BRIEF COMMUNICATION

Responsiveness of Daytime Sleepiness and Fatigue Scales in Myotonic Dystrophy Type 1

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ABSTRACT: Daytime sleepiness and fatigue are prominent symptoms of myotonic dystrophy type 1 (DM1) that can be amenable to treatment in the context of randomized controlled trials. No study has yet documented whether self-reported measures of daytime sleepiness and fatigue can detect change over time and the meaning of this change. The aim was to explore indicators of responsiveness to change and interpretability for the Daytime Sleepiness Scale and the Fatigue Severity Scale in 115 DM1 prospectively followed patients. Results suggest that these two self-reported questionnaires are sufficiently sensitive to detect changes beyond expected measurement error over time in this population.

RÉSUMÉ : Sensibilité des échelles de mesure de la somnolence diurne et de la fatigue dans la dystrophie myotonique de type 1. La somnolence diurne et la fatigue sont des symptômes importants de la dystrophie myotonique de type 1 (DM1), susceptibles de traitement dans le cadre d'essais comparatifs à répartition aléatoire. Toutefois, on ne sait pas si les mesures déclarées par les malades permettent de déceler les modifications de la somnolence diurne et de la fatigue ainsi que leur amplitude au fil du temps. L'étude ici exposée visait donc à examiner la sensibilité aux modifications des échelles Daytime Sleepiness Scale et Fatigue Severity Scale ainsi que leur possibilité d'interprétation chez 115 patients atteints de DM1 et suivis de manière prospective. Les résultats donnent à penser que ces deux questionnaires de déclaration par les malades sont suffisamment sensibles pour permettre la détection de modifications allant au-delà des erreurs de mesure prévisibles, au fil du temps, dans cette population.

Keywords: Myotonic dystrophy, Sleep, Fatigue, Responsiveness to change

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Myotonic dystrophy type 1 (DM1, MIM160900), the most common adult-onset form of muscular dystrophy, is a pleiotropic disorder caused by an expansion of a cytosine, thymine, and guanine (CTG) repeat in the *DMPK* gene.[1] While myotonia is the hallmark of this slowly progressive neuromuscular disease, daytime sleepiness and fatigue are frequently referred to as the most frequent nonmuscular symptoms of the condition, being present in up to 93% of patients.[2] Although the terms sleepiness and fatigue may often be used interchangeably by DM1 patients, they represent two interrelated but distinct phenomena that frequently coexist.[3,4] In addition, a recent study in DM1 patients revealed that a history of hypothyroidism was a predictor of higher daytime sleepiness levels, whereas a higher CTG repeat number and a shorter habitual sleep duration predicted higher fatigue levels.[5]

Clinicians often rely on self-reported measures to document symptoms' progression over time and guide treatment decisions. Moreover, it is well accepted that the soundness of clinical evidence largely depends upon the applicability and the metrological properties of an instrument to the population of interest.[6] In the context of clinical trials, reliability and responsiveness to change are key aspects that are taken into consideration in the selection of outcome measures to achieve primary or secondary endpoints. In addition, interpretability, although not defined as a metrological property as it does not refer to the quality of the instrument, is essential in the context of a therapeutic trial to understand the meaning of the change in patients' life, referring to how the patient feels and functions as described by the regulatory agencies. In DM1, reliability studies, a prerequisite for responsiveness to change and interpretability, were conducted for a relatively small number of daytime sleepiness and fatigue self-reported instruments, namely the Epworth Sleepiness Scale, Daytime Sleepiness Scale (DSS), Chalder Fatigue Scale, Fatigue Severity Scale (FSS), and Fatigue and Daytime Sleepiness Scale.[7,8] However, no study has yet examined whether such self-reported measures can be responsive to change and what is

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the meaning of those changes. It also seems that longitudinal study designs are necessary to determine whether patient-reported outcome instruments are responsive to change in absence of results of prior intervention study design.[9] As fatigue and daytime sleepiness are slowly progressive symptoms of DM1, capturing changes among patients through a prospective study necessarily requires a few years. The present study constitutes a secondary analysis of existing data to explore responsiveness to change and interpretability of two scales recommended by the Outcome Measures in Myotonic Dystrophy type 1 initiative.[3] The objective of the present study was to explore the responsiveness to change and interpretability of the DSS and the FSS in DM1 patients.

DM1 patients with adult and late phenotypes filled out the DSS[10] and the FSS[11] at Time 1 [$n = 200$; 79 males; mean age (SD) = 47.0 years (11.8)] and 9 years later at Time 2 [$n = 115$; 43 males; mean age (SD) = 52.3 years (10.3)]. Ten patients (5%) had no muscular impairment, 67 patients (33.5%) had distal weakness, and 123 patients (61.5%) had proximal weakness. The mean (SD) CTG repeat number was 809.2 (529.4). Twenty-four patients (12%) were taking methylphenidate and 12 patients (6%) were taking a sedative-hypnotic drug at Time 1. Sample characteristics, recruitment methodology, and procedures have been described in more detail elsewhere.[12] A DSS score of 7 or higher is indicative of excessive daytime sleepiness (EDS), whereas an FSS score of 4 or higher is indicative of excessive fatigue. In addition, DM1 patients were asked to complete a global rating of change (GRC) scale at T2 to assess whether their daytime sleepiness and fatigue symptoms have changed in recent years (1 = improvement, 2 = no change, 3 = worsening). The Ethics Review Board of the *Centre intégré universitaire de santé et de services sociaux du Saguenay–Lac-St-Jean* approved the study protocol and written informed consent was obtained from all participants. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) recommendation was used to assess responsiveness to change. In absence of an outcome measure as gold standard, GRC can be used in the criterion approach, which is based on hypothesis testing. Receiver operating characteristic curves were used to explore the ability of the scale to measure change according to the GRC. As proposed by COSMIN, an area under the curve (AUC) above 0.70 is considered indicative of responsiveness to change.[13] Paired *t*-tests were used to assess the statistical significance of the changes in patients' daytime sleepiness and fatigue scores between T1 and T2. For small subsamples ($n < 30$), exact *p* values were calculated using Wilcoxon signed-rank tests. Interpretability was assessed using the standard error of measurement (SEM) and the smallest detectable change (SDC) or minimal detectable change, which is defined as change beyond measure error. We used the intraclass correlation coefficient (ICC) from previous reliability estimates[7] to calculate the $SEM = SD \times (\sqrt{1 - ICC})$ and the $SDC = 1.96 \times \sqrt{2} \times SEM$. Statistical analyses were performed using G * Power 3 and SPSS version 25.0 for Windows (IBM SPSS, Inc., Chicago, IL, USA).

An increase in mean DSS (4.5 vs. 5.3, $p < 0.05$) and FSS (4.4 vs. 4.8, $p < 0.01$) scores was observed between T1 and T2 (data not shown). The proportion of DM1 patients who reported at T2 a deterioration of their daytime sleepiness and fatigue symptoms since T1 was 25.7% and 40.4%, respectively (Table 1). On the other hand, no significant difference was noted for patients who reported stable symptoms during that 9-year period. Moreover, the very small number of participants precludes from drawing conclusions regarding patients who reported an improvement of their symptoms at T2 (Table 1).

Table 1: Mean (SD) Daytime Sleepiness Scale (DSS; $n = 113$) and Fatigue Severity Scale (FSS; $n = 114$) scores in myotonic dystrophy type 1 (DM1) patients at a 9-year interval

	T1	T2	*p* value
Patients reporting a deterioration of symptoms at T2			
DSS score ($n = 29$)	5.4 (2.8)	7.8 (3.7)	<0.001
FSS score ($n = 46$)	4.7 (1.6)	5.6 (1.3)	<0.001
Patients reporting a stabilization of symptoms at T2			
DSS score ($n = 77$)	3.8 (2.6)	4.2 (2.8)	0.426
FSS score ($n = 59$)	4.1 (1.8)	4.2 (1.8)	0.838
Patients reporting an improvement of symptoms at T2			
DSS score ($n = 7$)	8.6 (3.6)	7.1 (3.0)	n/a
FSS score ($n = 3$)	3.7 (2.5)	4.7 (2.0)	n/a

T1, Time 1; T2, Time 2.

Responsiveness to change was documented with the AUC based on the GRC scale (no change vs. symptoms worsening) and was 0.72 for the DSS (95% confidence interval [CI] = 0.61 – 0.83) and 0.66 for the FSS (95% CI = 0.56 – 0.76).

For interpretability, Figure 1 (upper part) shows that changes between T1 and T2 mean DSS scores (4.5 and 5.3) lay within the SEM and the SDC, suggesting no significant change in daytime sleepiness levels in DM1 patients over the 9-year period. However, in the patient subgroup who reported at T2 a deterioration of their daytime sleepiness symptoms since T1 (bottom part of Figure 1), T2 mean DSS score (7.8) lies outside of the SEM, suggesting a change beyond measurement error but not above the smallest detectable change in daytime sleepiness levels over the 9-year period. It should though be specified that patients who reported a deterioration of their daytime sleepiness had higher sleepiness levels at T1 than those whose sleepiness levels remained stable ($p < 0.01$).

Figure 2 (upper part) illustrates that changes between T1 and T2 mean FSS scores lay within the SEM and the SDC, suggesting no change in fatigue levels in DM1 patients over the 9-year period studied. Yet, in the patient subgroups who reported at T2 a deterioration of their fatigue symptoms in recent years, the T2 mean scores for the FSS (5.6) lie outside of the SEM (bottom part of Figure 2), suggesting a change beyond measurement error but not above the SDC. Finally, it should be noted that that fatigue levels at T1 did not differ between patients who reported an increase in fatigue levels between T1 and T2 and those who did not.

The present study provides preliminary partial evidence for responsiveness to change for the DSS and the FSS according to COSMIN criteria. More specifically, it was demonstrated that these latter self-reported measures can document decline or stability of symptoms. For interpretability, DM1 patients who deem that their

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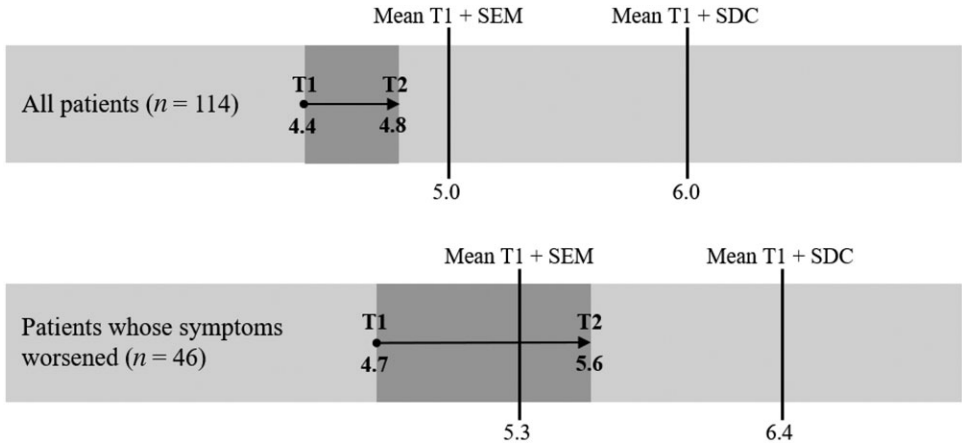

Figure 1: *Parameters of measurement error between Time 1 and Time 2 for Daytime Sleepiness Scale (DSS) scores. SDC = smallest detectable change; SEM = standard error of measurement.*

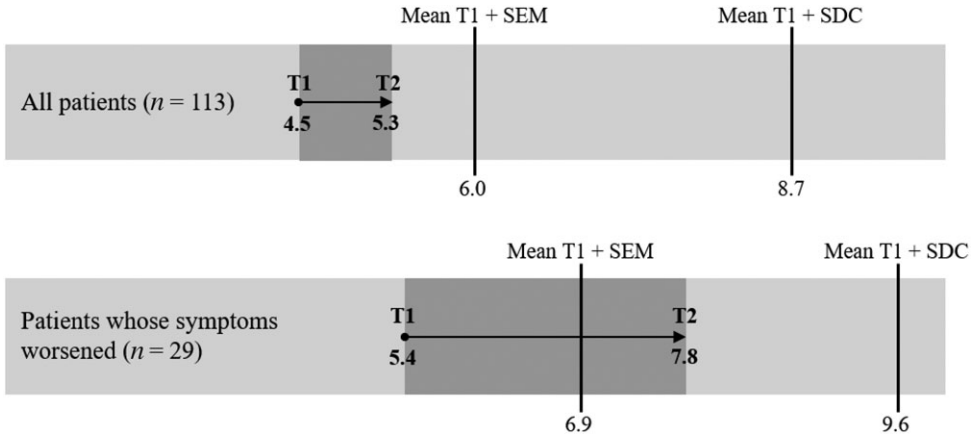

Figure 2: *Parameters of measurement error between Time 1 and Time 2 for Fatigue Severity Scale (FSS) scores. SDC = smallest detectable change; SEM = standard error of measurement.*

symptoms worsened had significantly increased DSS and FSS scores between Time 1 and Time 2 beyond measurement errors but not beyond minimal detectable changes. Since CIs are large, future interventions could require larger sample sizes depending on the effect size. Given that very few patients have reported an alleviation of symptoms, it was not possible to estimate the minimal important change for improvement of symptoms. Although cognitive impairment, a common feature in the DM1 population may theoretically influence patients' self-assessment of symptoms such as daytime sleepiness or fatigue, no evidence of such a situation has yet been reported in the literature and patient-reported outcome measures are strongly recommended instruments in DM1 clinical trials.

This study has some limitations. It must first be pointed out that shorter timeframes for evaluation are habitually used in randomized controlled trials and documenting the ability to track changes over a shorter period should also be done. However, given the slow nature of the disease progression and the actual results, measuring deterioration may be difficult with these instruments. In addition, patients who were part of this longitudinal study were not systematically evaluated for sleep-disordered breathing (SDB) nor were they prospectively followed for treatment of SDB, EDS, and fatigue. Even if patients were treated for EDS or fatigue in the context of this 9-year longitudinal study, one may hypothesize that it did not influence the ability of these instruments to detect changes according to patient's perception. Indeed, a given patient may have been treated for EDS and still feel that his/her sleepiness level has increased, with the scale able to grasp that patient's subjective perception. One should bear in mind that DM1 is a very slow progressive disease and the gradual worsening of daytime sleepiness and fatigue reported here shall necessarily differs from an intervention with psychostimulant, which aims to document an improvement in symptoms. Moreover, it would have been interesting to compare the findings of this study with that of a prospectively followed control group. Despite the aforementioned limitations, the present report is the first, to our knowledge, to show that DM1 patients' impressions as to the worsening of daytime sleepiness and fatigue symptoms is duly reflected by self-assessed instruments.

Patient-reported outcome measures from clinical trials can also bring insight into observed effects based on treatment comparisons and should be used to further determine responsiveness to change of self-report instruments of daytime sleepiness

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and fatigue in DM1 patients, including minimal detectable change and minimal clinically important change.[6]

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Disclosures

L.L. has acted as a consultant for Biogen, Ionis, and Harmony Biosciences. B.G. has acted as a consultant for Biogen, Ionis, and Expansion. Y.D. has acted as a consultant for UCB Pharma, Jazz, Theranexus, Flamel, Idorsia, Takeda, Harmony Biosciences, and Bioprojet. C.G. has acted as a consultant for Biogen and Ionis.

Statement of Authorship

C.G. and J.M. have initiated and supervised the longitudinal study; L.L. has written the paper with the help of B.G., J.A., Y.D., J.M., I.C., and C.G.; L.L., B.G., J.M., I.C., and C.G. have participated in the data collection; and L.L., J.A., and I.C. have performed the statistical analysis.

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