Clinical outcome measures in progressive multiple sclerosis

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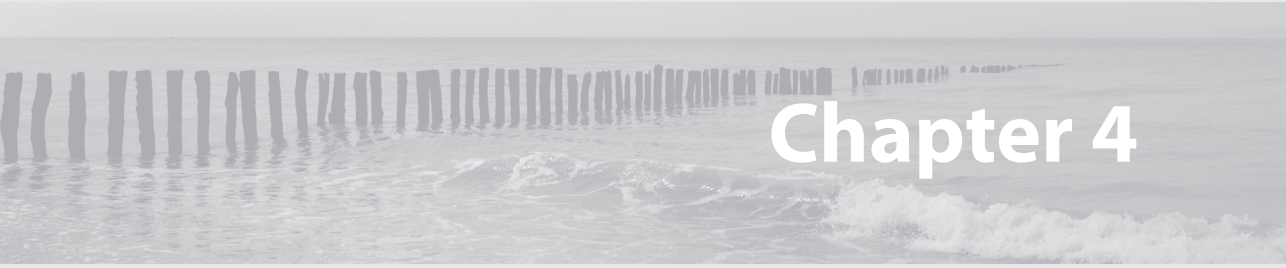

Chapter 4

Detecting clinically relevant changes in progressive MS

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Submitted

ABSTRACT

Objective: To study the relation between changes in different clinical outcome measures and disease impact as reported by the patient, in progressive MS, in order to find which changes contribute most to increased disease impact.

Methods: From a large cohort of MS patients who were prospectively followed-up, we selected all progressive patients with two visits 4-6 years apart. Long-term changes in disability were assessed on the Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT) and Guy's Neurological Disability Scale (GNDS). Presence or absence of clinically meaningful change was defined by using the Multiple Sclerosis Impact Scale (MSIS-29) as an anchor measure. Event rates for relevant changes and mean changes on the different scales were compared in relation to significant MSIS-worsening. Change on three recently identified sub-scales of the GNDS was included. We also studied patients in whom the observed changes in potential outcome measures and MSIS-29 were not matching.

Results: Change on the GNDS contributed most to increased disease impact. The spinal-plus subscale of the GNDS dominated the GNDS sum score. Also change on T25FW contributed largely to increased disease impact. Compared to EDSS and 9HPT, associations between T25FW change and change in patient-perceived impact were more apparent. Specific profiles of change in T25FW and MSIS-29 seemed to exist, with generally less increase in disease-impact in patients with longer disease duration and higher baseline impact and disability. In some patients a dissociation existed between indicating increased impact according to MSIS-29 Physical and objective physical worsening on the T25FW.

Conclusion: These results support the use of the GNDS, with special focus on the spinal-plus domain, but also of the T25FW, in outcome measurement in progressive MS. The results further suggest a relation between clinical characteristics at baseline and subsequently reported increase in impact at follow-up. This may have implications for patient selection in trials for progressive MS.

INTRODUCTION

Trial design in progressive multiple sclerosis (MS) poses many challenges, including the choice of the primary outcome measure. Disability progression based on the Expanded Disability Status Scale (EDSS) alone, the present gold standard to rate disability in clinical trials in MS, may be quite slow. As possible alternatives to the EDSS, other MS-specific clinical scales have been suggested, like the Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT) and Guy's Neurological Disability Scale (GNDS). However their responsiveness in progressive MS is not yet fully evaluated. Moreover, the clinical relevance of changes in the EDSS and the alternative scales also needs further appraisal.

Regulatory authorities require that changes in the primary clinical outcome measures are clinically meaningful. There is an increasing awareness that therapeutic effectiveness cannot be fully evaluated without incorporating the patient's perspective.[1] The Multiple Sclerosis Impact Scale (MSIS-29) is a patient-reported outcome measuring disease impact of MS on daily life.[2] It is an easy instrument to administer, is related to other measures of disease progression, and is of use in the full range of impairments, disabilities and handicaps seen in the MS population.[3] It seems particularly sensitive to change in the more disabled patients,[4] and allows to distinguish progressive MS patients, who are in the disease stage where ambulation impairment is predominant and dominates the EDSS score, whereas their experienced disease impact varies.

Trial design in progressive MS may be facilitated by studying the relation between changes in potential outcome measures and disease impact as reported by the patient. In a cohort of progressive MS patients we investigated long-term (4 to 6 years) changes on EDSS, T25FW, 9HPT and GNDS, using standard or suggested cut-off values for change. Presence or absence of a clinically meaningful change was defined by using the MSIS-29 as an anchor measure. In this study we focussed on the association between the observed changes.

METHODS

Patients

A large cohort of MS patients is prospectively followed up by several clinical assessments, as part of a health status programme designed to improve individual patient care at the MS Center of the VU University Medical Center. Of this cohort, we selected all progressive patients (PP and SP),[5] with two complete visits 4 to 6 years apart. Patients were diagnosed as having MS as

ascertained by Poser et al.[6] or revised McDonald criteria,[7] and were confirmed progressive by their treating neurologist.

Outcome measures

Impairment and disability were assessed using the EDSS, T25FW, 9HPT and GNDS, and impact was measured using the MSIS-29. The EDSS assesses neurological impairment and disability, leading to a score varying between 0 and 10.[8] T25FW and 9HPT are both components of the Multiple Sclerosis Functional Composite (MSFC).[9] The T25FW measures the time needed to walk 25 feet (ambulatory function). The 9HPT measures the time needed to insert and remove 9 pegs (arm function).[9] If patients were unable to perform either the T25FW or 9HPT due to MS-related symptoms, the maximum allowed time for this test was assigned (180 seconds for T25FW and 300 seconds for 9HPT).[10,11] The GNDS is an interview-based questionnaire measuring disability in MS from the patient's perspective, with items including cognition, mood, vision, speech, swallowing, upper limb function, lower limb function, bladder function, bowel function, sexual function, fatigue and 'others'. Each subcategory of the GNDS was scored separately ranging from 0 (normal) to 5 (maximal help required).[12] The MSIS-29, a self-administered questionnaire measuring disease impact of MS on daily life, can be divided into two subscales: a physical scale (MSIS Physical) consisting of 20 items and a psychological scale (MSIS Psychological) with 9 items.[2] Range of scores is 1 (no impact on daily life) to 5 (extremely influencing daily life). Two separate scores for the subscales are calculated[2] and converted to a 0-100 scale.[13] For this study we used the Physical scale only.

All assessments were obtained under standardized conditions, as part of routine outpatient care. Assessments of EDSS, T25FW, 9HPT and GNDS were obtained by well-trained examiners. In the SPMS patients, none of the assessments were obtained during or within three months of a relapse.

Statistical methods

Longitudinal changes on all scales were calculated. We used an anchor-based method with clinically relevant deterioration on the MSIS-29 Physical scale as anchor. First we defined the patients that showed increased disease impact on our anchor, according to the earlier demonstrated cut-off value for clinically meaningful change on the MSIS-29 Physical scale of 8 points or more.[4] Then we investigated concomitant changes on the other scales (EDSS, 9HPT, T25FW and GNDS). We also examined change on different domains of the GNDS: its 12 subcategories,[12] and three recently identified sub-scales (spinal-plus, mental and bulbar).[14] Those were identified as three group factors in a study evaluating the factor structure of the

GNDS. The spinal-plus factor includes the items lower limb, bladder, bowel, sexual and upper limb. The mental factor includes the items cognition, mood and fatigue. At last, the bulbar factor includes the items speech and swallow.

We calculated event rates on all scales (the percentages of patients that show clinically meaningful progression), according to commonly applied criteria for a relevant change: on the EDSS a change of at least 1 point in patients with an entry EDSS <5.5 and 0.5 point in patients with baseline EDSS of ≥5.5,[15] for the T25FW and 9HPT a change of at least 20%,[16-19] and for the GNDS a change of at least 3 points in the sum score.[12,20,21] Because the three-point change on the GNDS sum score is not well established (it might be too small a difference to be really clinically relevant), we also performed analyses for more stringent GNDS sum score changes of 4, 5 and 6.

We compared event rates for relevant changes in EDSS, 9HPT, T25FW and GNDS to event rates on MSIS-29 Physical. We checked whether the distribution of baseline characteristics differed between both MSIS-29 Physical strata (worsened/not worsened). Also, we compared the amount of change on EDSS, 9HPT, T25FW and GNDS between the two MSIS-29 Physical strata using the non-parametric Mann-Whitney test. We calculated correlations between the changes on all scales. All correlations were calculated using Spearman's correlation coefficient because – except for the GNDS – none of the change scores were normally distributed.

Finally we studied patients in whom the observed changes in T25FW and MSIS-29 Physical were concordant or in fact not matching, to understand the limitations of applying the T25FW in progressive MS.

Standard protocol approvals, registrations, and patients consent

The study was performed with approval of the medics ethics committee of the VU University Medical Center, and informed consent was obtained from all participants.

RESULTS

Descriptives of the study population

A total of 132 patients fulfilled our selection criteria, of which 39% was primary progressive and 61% secondary progressive. The mean interval-duration between the two visits was 5 years (SD 0.7). At the time of the first visit the mean disease duration was 13 years and mean age was 50 years (**Table 4.1**).

Table 4.1 Clinical characteristics at baseline (first visit; total n=132)

Type MS	
PP	52 (39%)
SP	80 (61%)
Gender	
Female	71 (54%)
Male	61 (46%)
Disease duration, mean (SD), y	12.7 (8.9)
Age, mean (SD), y	50.0 (8.9)

MS: multiple sclerosis, PP: primary progressive, SP: secondary progressive, y: years.

Missing data

Because patients were selected on the basis of two complete examinations being available of EDSS, T25FW, 9HPT, GNDS and MSIS-29, there were no missing data.

Disease Modifying Therapy (DMT)

Only 19 patients (14%) were exposed to a DMT during (part of) the study: fourteen patients were treated with interferon beta, four with glatiramer acetate and one with methotrexate. Forty six patients (35%) had ever used DMT (interferon beta, glatiramer acetate or methotrexate). Given the purpose of the study, the lack of proven effective therapies for progressive MS, and the relatively small number of patients exposed during the time frame of our study, treatment was not taken into account in the analyses.

Clinical scores on all scales at both visits

Table 4.2 shows median scores on all clinical scales at the two visits. On all scales median scores increased over time. The EDSS and MSIS-29 Physical scores covered almost the full range of both scales. So did the T25FW and 9HPT scores, but with a ceiling effect. The GNDS scores mainly covered the lower half of the scale. The EDSS showed a bimodal distribution with baseline peak scores at EDSS 4.0 and 6.0 and follow-up peak scores at 4.0 and 6.5. **Figure 4.1** gives an overview of the EDSS distributions during both visits.

Event rates on the MSIS-29 Physical scale and on the other scales

Of all patients, 47% showed a clinically meaningful worsening on the MSIS-29 Physical Scale during our follow-up of 4-6 years. Of all scales, the event rate was highest on the

T25FW. **Table 4.3** shows event rates on all scales for all patients (left column of percentages). Stratifying patients based on relevant worsening on the MSIS-29 Physical resulted in expected higher event rates in the group with relevant worsening. This was obvious for the GNDS

Table 4.2 Median scores on all scales at both visits (total n=134)

	Visit 1	Visit 2
EDSS		
median (IQR)	5.0 (4.0-6.0)	6.5 (5.1-7.0)
range	1.0-7.5	2.0-9.0
9HPT		
median (IQR), s	25 (21-35)	29 (22-47)
range, s	16-170	16-300
T25FW		
median (IQR), s	8 (5-13)	14 (8-180)
range, s	3-180	3-180
GNDS		
median (IQR)	17 (11-20)	20 (14-26)
range	0-33	1-36
MSIS Physical		
median (IQR)	44 (32-57)	54 (41-68)
range	1-85	1-98

EDSS: Expanded Disability Status Scale, GNDS: Guy's Neurological Disability Scale, 9HPT: 9-Hole Peg Test, IQR: inter quartile range, MSIS: Multiple Sclerosis Impact Scale, s: seconds, T25FW: Timed 25-Foot Walk.

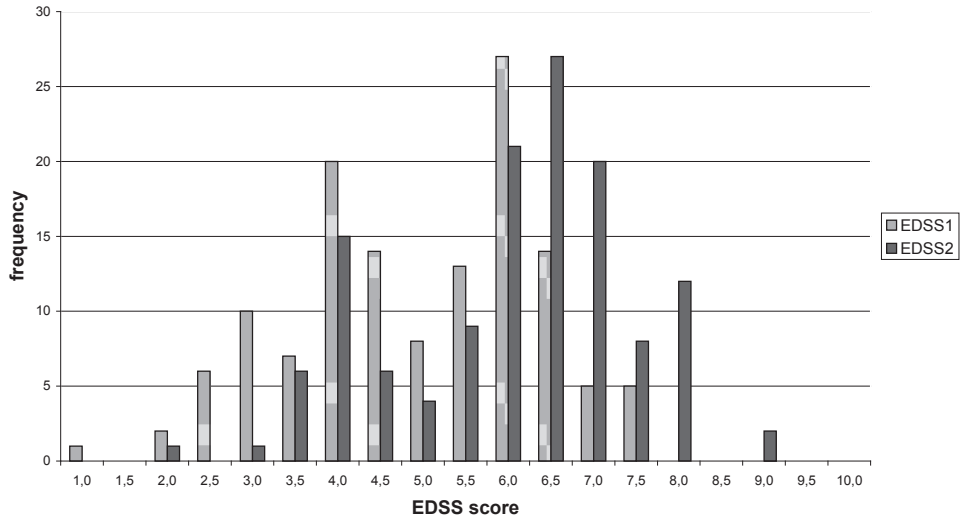

Figure 4.1 Disability levels during the two visits.
EDSS: Expanded Disability Status Scale.

and T25FW, but less clear for EDSS and 9HPT. This indicates an association between the presence of clinically meaningful MSIS-29 Physical worsening, and the degree of relevant worsening on the GNDS and to a lesser extent the degree of relevant worsening on the T25FW. The percentages of patients that show relevant worsening on EDSS and 9HPT hardly differ between both strata, indicating a lack of association (**Table 4.3**).

Table 4.3 Event rates on all scales

	All patients n=134	Relevant worsening MSIS Physical n=62	No relevant worsening MSIS Physical n=70
MSIS Physical	47%		
EDSS	67%	73%	63%
9HPT	39%	45%	34%
T25FW	72%	84%	61%
GNDS (≥3 points increase in sum score)	59%	82%	39%
GNDS (≥4 points increase in sum score)	51%	73%	31%
GNDS (≥5 points increase in sum score)	42%	63%	24%
GNDS (≥6 points increase in sum score)	36%	55%	19%

EDSS: Expanded Disability Status Scale, GNDS: Guy's Neurological Disability Scale, 9HPT: 9-Hole Peg Test, MSIS: Multiple Sclerosis Impact Scale, T25FW: Timed 25-Foot Walk.

Comparison of baseline characteristics between the two MSIS-29 strata

Gender, type of MS, mean disease duration, mean age, median EDSS score, mean T25FW score, mean 9HPT score, and mean GNDS score at the first visit did not significantly differ. Only the mean baseline MSIS-29 Physical score differed between both MSIS-29 Physical strata: the patients who did not show relevant worsening on the MSIS-29 had a higher baseline MSIS-29 score than those who showed relevant worsening on the MSIS-29 Physical ($p<0.001$).

Comparison of amount of concomitant change on all scales between the two MSIS-29 strata

We also compared the two MSIS-29 Physical strata concerning the amount of concomitant mean change on the other scales instead of examining event rates. In order to see which concomitant changes differed significantly between the two strata. On all scales mean changes were higher in the group with relevant MSIS-29 Physical worsening. MSIS-29 worsening was significantly

related to the amount of change on the GNDS (sum score and spinal-plus sub-scale equally) and T25FW, and not significantly to EDSS and 9HPT change (**Table 4.4**).

Table 4.4 MSIS Physical relevantly worsened versus not relevantly worsened:

Mann-Whitney test	p-value
Δ EDSS	0.114
Δ 9HPT	0.082
Δ TWT	*0.001*
Δ GNDS sum score	*<0.001*
Δ GNDS spinal plus	*<0.001*
Δ GNDS mental	*0.032*
Δ GNDS bulbar	*0.030*

EDSS: Expanded Disability Status Scale, GNDS: Guy's Neurological Disability Scale, 9HPT: 9-Hole Peg Test, MSIS: Multiple Sclerosis Impact Scale, T25FW: Timed 25-Foot Walk, Δ: change.

Correlations between change scores on the MSIS-29 Physical and all other scales

Since we investigated changes on different clinical domains, we here only present correlations between change scores, which were all lower than cross-sectional correlations. Highest correlations were found between change on MSIS-29 Physical and change on the GNDS sum score, GNDS spinal plus and T25FW. **Table 4.5** shows correlations between change on MSIS-29 Physical and changes on all other scales. The spinal plus sub-scale of the GNDS provided by far the largest (almost entire) contribution to this relatively high correlation with MSIS-29 change. Also T25FW change correlated relatively well with MSIS-29 change.

We repeated all correlations for different subgroups based on baseline EDSS scores and similar patterns were observed (data not shown). The pattern described above is thus not dependent on the baseline EDSS level.

Table 4.5 Correlations between change on MSIS-29 Physical and changes on all other scales

ρ (Spearman)	**Δ EDSS**	**Δ 9HPT**	**Δ T25FW**	**Δ GNDS sum score**	**Δ GNDS spinal plus**	**Δ GNDS mental**	**Δ GNDS bulbar**
Δ MSIS Physical	0.23	0.21	0.34	0.39	0.36	0.14	0.23

EDSS: Expanded Disability Status Scale, GNDS: Guy's Neurological Disability Scale, 9HPT: 9-Hole Peg Test, MSIS: Multiple Sclerosis Impact Scale, T25FW: Timed 25-Foot Walk, Δ: change.

From *associations* to *dissociations* with change in disease impact

Graphical report of the relation between changes on all scales suggested existence of four subgroups with specific profiles, based on MSIS-29 Physical change and T25FW change (absolute changes). **Figure 4.2** shows the four groups: group 1 (no relevant worsening on MSIS-29 Physical and T25FW increase <100 seconds, 43% of all patients), group 2 (no relevant worsening on MSIS-29 Physical and T25FW increase >100 seconds, 10% of all patients), group 3 (relevant worsening on MSIS-29 Physical and T25FW increase <100 seconds, 30% of all patients) and group 4 (relevant worsening on MSIS-29 Physical and T25FW increase >100 seconds, 17% of all patients).

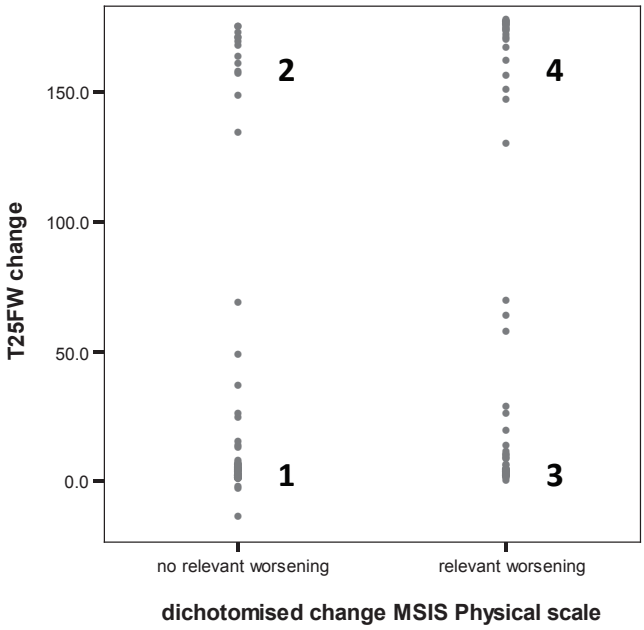

Figure 4.2 Relation between change on MSIS Physical and T25FW.
MSIS: Multiple Sclerosis Impact Scale, T25FW: Timed 25-Foot Walk.

Groups 1 and 4 are in line with expectations, whereas groups 2 and 3 are counterintuitive. Especially group 2 is surprising, since the observed huge increase in T25FW, predominantly caused by a marked loss of mobility in such a way the test could not be performed at follow-up, is apparently not accompanied by a subjective report of worsening of physical disease impact. When dividing all patients in three subgroups based on baseline EDSS scores, it is revealed that group 2 consists mainly of patients with a higher baseline EDSS level. **Figure 4.3** shows

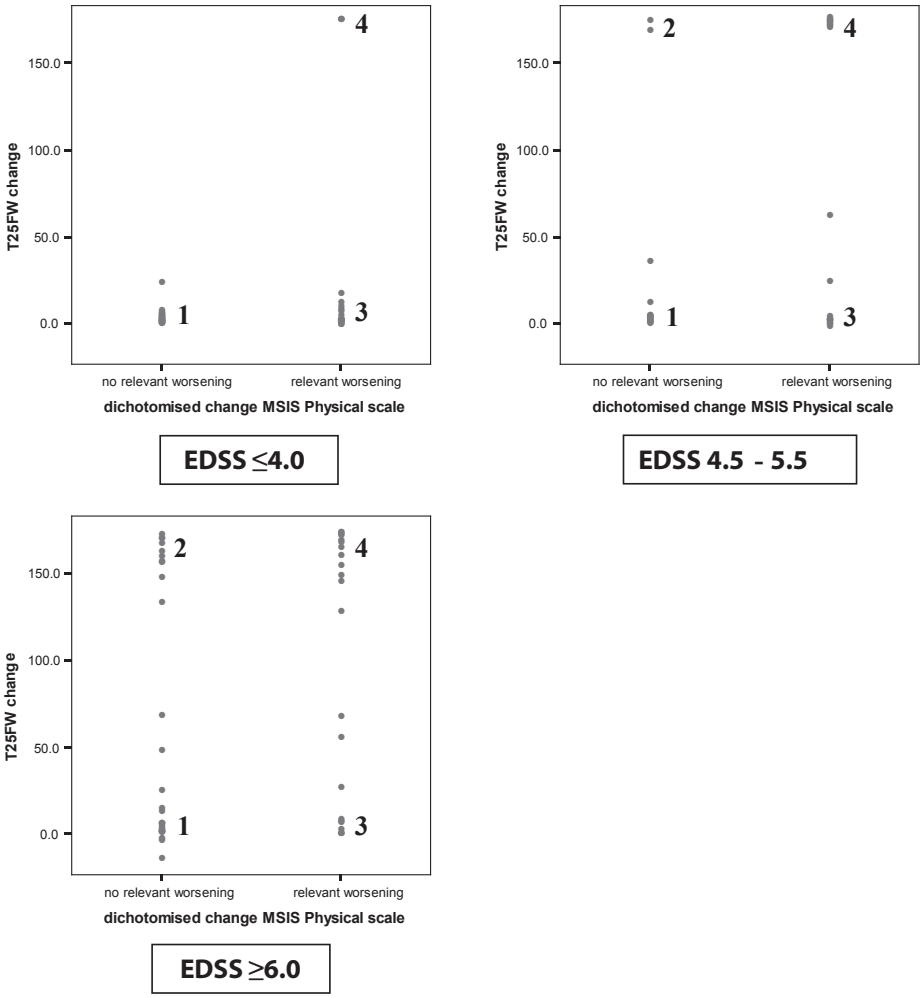

Figure 4.3 Representation of the subgroups according to baseline disability level.
EDSS: Expanded Disability Status Scale, MSIS: Multiple Sclerosis Impact Scale, T25FW: Timed 25-Foot Walk.

the distribution for three baseline disability levels (EDSS ≤4.0: n=46, EDSS 4.5-5.5: n=35, and EDSS ≥6.0: n=51). In the group with baseline EDSS ≥6.0, 20% (10/51) of the patients eventually ends up in group 2 at follow-up.

In addition, group 3 might also be considered as unexpected. However, the division concerning the amount of T25FW change was with a high cut-off value. In fact many patients in this group did not show a large change in absolute time, but did worsen more than 20%, the usual cut-off value for clinically relevant worsening.

The clinical characteristics of the four subgroups are shown in **Table 4.6**. Group 2 appears to be somewhat older and having a longer disease duration. Moreover the scores on all clinical scales were higher, indicating a worse situation at baseline.

Table 4.6 Clinical characteristics of the 4 subgroups based on MSIS-29 Physical and T25FW change

	Group 1 n=57	**Group 2** n=13	**Group 3** n=39	**Group 4** n=23
Disease duration at V1, mean (y)	13.7	13.8	12.4	10.4
Age at V1, mean (y)	50.9	53.2	49.6	46.9
EDSS 1, median (range)	5.0 (2.0-7.5)	6.0 (4.5-6.5)	4.5 (1.0-7.5)	6.0 (2.5-7.5)
MSIS Phy 1, mean	47	62.0	35.6	42.3
GNDS 1	17	20	14	16

EDSS: Expanded Disability Status Scale, Guy's Neurological Disability Scale, MSIS Phy: Multiple Sclerosis Impact Scale; Physical Scale, T25FW: Timed 25-Foot Walk, V1: visit 1, y: years.

DISCUSSION

In this study, using MSIS-29 Physical as anchor for a clinically relevant change as experienced by the patient, the T25FW proved to be the most sensitive objective outcome measure. Both EDSS and 9HPT were not clearly associated with relevant change as experienced by the patient when analysed as event rates, a commonly applied approach in clinical trials. The patient-derived GNDS performed better than the T25FW, which was expected since both GNDS and MSIS-29 assess from the same subjective patient perspective.

The change in MSIS-29 Physical (either dichotomous or continuous) was significantly correlated to the amount of change on the GNDS (sum score and spinal-plus subscale) and T25FW. There was no significant relation with the amount of change on the EDSS and 9HPT. Of the three different GNDS subscales, the spinal-plus subscale forms by far the largest (almost entire) contribution to the experienced disease impact. Mobility in addition to bladder, bowel, sexual and arm function are domains which are frequently affected in progressive MS, and we know that impaired mobility is one of the greatest concerns for MS patients,[22] so it seems to be congruent that this subscale contributes most to disease impact.

These results emphasize the importance of locomotor function in the disease course of MS, according to not only objective physician-based measures but also according to the patient

her- or himself. The results of this study support the use of the GNDS, with special focus on the spinal-plus domain, in outcome measurement in progressive MS.

Furthermore, T25FW change scores correlated relatively well with change scores on the MSIS-29, indicating a large contribution of the T25FW to experienced disease impact. This is in line with results of the group comparisons. Associations between T25FW change and change in disease impact were more apparent than between EDSS change and change in impact. Previous research has already shown that change in the T25FW is associated with the experienced impact of MS on the long term.[23] The results of the current study demonstrate that change in the T25FW is also associated with *change* in disease impact. This justifies the use of T25FW examinations in progressive MS, because strong correlation with disease impact is an important requisite for appropriate outcome measurement. Compared to the EDSS (and 9HPT), the relation between T25FW and patient-perceived impact seems to be stronger.

However, when applying the T25FW in progressive MS, we came across a phenomenon that should be carefully considered. In a subgroup of patients who were able to walk at baseline and showed an unambiguous worsening in mobility over time (in most cases the loss of the ability to walk), no associated increase in disease impact was recorded by the MSIS-29 Physical. When trying to explain this discrepancy, we observed that, on the whole, more increase of impact was observed in patients with a significantly lower baseline score on the MSIS-29 Physical, and shorter disease duration. Less increase of disease-impact was associated with patients with a significantly higher baseline score on the MSIS-29 Physical scale and longer disease duration. This might indicate a possible response shift for the MSIS-29: patients grow accustomed to their situation with impairments and disabilities and their coping improves. Because they reassess their perceived limitations of everyday life, they may consider that the impact of their MS is less heavy than they thought formerly.[4] This seems to be a pattern: during the earlier phase when there is not much impairment and disability, every single point of deterioration seems to have more impact than during a later phase, when there already is an established amount of impairment the patient has learned to cope with and, although still terribly invalidating, the experienced impact is less. Possibly, when a certain threshold is reached the experienced impact is less overwhelming and less related to the objective physical deterioration, although this does not count for all patients. Looking at **Figure 4.3**, this threshold seems to be reached around the time the patient approaches the level of EDSS 6.0. However, based on this figure we only get an impression and we cannot define an exact threshold. This needs to be further elucidated since it may have implications for patient selection in clinical trials in progressive MS. Including a patient group that will not report a change in disease impact, even when showing an objective physical worsening, may affect the persuasiveness of the trial.

Finally, we would like to address some limitations of our study. The time interval between the two visits was defined as 4-6 years and consequently has a certain variability, which could theoretically have influence on the scores of visit 2. However there was no significant difference in the mean interval-duration between the two MSIS groups that we used for comparison. Another limitation is the fact that the scores and changes on all scales were based on single testing, and were therefore not confirmed by repeated measurements (after 3 or 6 months).

In conclusion, in this study we showed that change in the GNDS (especially the spinal-plus domain) contributed most to the experienced increase in disease impact in this population of progressive MS patients. Based on the results of this study, the T25FW proved superior to the EDSS (and 9HPT), concerning its relation to the experienced disease impact, which is an important feature of a solid outcome measure. However, in a subgroup of patients, unambiguous worsening on T25FW was not accompanied by an increase in reported disease impact, pointing to a possible response shift for the MSIS-29. This phenomenon was related to disability, disease impact, and disease duration at baseline and may have implications for patient selection in trials for progressive MS.

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