auley EJ et al: Demographic correlates of physical activity in individuals with multiple sclerosis. Disabil Rehabil, 2007; 29: 1501–4
28. Doerrsen SC, Mc Auley EJ: Environmental correlates of physical activity in multiple sclerosis: a cross-sectional study. Int J Behav Nutr Phys Act, 2007; 4: 49
29. Molloy LW, Goldman MD, Benedict RH: Walking impairment in patients with multiple sclerosis: exercise training as a treatment option. Neuropsychiatr Dis Treat, 2010; 6: 767–74
30. Nikfar S, Rahimi R, Rezaie A, Abdollahi M: A meta-analysis on the effectiveness of choline citrate infusions monitored by lymphocyte transformation test (LTT) in multiple sclerosis: 1. Clinical effects. J Neurol Neurosurg Psychiatry, 1987; 50: 511–16
31. Winkler M, Molloy LW, Sub Y et al: Accelerometry in persons with multiple sclerosis: measurement of physical activity or walking mobility? J Neurol Sci, 2010; 290: 6–11
32. Molloy LW, Snook EM, Agorvalis S: Does an accelerometer accurately measure steps taken under controlled conditions in adults with mild multiple sclerosis? Disabil Health J, 2011; 4: 52–57
33. Molloy LW, Snook EM, Mc Auley EJ et al: Demographic correlates of physical activity in individuals with multiple sclerosis. Disabil Rehabil, 2007; 29: 1501–4
34. Doerrsen SC, Molloy LW, Mc Auley EJ: Environmental correlates of physical activity in multiple sclerosis: a cross-sectional study. Int J Behav Nutr Phys Act, 2007; 4: 49
35. Molloy LW, Goldman MD, Benedict RH: Walking impairment in patients with multiple sclerosis: exercise training as a treatment option. Neuropsychiatr Dis Treat, 2010; 6: 767–74
36. Nikfar S, Rahimi R, Rezaie A, Abdollahi M: A meta-analysis on the effectiveness of choline citrate infusions monitored by lymphocyte transformation test (LTT) in multiple sclerosis: 1. Clinical effects. J Neurol Neurosurg Psychiatry, 1987; 50: 511–16
37. Muss C, Stejskal V, Titel E: The effectiveness of choline citrate infusions monitored by lymphocyte transformation test (LTT) in multiple sclerosis: 1. Clinical effects. J Neurol Neurosurg Psychiatry, 1987; 50: 511–16
38. Kurtzke JF: Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology, 1983; 33: 1444–52
39. Liepert B, Lechner-Scott J, Müller U, Kappos L: Reliability of EDSS and FS-score rating can be improved by standardised training. Mult Scler, 2002; 8: S33
40. Hobart JC, Riazi A, Lamping DL et al: Measuring the impact of MS on walking ability: the 12-item MS Walking Scale (MSWS-12). Neurology, 2005; 65: 31–36
41. Cutter GR, Baier ML, Rudick RA et al: Development of a multiple sclerosis functional composite as a clinical trial outcome measure. Brain, 1999; 122: 871–82
42. Nieuwenhuis MM, Van Tongeren H, Sorensen PS, Ravnborg M: The Six Spot Step Test: a new measurement for walking ability in multiple sclerosis. Mult Scler, 2006; 12: 495–500
43. American Thoracic Society Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med, 2002; 166: 111–17
44. Kissel JT, Anderson JJJ, Meenan RF: Effect size for interpreting changes in health status. Med Care, 1989; 27: 178–89
45. Kaz JN, Larson MG, Phillips CB et al: Comparative measurement sensitivity of short and longer health status instruments. Med Care, 1992; 30: 917–25
46. Liang MH: Evaluating instrument responsiveness. J Rheumatol, 1995; 22: 1101–92
47. Cohen J: Statistical power analysis for the behavioural sciences, 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988
48. Liang MH, Larson MG, Gullen KE, Schwartz JA: Comparative measurement efficiency and sensitivity of five health status instruments for arthritis research. Arthritis Rheum, 1985; 28: 542–47
49. Durelli L, Cocito D, Roccio A et al: High-dose intravenous methylprednisolone in the treatment of multiple sclerosis: clinical-immunological correlations. Neurology, 1986; 36: 238–43
50. Milligan GM, Newcombe RH, Compston DAS: A double-blind controlled trial of high dose methylprednisolone in patients with multiple sclerosis: 1. Clinical effects. J Neurol Neurosurg Psychiatry, 1987; 50: 511–16
51. Winkler M, Molloy LW, Sub Y et al: Accelerometry in persons with multiple sclerosis: measurement of physical activity or walking mobility? J Neurol Sci, 2010; 290: 6–11