Responsiveness of the Expanded Disability Status Scale (EDSS) to disease progression and therapeutic intervention in progressive forms of multiple sclerosis

Diego Cadavid, Yongqiang Tang, Gilmore O'Neill

Introduction. The standard approach in relapsing forms of multiple sclerosis (MS) has been to measure therapeutic effects on clinical exacerbations and physical disability as determined by the Expanded Disability Status Scale (EDSS). However, measuring clinical relapses is not a viable option in the progressive forms of MS because of their low frequency. Therefore, the standard approach in clinical trials of progressive forms of MS has been to use the EDSS as primary outcome measure.

Patients and methods. We examined the responsiveness of the EDSS to disease progression and treatment effects in the context of clinical trials of secondary progressive (SPMS) and primary progressive (PPMS) MS and compared it to the three functional tasks of the Multiple Sclerosis Functional Composite (MSFC): the Timed 25 Foot Walk (T25FW), the 9 Hole PEG (9HP), and the Paced Auditory Serial Attention Test (PASAT).

Results. The effect size of the EDSS after two years on placebo was only 0.2-0.3 in both SPMS and PPMS, similar to the 9HP and the PASAT. In contrast, the effect size of the T25FW was much greater and driven to a large extent by subjects who could not complete the task.

Conclusions. The EDSS shows poor responsiveness to both disease progression and treatment effects in SPMS and PPMS. The use of alternative primary outcome measures is recommended for therapeutic trials of progressive MS.

Key words. Disability. EDSS. Effect size. Multiple sclerosis. PPMS. SPMS.

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Introduction

The last two decades have been successful at producing novel effective treatments for relapsing forms of multiple sclerosis (RFMS). However, the same has not been the case for the progressive forms of MS (PFMS) that include both secondary and primary progressive MS. A critical factor for testing the efficacy of MS therapeutics is the availability of valid primary outcome measures. The traditional primary efficacy measure in clinical trials of PFMS has been the Expanded Disability Status Scale (EDSS) [1-4]. The EDSS was originally developed in the 1950s from John Kurtzke from the US Veterans Administration to consolidate all the findings of the neurological examination of subjects with MS into separate and mutually exclusive neuro-anatomical systems that could be added together into a single score [1]. The original DSS scale was revised in 1983 to include a total of 20 steps ranging from a score of no disability due to MS (score = 0) to death from MS (score = 10) [3]. However, by nature of its design the EDSS is a complex scale with markedly different performance in the lower range (score 0-3.5) typically found in the relapsing forms of MS (RFMS) compared to the higher range (score 4-10) that characterizes the PFMS: the first 7 of 20 steps (scores 0-3.5) are determined by changes in the neurological history and examination independently of ambulation while the next 8 steps (scores 4-7.5) are determined primarily by the ability to ambulate. The three highest steps (8-9.5) apply to severely disabled, bed-bound patients who are usually not candidates for clinical trials.

Although the EDSS has served us well to demonstrate treatment effects in clinical trials of RFMS, the same cannot be said about clinical trials of the PFMS [5-12]. One of the contributors to the failure

of therapeutic trials of progressive MS may be the poor responsiveness of the EDSS in more disabled patients with effect sizes as low as 0.1 [13]. Since the 1990s there has been an effort to develop and validate alternative clinical outcome measures for MS clinical trials based on objective functional tasks [14,15]. The most studied is the Multiple Sclerosis Functional Composite (MSFC) that measures ambulatory, upper extremity, and cognitive function [16,17]. However, it is becoming clear that the MSFC as a composite also suffers from lack of responsiveness in progressive MS [18]. However, recent studies indicate that a confirmed worsening of at least 20% in the ambulatory or upper extremity components of the MSFC provide a meaningful measure of progression [19, 20]. Here we compared the responsiveness of the EDSS to that of the individual components of the MSFC in large clinical trial of progressive forms of MS [21,22]. The results confirmed that the EDSS shows minimal responsiveness to both natural history and therapeutic intervention in progressive forms of MS.

Patients and methods

Change over time in the EDSS [3] and the MSFC [3,16,22] components from two progressive MS studies were selected for this analysis, one secondary progressive (IMPACT) [21] and one primary progressive (PPMS) (OLYMPUS) [7]. The three individual MSFC components analyzed were the Timed 25 Foot Walk (T25FW), the 9 Hole-PEG (9HP) test, and the 3 seconds Paced Auditory Serial Addition Test (PASAT). The T25FW is a quantitative mobility and leg function performance test based on a timed 25-foot walk. The patient is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the patient has reached the 25-foot mark. The task is immediately administered again by having the patient walk back the same distance. The 9HP is a brief, standardized, quantitative test of upper extremity function. Both the dominant and non-dominant hands are tested twice. The patient is seated at a table with a small, shallow container holding nine pegs and a wood or plastic block containing nine empty holes. On a start command when a stopwatch is started, the patient picks up the nine pegs one at a time as quickly as possible, puts them in the nine holes, and, once they are in the holes, removes them again as quickly as possible one at a time, replacing them into the shallow container. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are immediately followed by two consecutive trials with the non-dominant hand. The 3 seconds PASAT is a measure of cognitive function that assesses auditory information processing speed and flexibility, as well as calculation ability. The PASAT is presented using audio cassette tape or compact disk to ensure standardization in the rate of stimulus presentation. Single digits are presented every 3 seconds and the patient must add each new digit to the one immediately prior to it.

Responsiveness of the EDSS and the MSFC components to disease progression over 2 years were compared using effect size [24]. Effect size was calculated as the difference between the average score at each time point compared to the average baseline values divided by the standard deviation at baseline. For all 3 MSFC components the effect size was calculated with three different approaches to deal with subjects who could not/did not complete the task:

- With extreme value imputation (EVI) using the largest resulting Z scores in the Task Force data sets as specified in the MSFC scoring manual [23].
- 'Last observation carried forward' (LOCF), a statistical analysis technique that replaces a participant's values that could not be obtained with the last available measurement and assumes that the participant's responses (e.g., outcome measures) would have been stable from the point of dropout to trial completion, rather than declining or improving further.
- Without any imputation.

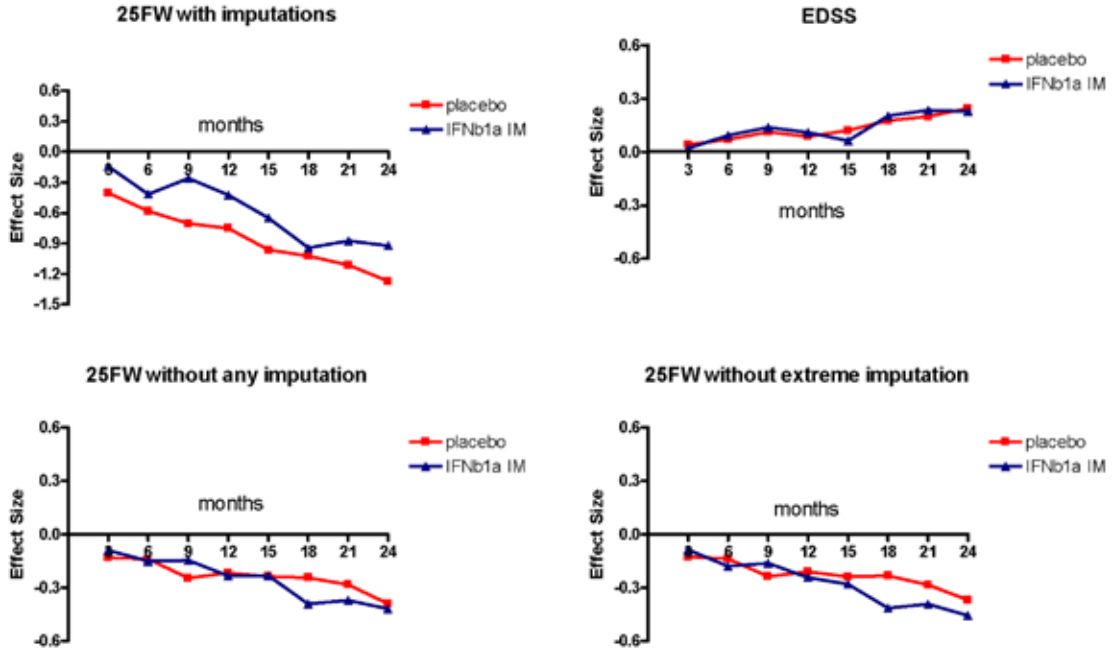
The EDSS is not subject to imputation because there are no issues with completing the 'task'. For the EDSS worsening results in a positive effect size, e.g. increase in disability, while for all MSFC components worsening results in a negative effect size, e.g. loss of function.

Results

Responsiveness of the T25FW compared to the EDSS to disease progression in SPMS

Since the EDSS in the progressive range (steps ≥ 3.5) measures mostly ambulation, we began by comparing its responsiveness to disease progression and treatment with intramuscular interferon beta 1a to that of the ambulatory functional component of the

Figure 1. Responsiveness of the EDSS and the T25FW to disease progression and treatment with intramuscular interferon beta 1a in SPMS. We compared the responsiveness of the Expanded Disability Status Scale (EDSS) and the Timed 25 Foot Walk (T25FW) in secondary progressive MS using data from the IMPACT study. Responsiveness was studied by calculating the effect size of the T25FW with imputations (both extreme value imputation [EVI] and last observation carried forward [LOCF]), with LOCF and/or EVI, using LOCF but not EVI, and without the use of any imputation. Notice the much larger effect size for the T25FW calculated with imputations compared to the EDSS.



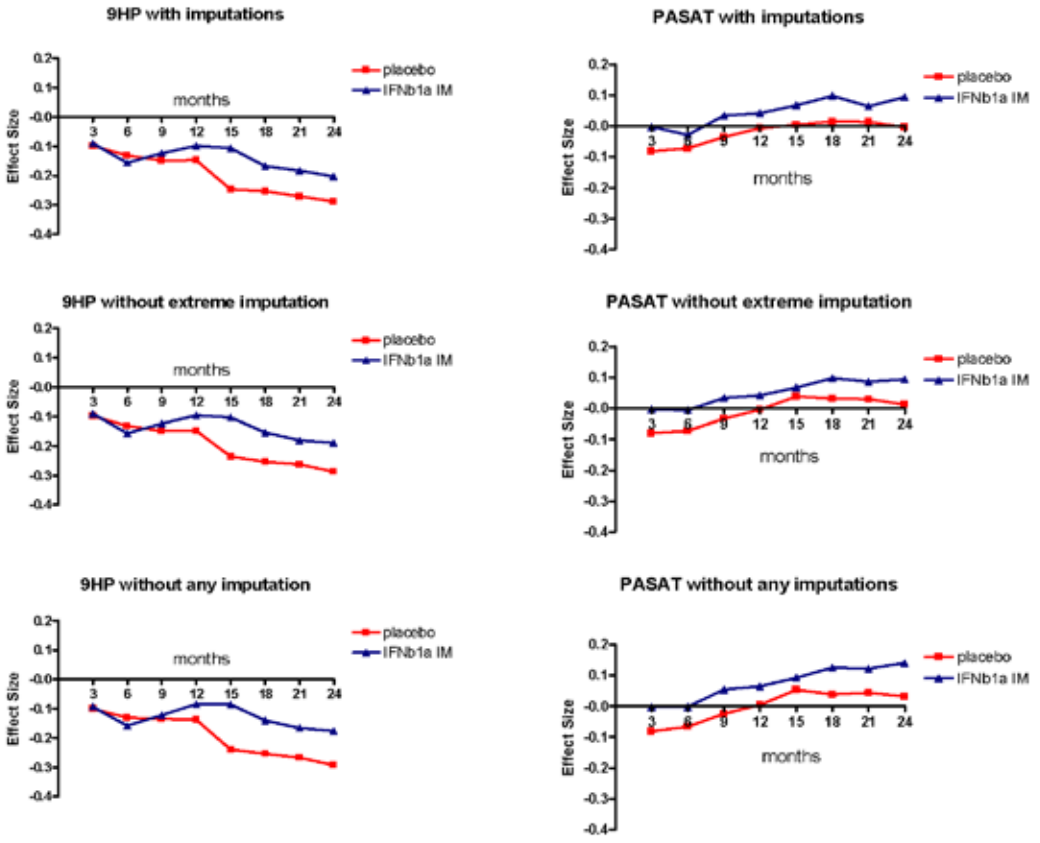
MSFC, the T25FW. For this we calculated the effect size of the T25FW and the EDSS over 2 years in the group of SPMS patients from the IMPACT study that were randomized to placebo (n = 219, of whom 89.5% completed 2 years of follow up) or weekly intramuscular injections of 60 µg of interferon β 1a (*n* = 217, of whom 87% completed 2 years of follow up). For the T25FW, the effect size was calculated using LOCF and EVI, LOCF without EVI, and neither LOCF or EVI. The results showed that the effect size on the placebo group for the T25FW using the standard calculation (with LOCF and EVI) was 5 times larger than that of the EDSS, –1.27 compared to 0.24 (Fig. 1). Both the T25FW and the EDSS begin to diverge from zero after about 6 months but while the T25FW showed a steady decline the EDSS remained relatively flat for most of the 2 years. Eliminating EVI or both EVI and LOCF from the calculation reduced the effect size of the T25FW from –1.27 to –0.37 and –0.38, respectively, an indication that the large effect size observed with the T25FW was driven to a large extent by those subjects unable to complete the walking task.

Next we examined the effect size of weekly IM injections of interferon β 1a on the EDSS compared to the T25FW. The results showed that while the effect size curve of the treated group completely overlapped with that of the placebo group in the EDSS, a clear and sustained reduction in effect size was observed with the T25FW (Fig. 1). Similar to the previous analysis of the placebo group, the observed separation of the T25FW effect size curves between the placebo and treated groups was greatly reduced when the extreme value imputation was not applied. We concluded that the T25FW is much more responsive than the EDSS in SPMS to both disease progression and therapeutic intervention with interferon β 1a; this greater responsiveness appears to be explained mostly by subjects unable to complete the T25FW task.

Responsiveness of the 9HP and the PASAT to disease progression in SPMS

Next we studied the effect size of the upper extremity functional task of the MSFC, the 9HP, on both dis-

Figure 2. Responsiveness of the 9 hole PEG and PASAT to disease progression in SPMS. We compared the responsiveness of the 9 hole PEG test and the 3 seconds PASAT using effect size with imputations (last observation carried forward and/or extreme value imputation) and without imputations. Notice that there is a net loss of performance in the 9HP (negative effect size) while there is a net gain in performance in the PASAT, with no impact of imputations on the results. For both functional tests the effect size is trivial after 1 year and mild after 2 years. The effect size curves diverge between subjects randomized to placebo and treatment with interferon beta 1a for both tests.



ease progression and therapeutic intervention with intramuscular interferon β 1a in SPMS. The results showed the effect sizes in the placebo group were –0.15 after 12 months and –0.29 after 24 months (Fig. 2), both unaffected by imputations (LOCF and EVI). A separation from '0' was apparent from the first on treatment assessment at the 3 month time point. The effect size in the interferon beta 1a treated group was –0.10 after 12 months and –0.20 after 24 months, a reduction of 0.5 and 0.9, respectively, relative to placebo (Fig. 2). We concluded that the 9HP showed rather mild effect sizes even after 2 years but was able to detect both the effects of disease progression and therapeutic benefits of intramuscular interferon β 1a on upper extremity function.

Next we examined the effect size of the single cognitive task of the MSFC, the 3 seconds PASAT, on both disease progression and therapeutic intervention with intramuscular interferon β 1a. The results for the placebo group revealed that unlike the two ambulatory (EDSS and T25FW) and the upper extremity tasks (9HP), there was no change in PASAT performance after 12 and 24 months (effect size = 0 in both; Fig. 2). The effect sizes of the PASAT were not influenced by the imputations, either LOCF or EVI. The only change observed in the placebo SPMS group was a slight loss of processing speed that occurred early on and gradually resolved over the second 6 months of year 1 (Fig. 2). Analyses of the effect size of treatment showed that the

Figure 3. Yearly responsiveness to disease progression in SPMS of the EDSS compared to the functional tests of the MSFC. The effect size one and two years after randomization of 219 SPMS subjects to placebo was calculated for the EDSS, the Timed 25 Foot Walk (T25FW), the 9 Hole PEG (9HP), and the Paced Auditory Serial Addition Test (PASAT) (all MSFC components with imputations). Notice that the effect size is much larger for the T25FW than for the EDSS or the other MSFC components both after 1 and 2 years. Also notice that for all 4 measurements the effect size was larger after 2 years than after 1 year. The PASAT had the lowest effect size among all 4 measurements.

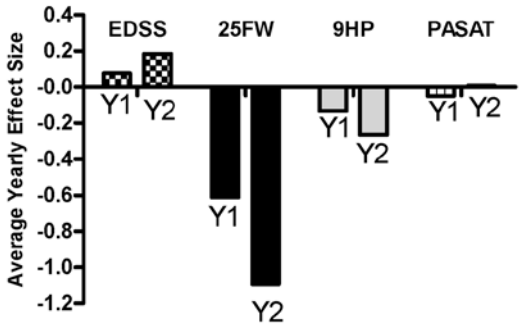
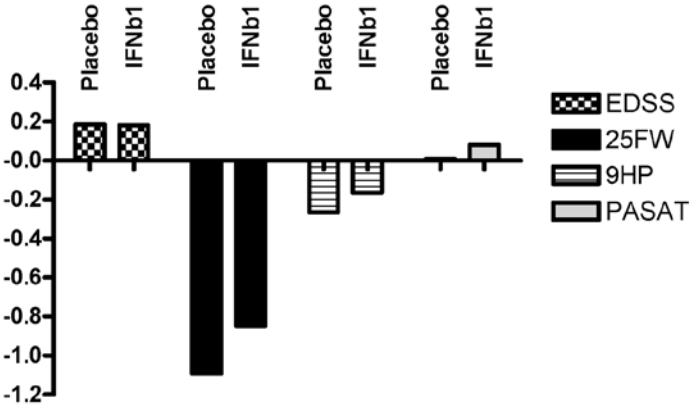


Figure 4. Responsiveness to SPMS treatment with intramuscular interferon beta 1a for 2 years of the EDSS compared to the functional tests of the MSFC. The effect size over two years after randomization of SPMS subjects to placebo (n = 219) or weekly intramuscular injections of 60 μg of interferon beta 1a (n = 217) was calculated for the EDSS, the Timed 25 Foot Walk (T25FW), the 9 Hole PEG (9HP), and the Paced Auditory Serial Addition Test (PASAT) (all MSFC components with extreme value imputation). Notice that the effect size observed in the placebo group was reduced by treatment with interferon beta 1a for all 3 MSFC components but not with the EDSS.



interferon β 1a group did not show this early loss of processing speed observed in the placebo group (Fig. 2). There was also a mild increase in effect sizes over the second year of the study. As a result, the effect sizes of the interferon group at 12 and 24 months were larger than in the placebo group, 0.042 and 0.094, respectively. We concluded that the PASAT was not capable of detecting the effects of disease progression on cognition in SPMS over 2 years. However, it appeared capable to detect therapeutic effects of interferon β 1a on cognition, both early on and gradually over the second year.

Yearly responsiveness of the EDSS compared to the MSFC individual components to disease progression and treatment with interferon β 1a in SPMS

Next we compared the yearly responsiveness after 1 and 2 years of the EDSS to that of the T25FW, the 9HP, and the PASAT to both disease progression (Fig. 3) and weekly treatment with intramuscular injections of 60 micrograms of interferon beta 1a (Fig. 4). The results showed that the T25FW was much responsive to disease progression in SPMS after both 1 and 2 years than the EDSS and the other two MSFC components (Fig. 3). The lowest responsiveness both after 1 and 2 years was observed for the PASAT followed by the EDSS. The effect size in response to 2 year treatment with interferon β 1a relative to placebo was highest for the T25FW, 0.245 compared to 0.10 for the 9HP, 0.074 for the PASAT, and 0.003 for the EDSS (Fig. 4).

Responsiveness of the EDSS and the T25FW in SPMS compared to PPMS

Next we examined the responsiveness of the EDSS and the T25FW to disease progression in SPMS compared to PPMS. For this we calculated the effect size of the EDSS and the T25FW (with LOCF and EVI) in the placebo groups of the IMPACT (n = 219, 89.5% completed 2 years) and OLYMPUS (n = 147, 84% completed 2 years) studies. The results showed that the effect size curves for the EDSS were similar in SPMS and PPMS, although of larger magnitude for PPMS than for SPMS, 0.33 and 0.24, respectively, after 2 years (Fig. 5). PPMS but not SPMS showed EDSS improvement at the first post-randomization visit (effect size –0.06 for PPMS versus 0.4 for SPMS). The greatest increase in effect size occurred between months 15 and 21, 0.16 for PPMS and 0.08 for SPMS. Examination of the effect size curves for the T25FW revealed similar curves for SPMS and PPMS (Fig. 5), although this time the effect size after 2 years was larger for SPMS than for PPMS, –1.09 compared to –0.76, a difference of 0.33 (Fig. 3).

Table. Loss of ambulation required to be considered a 'progressor' with the Expanded Disability Status Scale (EDSS) for multiple sclerosis subjects who enter clinical trials with scores of 3.5-6.

Baseline EDSS	Change required	Meaning of the loss of ambulation	Magnitude of loss
3.5	1 point	Go from unrestricted ambulation to walk up to 300 m	> 200 m
4	1 point	Go from walking 500 m to walking no more than 300 m	200 m
4.5	1 point	Go from walking 300 m to walking no more than 100 m	200 m
5	1 point	Go from walking 200 m independently to 100 m with a cane	100 m + cane
5.5	1 point	Go from walking 100 m independently to 20 m with walker	80 m + walker
6	0,5 point	Go from 100 m with cane to 20 m with walker	80 m
6.5	0,5 point	Go from 20 m with walker to < 5 m with walker	> 15 m

This larger effect size on SPMS compared to PPMS was already apparent at the 3 months study visit (–0.39 versus –0.13, a difference of 0.26). We concluded that the T25FW is more responsive to disease progression than the EDSS in both SPMS and PPMS.

Discussion

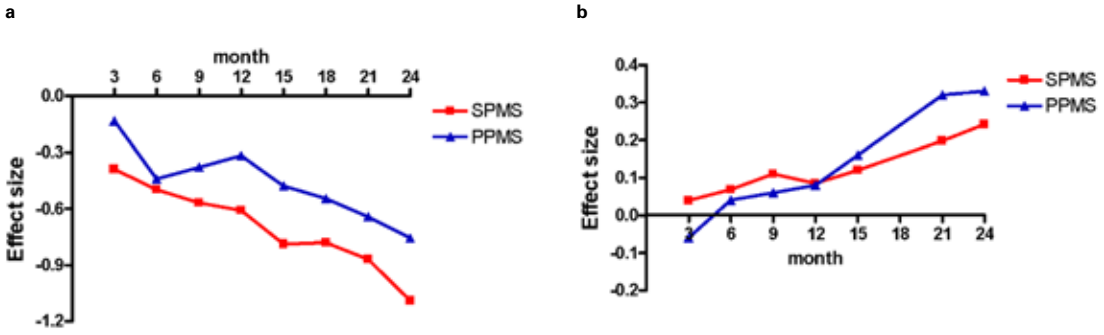
The EDSS in the higher ambulatory steps (range 3.5-7) requires large losses of ambulatory function to classify a patient as 'progressor' (Table). The main advantage of using EDSS for therapeutic trials of progressive forms of MS is that it minimizes the risk of judging progression of disability based on minor or fluctuating differences in ambulatory performance. However, the consistent failure of clinical trials of progressive forms of MS that have used the EDSS to demonstrate treatment effects raises the issue of whether the EDSS has set the bar for regulatory approval too high. Our analysis of two large clinical trials of SPMS and PPMS confirms the low responsiveness of the EDSS for detection of changes as a result of disease progression and treatment. The poor responsiveness of the EDSS has been previously recognized [13], yet it continues to be used as primary outcome measure in clinical trials of SPMS and PPMS [5,7,8].

Responsiveness of clinical outcome measures is defined as their ability to detect clinically apparent changes even if they are small [13]. The effect size provides a useful tool to compare the responsiveness of different clinical measurements [24]. Our analysis revealed that the effect size of the EDSS is quite small in both SPMS and PPMS even after 2 years, the length of time usually used in most registrational MS clinical trials.

Generally, the larger the effect size, the greater is the impact of the intervention or underlying disease condition being tested. Jacob Cohen has written the most on this topic [24]. In his well-known book he suggested that an effect size of 0.8 is large, 0.3 is moderate, and 0.2 is small. The usual interpretation of this statement is that anything smaller than 0.2 is trivial. Accordingly, the ability of the EDSS to capture the effects of disease progression in SPMS and PPMS over 1 year is trivial (effect size ≤ 0.1) and over 2 years is small (Fig. 5). Distribution based approaches are often used to define the minimally important change (MIC) of an intervention. One study of Parkinson's disease used an effect size of 0.2 to define the MIC for the Unified Parkinson's Disease Rating Scale (UPDRS) [25]. Other study of breast cancer scales used an effect size of 0.33 to define the MIC [26]. Recent authors have used percentage rather than effect size criteria to define the MIC of the T25FW [27,28]. Although percentage change works well for ratio statistics where the variance is proportional to the mean (i.e, log-normal distribution), the effect size is better for mean-shift statistics.

The small effect size observed in the placebo arms of IMPACT and OLYMPUS raises the possibility that perhaps the subjects enrolled in these trials did not have active progressive disease. The inclusion criteria for the IMPACT [21] study were interferon-naive male and female subjects aged 18 to 60, inclusive, with SPMS [29] as defined by gradual progressive disease over the last 12 months and EDSS score between 3.5 and 6.5, inclusive. The inclusion criteria for the OLYMPUS trial [7] were age 18-65 years, definitive diagnosis of PPMS as defined by 2001 McDonald's criteria, disease duration of ≥ 1 year, EDSS at baseline between 2.0 and 6.5 points, inclusive, and score of ≥ 2.0 on the Functional Systems scale for the pyramidal system due to lower extremity findings. Therefore, at least in the SPMS trial an effort was made to recruit subjects with actively progressive disease. The other possibility for the observed small effect size of the placebo groups in both trials is that the EDSS is not responsive to disease progression in both SPMS and PPMS. Al-

Figure 5. Responsiveness of the T25FW (a) and the EDSS (b) to disease progression in SPMS compared to PPMS. We compared the effect size of the Timed 25 Foot Walk (T25FW) and the EDSS in SPMS (n = 219, 89.5% completed 2 years) and PPMS (n = 147, 84% completed 2 years) patients randomized to placebo. Notice that for both T25FW and EDSS the effect size curves are similar in SPMS and PPMS. Also notice that the effect size is much larger with the T25FW than with the EDSS in both SPMS and PPMS. After two years, the effect size is larger in SPMS than in PPMS with the T25FW while the opposite happened with the EDSS.



though effect sizes similar to the EDSS were observed with the 9HP and the PASAT, the same was not true for the T25FW: progressive worsening of ambulatory capacity on the T25FW task was observed in the placebo arms of both the SPMS and PPMS studies, and as early as the 3 month visit in SPMS (Fig. 5). Similarly, while the EDSS was unable to capture any therapeutic benefit of weekly intramuscular injections of 60 μg of interferon β 1a in SPMS, all 3 functional tests of the MSFC detected differences between the placebo and treatment arms in the IMPACT study (Fig. 4). This was strongest for the T25FW with a difference in effect size of 0.245.

These findings raise the important question of what constitutes a clinically important change in ambulatory function in MS. In a recent 2 year longitudinal study of ambulatory persons with MS from Finland (n = 120), 51% of patients self-reported deterioration in ambulation while this was reported only by 26% of their clinicians [30-33]. The MIC in ambulation for the group as a whole over 2 years was calculated as 53 meters using as external criterion the EDSS [3] and the RAND 36 item health survey [34]. The MIC for the subgroup of patients with higher EDSS (steps 4-6.5) was lower, about 40 meters over 2 years [J. Paltamaa, personal communication]. In healthy elderly population the MIC has been estimated to be similar, about 20 meters, and a loss of about 40-50 m is considered substantial [35]. This indicates that the magnitude of change required to classify an MS patient as 'progressor' on the EDSS (Table) is far in excess of the MIC.

There have been several studies of the magnitude of change in T25FW that is clinically meaningful. Most [19,20,27,28,36,37] although not all [38,39] studies have found that a loss ≥ 20% in T25FW constitutes a clinically meaningful change in ambulatory function. Our analyses indicate that the T25FW is able to detect clinically meaningful changes in ambulation (effect size > 0.2) as a result of either disease progression or treatment with interferon beta 1a that the EDSS is not able to detect (Figs. 1 and 5). This is consistent with the previous finding that the measurements of maximum distance walked and the timing of short walks provide more precise information about ambulatory impairment in MS than do the EDSS [40]. This in turn should allow for better discrimination of differences between patients and provide greater sensitivity to detect therapeutic effects in clinical trials of progressive forms of MS. These results indicate that the EDSS alone should not be used as the primary outcome measure in therapeutic trials of the progressive forms of MS.

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Sensibilidad de la escala ampliada del estado de discapacidad (EDSS) a la progresión de la enfermedad y la intervención terapéutica en las formas progresivas de la esclerosis múltiple

Introducción. El planteamiento habitual en las formas recidivantes de la esclerosis múltiple (EM) ha consistido en medir los efectos del tratamiento sobre las exacerbaciones clínicas y la discapacidad física determinados por la escala ampliada del estado de discapacidad (EDSS). Sin embargo, medir las recidivas clínicas no constituye una opción viable en las formas progresivas de la EM debido a su baja frecuencia y, por consiguiente, el planteamiento habitual en los ensayos clínicos centrados en las formas progresivas de la EM ha consistido en utilizar la EDSS como criterio de valoración primario.

Pacientes y métodos. Se examina la sensibilidad de la EDSS a la progresión de la enfermedad y los efectos del tratamiento en el contexto de ensayos clínicos de la EM secundaria progresiva (EMSP) y primaria progresiva (EMPP), y se compara con la correspondiente a las tres tareas funcionales de la escala funcional compuesta de la EM (MSFC): el *Timed 25 Foot Walk* (T25FW), el *9 Hole PEG* (9HP) y el *Paced Auditory Serial Attention Test* (PASAT).

Resultados. El tamaño del efecto de la EDSS tras dos años con placebo apenas alcanzó un valor de 0,2-0,3, tanto en la EMSP como en la EMPP, un resultado similar al obtenido en el 9HP y en el PASAT. Por el contrario, el tamaño del efecto del T25FW fue mucho mayor y estuvo condicionado en gran medida por los pacientes que no pudieron acabar la prueba.

Conclusiones. Se confirma la escasa sensibilidad de la EDSS frente a la progresión de la enfermedad y los efectos del tratamiento en el ámbito de la EMSP y la EMPP. Así, es recomendable utilizar otros criterios de valoración primarios en los ensayos terapéuticos de la EM progresiva.

Palabras clave. Discapacidad. EDSS. EMPP. EMSP. Esclerosis múltiple. Tamaño del efecto.