FATIGUE AND DAYTIME SLEEPINESS SCALE IN MYOTONIC DYSTROPHY TYPE 1

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ABSTRACT: *Introduction*: Fatigue and excessive daytime sleepiness are frequent complaints in myotonic dystrophy type 1 (DM1) that often overlap. We aimed to construct a combined fatigue and daytime sleepiness rating scale for DM1 using the Rasch measurement model. *Methods*: Questionnaires, including the Epworth Sleepiness Scale, Fatigue Severity Scale, and Daytime Sleepiness Scale, were completed by 354 patients. Data were subjected to Rasch analyses and tested for required measurement issues such as appropriate response categories, absence of item bias, local independence, and unidimensionality. *Results*: The initial 22 items did not meet Rasch model expectations. After rescoring and removing misfitting items, the final 12-item scale showed good model fit and unidimensionality. High internal consistency (person separation index = 0.80) and validity were demonstrated. *Conclusions*: The Rasch-built Fatigue and Daytime Sleepiness Scale, developed specifically for DM1 patients, provides interval measures on a single continuum. Its use is suggested for future clinical trials and therapeutic follow-up.

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Myotonic dystrophy type 1 (DM1) is an autosomal dominant inherited multisystem disorder. It affects skeletal and smooth muscles, the heart, the eyes, the endocrine system, and central nervous system. The diagnosis of DM1 is confirmed by molecular genetic testing of an expansion of a CTG trinucleotide repeat in the *DMPK* gene.[1] Based on age at onset and severity of symptoms, 4 clinical DM1 types can be distinguished: mild; adult onset; early childhood; and congenital onset.[2]

Excessive daytime sleepiness (EDS) is an important and common clinical feature of DM1, which occurs in about one-third of patients.[3,4] Unlike narcolepsy, daytime sleepiness in DM1 patients is not episodic, and sleep tendency occurs when attention is not being held, rather than during activity. EDS can be a symptom of sleep-disordered breathing, chronic hypercapnia, or depression, but these conditions alone cannot entirely explain EDS in DM1.[5–7] Complaints of excessive fatigue appear even more frequently than those of EDS in patients with DM1.[8] DM1-related fatigue is characterized by a subjective lack of physical and/or mental energy. Although fatigue is an important symptom in any progressive physically disabling disease, it is more common in DM1 than in other neuromuscular disorders and may even be prominent when muscular impairment is relatively mild.[9] The presence of fatigue can have a major impact on daily life, general well-being, and social participation.[9]

EDS and fatigue have overlapping features, and both patients and physicians may have difficulty distinguishing between these 2 entities. Patients cannot always specify whether their complaint relates to sleepiness, fatigue, or both.[10] Several patient-based measures are available to evaluate daytime sleepiness or fatigue levels, but generally as separate entities. However, fatigue and EDS levels are associated in DM1 patients,[8,9] suggesting that available outcome measures do not necessarily represent separate constructs.

Current outcome measures are all ordinal scales based on classical test theory (CTT).[11] A major limitation of CTT is that scores create measurement at an ordinal level with unequal intervals that hamper accurate measurement of differences in scores and changes over time among individuals. Rasch analysis attempts to transform ordinal scores into interval measures that are scale-independent and suitably accurate for individual patient assessment.[12,13] This methodology has been used previously to develop an outcome measure of activity limitations and participation restrictions for DM1 patients (DM1-Activ).[14] In view of the multisystem nature of this disease, health outcome measures at several levels of outcome are necessary for patient assessment. We aimed to construct a combined scale for assessing fatigue and daytime sleepiness [i.e., the Fatigue and Daytime Sleepiness Scale (FDSS)] for DM1 using the Rasch method, provided that fatigue and daytime sleepiness items address the same underlying health construct.

Abbreviations: DIF, differential item functioning; DM1, myotonic dystrophy type 1; DSS, Daytime Sleepiness Scale; EDS, excessive aytime sleepiness; ESS Epworth Sleepiness Scale; FDSS, Fatigue and Daytime Sleepiness Scale; FSS, Fatigue Severity Scale; MIRS, Muscular Impairment Rating Scale; PSI, person separation index

Key words: excessive daytime sleepiness, fatigue, myotonic dystrophy, outcome measures, Rasch model

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METHODS

Participants. Our study population comprised 354 adult DM1 patients (167 recruited at Maastricht University Medical Center in The Netherlands and 187 patients at the Neuromuscular Clinic of the Centre de Santé et de Services Sociaux de Jonquière in Canada).[8] The study was approved by both local medical ethics committees, and informed consent was obtained from all participants. A description of the patient sample is shown in Table 1.

Questionnaire Development. The concept scale was composed of all 22 items from the Epworth Sleepiness Scale (ESS), Daytime Sleepiness Scale (DSS), and Fatigue Severity Scale (FSS). The ESS is a widely used questionnaire intended to measure daytime sleep propensity.[15,16] Patients rate their chances of dozing in 8 every day situations on a 4-point scale. Good reliability aspects have been demonstrated for the ESS in subjects with sleep-disordered breathing, primary sleep disorders, and in healthy subjects.[17–19] However, in DM1, weak internal consistency was reported, possibly because some items were irrelevant or inappropriate for these patients.[20] The 5-item DSS was built to assess daytime sleepiness in DM1 and showed good validity and reliability.[4,20] The FSS is the questionnaire used most commonly to assess the impact of fatigue on daily activities. It contains 9 items, and each item is scored on a 7-point Likert scale. This scale has demonstrated high internal consistency and adequate validity.[21] An evaluation in DM1 patients showed good reliability of the FSS.[20]

Procedures. All patients completed a questionnaire including sociodemographic and clinical information, and it contained ESS, FSS, and DSS items placed randomly. Patients were examined by a neurologist, and muscular impairment was categorized according to the Muscular Impairment Rating Scale (MIRS).[22]

Rasch Analysis. The Rasch unidimensional measurement model was used to construct the fatigue and sleepiness scale. A supplementary article is provided that clearly explains the various steps of the Rasch method (see Supplementary Material). In brief, the Rasch model can be seen as the ideal response pattern, where persons with a high level of the measured trait should have a higher probability of receiving a higher score on any item compared to persons with lower levels. Also, any person should always have a greater probability of receiving a higher score on an easier item than on a more difficult one.[12] To obtain an interval scale, the final scale should fulfill the model's expectations, such as good item and person statistical fit, threshold ordering, and lack of item bias or local dependency, as well as demonstrated unidimensionality.[23–26] We assessed potential differential item functioning (DIF, or item bias) for 6 person factors: gender; age group (<30 years, 30–50 years, >50 years); diagnosis type (mild, adult, childhood/congenital); use of psychostimulants (yes, no); degree of education (elementary school, high school, university); and possible cultural differences (Dutch vs. Canadian). Items and persons not fulfilling Rasch model criteria were evaluated and removed one by one, if necessary.

Table 1. Patient sample description.

	Dutch population (n = 167)	Canadian population (n = 187)
Mean age in years (SD), range	44.1 (11.6) 18–69	46.0 (11.0) 20–80
Gender (n, %)		
Female	81 (48.5)	115 (61.5)
Male	86 (51.5)	72 (38.5)
Diagnosis type (n, %)		
Mild type	14 (8.4)	36 (19.3)
Adult type	137 (82.0)	151 (80.7)
Childhood/congenital type	16 (9.6)	

Validity and Reliability. The external construct validity of the scale was assessed by correlation with the MIRS. An estimate of the internal consistency reliability of the scale is available, based on the person separation index (PSI). The PSI (equivalent to Cronbach's alpha) should be >0.7 for group comparison.[23]

Statistics. All analyses were conducted using the Rasch model (partial credit model), as implemented in RUMM 2030 software.[25] Further analyses were undertaken using Stata (release 11.0) statistical software for Windows XP. One-way analysis of variance with correction according to Bonferroni multiple testing was used to compare FDSS scores between subgroups.[27]

RESULTS

Rasch Analysis of the Questionnaire. The draft 22-item scale did not meet the Rasch model expectations. The item–trait chi-square probability was significant ($P < 0.00001$), indicating lack of invariance of item difficulty across the scale. The mean residual for items was 0.24 [standard deviation (SD) = 2.44]. The mean residual for persons was −0.26 (SD 1.14), indicating no serious misfit among the respondents. The PSI was 0.91.

Data Modifications for Rasch Model Fit. Thresholds were examined to determine whether disordering affected fit. Category probability curves showed

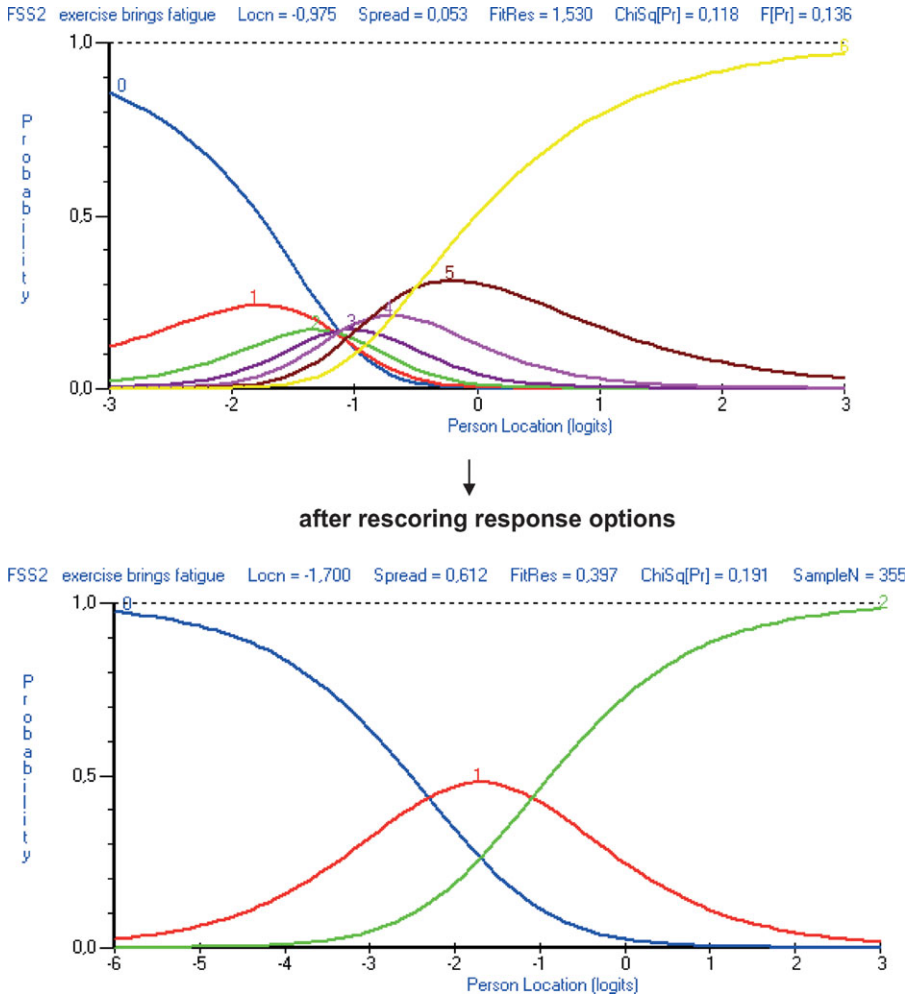

FIGURE 1. Upper panel: category probability curve for item FSS2 ('exercise brings on my fatigue') with 7 response categories (colored curves correspond to score options 0–6), showing the relation between the probability of a given category as a function of person location. The boundaries between response categories, called thresholds, were disordered and crowded together. Lower panel: category probability curve for item FSS2 ('exercise brings on my fatigue') after rescoring into 3 response categories (colored curves correspond to score options 0–2), showing ordered response categories and ordered thresholds. Note that each response category has a point along the fatigue and sleepiness continuum where it is the most likely response.

disordered thresholds for four ESS items, one DSS item, and for all FSS items. To restore threshold ordering, response options for all items were rescored with the aim of creating a uniform set of response categories and strengthening the category frequencies.[28] For the ESS and DSS items, the original 4 response options (coded 0-1-2-3) were collapsed into 3 categories (coded 0-1-1-2). The original FSS items with 7-point response categories (coded 1-2-3-4-5-6-7) demonstrated a uniform disordered pattern and were subsequently collapsed into 3 categories (coded 0-0-1-1-1-2-2) (Fig. 1).

Next, we systematically checked for item misfit, local dependency, and DIF. A total of 10 items were removed one by one based on the following: item ESS2 ("fall asleep while watching TV") was removed due to local dependency; items ESS5 ("fall asleep while lying down to rest in the afternoon when able"), EES7 ("fall asleep while sitting quietly after a lunch without alcohol"), DSSd ("difficulty being inactive for prolonged periods"), FSS4 ("fatigue interferes with my physical functioning"), FSS6 ("my fatigue prevents sustained physical functioning"), and FSS3 ("I am easily fatigued") were removed for showing significant misfit; FSS7 ("fatigue interferes with carrying out certain duties and responsibilities") was removed due to item misfit and local dependency; and items DSSb ("at times, sudden need to sleep during the day") and FSS9 ("fatigue interferes with my work, family or social life) showed differences in response between Dutch and Canadian patients with equal levels of excessive daytime sleepiness or fatigue (DIF related to cultural differences) and were also removed.

Clinimetric Properties of the Final FDSS. After these steps, we succeeded in obtaining a 12-item scale that fulfilled all model expectations. Adequate

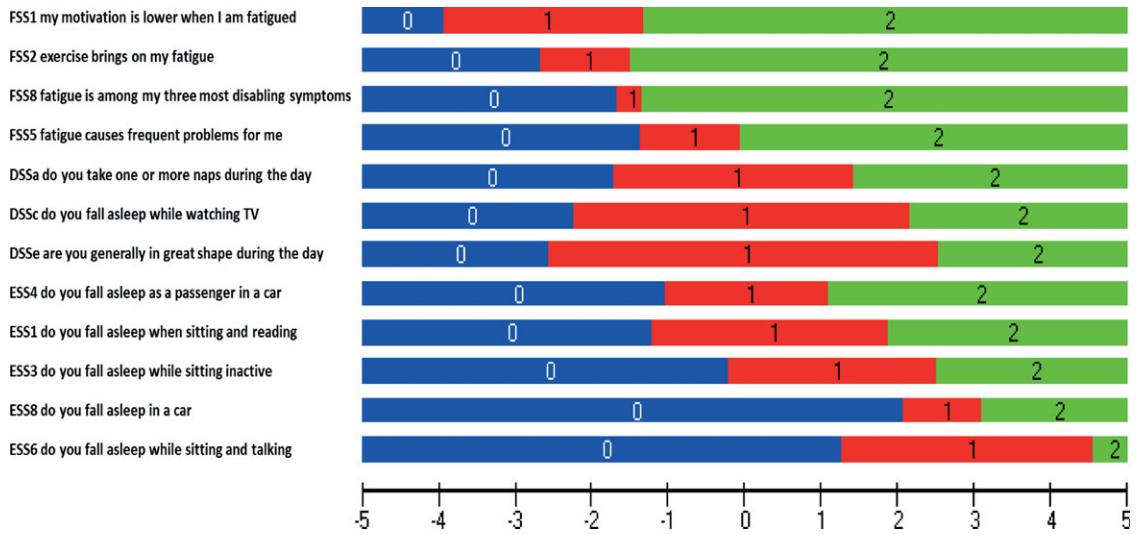

FIGURE 2. Threshold map of the 12-item FDSS indicating a patient's expected response for each item as a function of the level of fatigue and sleepiness (0 = seldom or never, 1 = sometimes, 2 = almost always). Items are ordered by increasing difficulty. The item 'my motivation is lower when I am fatigued' was the easiest item, and the item 'do you fall asleep while sitting and talking?' was the most difficult.

item and patient fit statistics were obtained [−0.36 (SD 1.07) and −0.38 (SD 0.96), respectively]. The overall item–trait interaction chi-square probability was non-significant ($P = 0.61$), thereby showing invariance. Finally, 2 item subsets were defined by the 4 most positive (ESS1, ESS3, ESS4, ESS6) and negative loading items (FSS1, FSS2, FSS5, FSS8) using a principal component analysis of residuals (see Fig. 2 for item identification). An independent *t*-test between person estimates from these 2 subsets of items demonstrated a proportion of 0.05 (95% confidence interval 0.03–0.08) of the tests falling outside the ±1.96 range, supporting unidimensionality of the scale (see Supplementary Material for the final scale).

The threshold distribution map of the FDSS shows the expected response to a given item as a function of the underlying fatigue and sleepiness measure (Fig. 2). Item difficulty ranged from −2.624 to +2.924 logits, and patient location ranged from −5.122 to +3.137 logits. Only 0.3% of patients were not fatigued or sleepy at all (floor effect), and 0.6% graded themselves as having the maximum score (ceiling effect). To compare targeting of the outcome measures, that is, the difficulty range of outcome measures in relation to the levels of fatigue and sleepiness of the sample, various FDSS items were used for anchoring each of the scales to the FDSS ruler separately. Figure 3 shows that the item locations of the ordinal DSS, ESS, and FSS were poorly targeted to the sample population and cover a narrow range of measurement. By contrast, the targeting graph of the FDSS shows that the items were well spread across the continuum and sufficiently covered the patient sample (mean patient location of −0.38 logit).

Validity and Reliability. The interval FDSS scores differed significantly between MIRS grades, a measure of the disease involvement ($F = 5.77$, $P = 0.0002$). A significant trend ($P = 0.003$) was seen toward higher fatigue and sleepiness levels in patients with more severe muscular impairment. However, at the subgroup level, only the FDSS scores of patients with MIRS score 1 differed significantly from those with MIRS scores of 3, 4, and 5 (Fig. 4). There was no association between FDSS measures and CTG repeat length ($F = 2.39$, $P = 0.07$). The PSI was 0.80, demonstrating acceptable internal consistency reliability.

DISCUSSION

In this study we constructed a Rasch-built combined fatigue and daytime sleepiness scale (FDSS) specifically designed for patients with DM1. The FDSS is composed of items from the ESS, DSS, and FSS. The 12 items selected for the final scale fulfilled all Rasch model expectations, and the hierarchy of items was invariant across DM1 patients of different age, gender, disease type, education level, and use of psychostimulants, and between patients from different countries (The Netherlands and Canada). Items retained for the FDSS are shown to measure a single construct combining aspects of sleep propensity as well as behavioral consequences of fatigue, which argues strongly in favor of a combined clinical outcome measure of these attributes. Fatigue items were the easiest

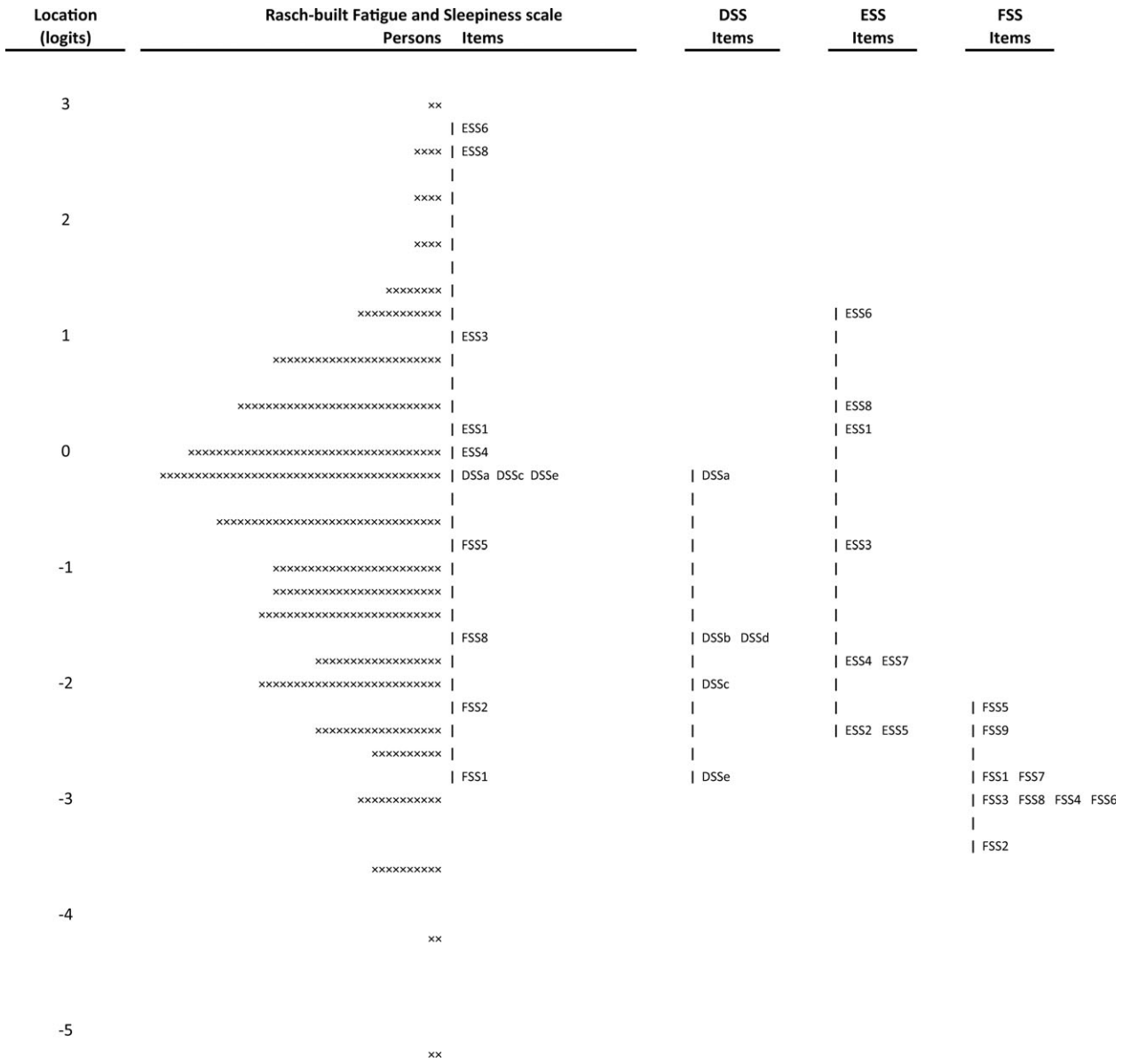

FIGURE 3. Graph showing person distribution and item distribution on a logit scale (y-axis). The numbers −5 to 3 represent corresponding logits on a linear ruler. The crosses under persons represent the number of patients who had a person location at that point on the ruler. Item locations are presented on the right side. Positive values on the logit scale represent the more fatigued or sleepy patients and the more difficult items. Negative values on the logit scale represent the less fatigued or sleepy persons and the least difficult items. For a well-targeted scale (not too easy, not too hard), items should represent a wide range in difficulty.

items, whereas sleepiness items were the most difficult. A significant association was found between FDSS measures and MIRS grade. This is in line with previous reports showing that patients with fatigue and/or EDS had greater muscular impairment than those without these symptoms.[4,8]

Previous reports in inflammatory neuropathies and multiple sclerosis demonstrated the inability of patients to differentiate between the original FSS response categories.[29,30] Similar disordered threshold patterns were seen in patients with DM1 and can only be visualized using a modern technique like the Rasch method. In addition, Rasch analysis allows one to investigate targeting. As shown in this study, conclusions based on FSS, ESS, and DSS data may be questioned, because the sets of items may not be at the appropriate level of difficulty for the patients being examined (Fig. 3).

FDSS raw scores can be transformed into interval measures that may be used for parametric statistical analyses. It is also possible to describe patients with a given sum-score in functional terms using the logit measure or the modeled probability of a category score for each item (e.g., the percent difference in the probability of "fall asleep when sitting and reading"), thereby improving the interpretation of test scores and trial effects.[31]

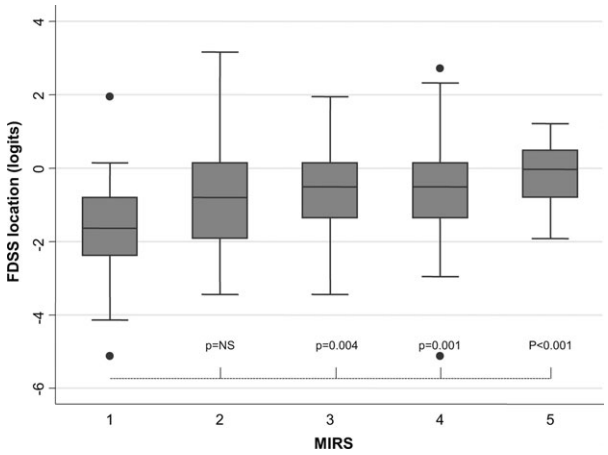

FIGURE 4. Relationship between FDSS outcomes and MIRS grades. FDSS values are presented in boxplot form. A progressive increase in fatigue and sleepiness level was seen on the FDSS with increased muscular impairment demonstrated by higher MIRS grade. FDSS scores did not differ significantly between all subgroups.

The high PSI is supportive of a good discriminatory capacity of the scale among patients with various degrees of fatigue and sleepiness, suggesting that the scale can measure change in fatigue induced by, for example, medical intervention. The FDSS scale would be a more suitable patient-based outcome measure for randomized trials of psychostimulants, as it is specifically devised and validated for DM1 and overcomes the limitations of ordinal-based measures.

The ability of the FDSS to detect relevant clinical changes over time (responsiveness) needs further evaluation. Also, the use of this new scale should be complemented whenever possible by monitoring of multiple physiological parameters during sleep (polysomnography), determination of physiological sleepiness during the daytime (multiple sleep latency test), and assessment of potential immunological and neuroendocrine disturbances, impaired psychophysiological responses, and dysfunction in central and peripheral motor pathways.[32–34]

In conclusion, in this study we have addressed the various measurement issues involved in the construction of a clinically meaningful combined fatigue and daytime sleepiness scale (the FDSS) specifically for patients with DM1, using Rasch analysis. The FDSS interval measure meets all Rasch model expectations and bypasses the difficulty of differentiating between fatigue and sleep problems by providing interval measures on a single continuum for both entities. Its use is therefore suggested in future clinical trials and follow-up studies in DM1 in order to determine its responsiveness.

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APPENDIX

Rasch-built 12-item Fatigue and Daytime Sleepiness Scale (FDSS) for patients with DM1.

		Seldom or never	Sometimes	Almost always
1	My motivation is lower when I am fatigued	0	1	2
2	Exercise brings on my fatigue	0	1	2
3	Fatigue is among my three most disabling symptoms	0	1	2
4	Fatigue causes frequent problems for me	0	1	2
5	Do you take one or more naps during the day?	0	1	2
6	Do you fall asleep while watching TV?	0	1	2
7	Are you generally in great shape during the day?	2	1	0
8	Do you doze off or fall asleep as a passenger in a car for an hour without a break?	0	1	2
9	Do you doze off or fall asleep when sitting and reading?	0	1	2
10	Do you doze off or fall asleep while sitting inactive in a public place?	0	1	2
11	Do you doze off or fall asleep in a car while stopped for a few minutes in traffic?	0	1	2
12	Do you doze off or fall asleep while sitting and talking to someone?	0	1	2

The raw sum-score varies between 0 and 24. The raw sum-scores should not be used as such, but must first be transformed into an interval measure that can be used for parametric statistical analyses. The nomogram allowing the translation of raw sum-scores of the FDSS (range 0–24) into logits or into a metric score (range 0–100) is available on request.

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