P1061

The interpretation and clinical application of the PROMIS® SF v1.0 - Fatigue (MS) 8b: a PROMIS short form for assessing fatigue in multiple sclerosis

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Disclosures

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- Employed by Merck KGaA, Darmstadt, Germany

Karon Cook

- Consultant to Merck KGaA, Darmstadt, Germany

Sam Salek

- Consultancy contract with Merck group; unrestricted educational grant from the GSK and European Haematology Association

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- Consultant/speaker for Alexion, Biogen, Celgene, EMD Serono, Medison, Novartis, Roche, Sanofi Genzyme, and Viela Bio

Annette Wundes

- Research for Alkermes, Biogen, AbbVie; consultant for AbbVie

Dagmar Amtmann

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Rana Salem

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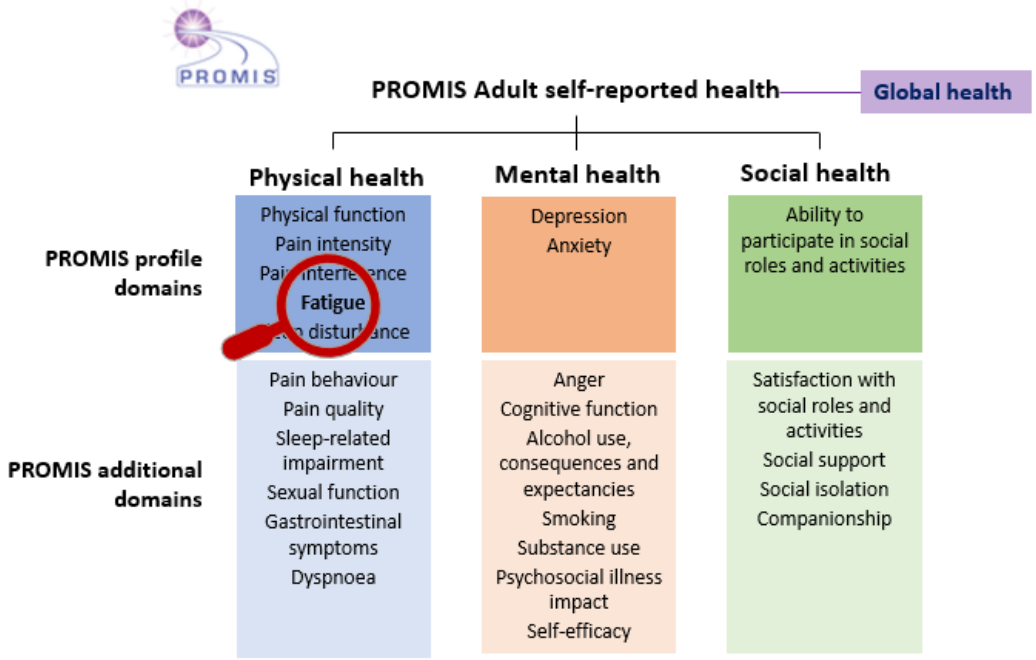
Jeffrey Johns, Kevin N. Alschuler, Gloria von Geldern and Rod Middleton

- Nothing to disclose

Background

- Fatigue is a very common and disabling symptom of MS that is challenging to characterize appropriately for both research and clinical practice
- The emergence of the NIH PROMIS item banks provides new possibilities for the development of health outcome measures that are brief and optimally targeted
- An MS-specific 8-item PROMIS short form for fatigue, developed based on input from MS patients and clinicians, is available and has been extensively validated
- This short form is being applied in various settings:
  - EVOLUTION I & II, Phase III RCTs of evobrutinib in relapsing MS (NCT04338022; NCT04338061)
  - FDA DDT qualification process by the Critical Path Institute PRO Consortium Multiple Sclerosis Working Group

Figure 1. Adult NIH PROMIS item banks



Source: http://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis

Objectives and rationale

- To establish minimal important difference estimates and interpretation tools for the PROMIS Fatigue (MS) 8b short form in MS populations
- Information facilitating interpretation of the PROMIS Fatigue (MS) 8b scores and their integration in clinical decision-making is vital for the applicability of short forms in different settings

DDT, drug development tool; **FDA**, Food and Drug Administration; **MID**, minimal important difference; **MS**, multiple sclerosis; **NIH**, National Institutes of Health; **PRO**, patient-reported outcomes; **RCTs**, randomized controlled trials

Methods 1/2

STUDY DESIGN

Two observational studies were conducted in MS populations:

1. A cross-sectional study at two tertiary MS centers in the US (n=296) [**US sample**]
2. A longitudinal study amongst members of the UK MS Register in the UK (n=384) [**UK sample**]

STUDY POPULATION

Inclusion criteria

- A clinician-confirmed MS diagnosis
- 18–65 years of age
- Able to use a computer or tablet
- Able to read and write in English, for study consent and completion of the survey questionnaire

Exclusion criteria

- Presence of cognitive or other impairment (e.g. visual) that would interfere with questionnaire completion
- Use of a wheelchair or scooter as the main form of mobility
- Patient-reported WebEDSS scores >6.5

WebEDSS, patient-reported Expanded Disability Status Scale available at: https://edss.clinicspeak.com/en/#!/welcome
MS, multiple sclerosis

Methods 2/2

MINIMAL IMPORTANT DIFFERENCE ANALYSIS

- **Anchor-based approaches** were applied to establish MID estimates for PROMIS Fatigue (MS) 8b score changes from baseline to Week 52, supported by distribution-based metrics
- Out of 11 potential variables evaluated, **three variables were selected as anchors**, based on multiple criteria:
  - ✓ Measuring fatigue or related concepts (e.g. physical health)
  - ✓ A Spearman's rho of >0.3 with PROMIS Fatigue (MS) 8b change score
  - ✓ At least 10 observations in each change group (i.e. minimal worsening, minimal improvement)

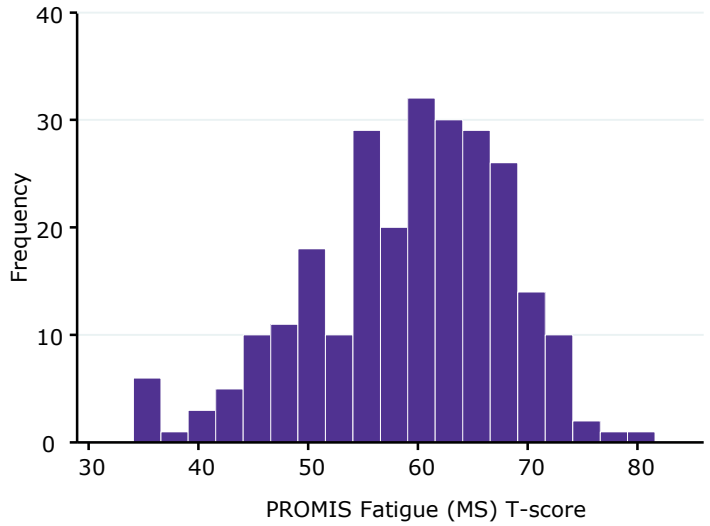
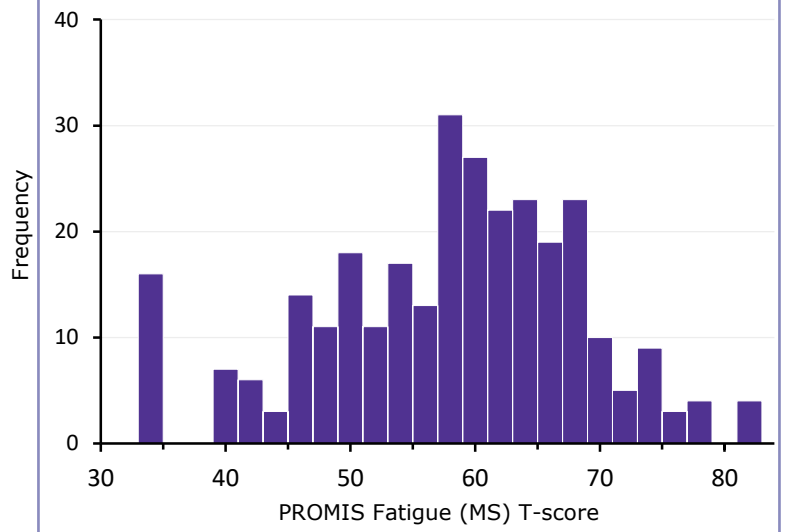
SCORE INTERPRETATION TOOL

- A **T-score map** was created that categorizes the PROMIS Fatigue (MS) 8b T-scores in terms of expected responses on each item of the short form
- Results are displayed as a heatmap showing the most likely response for each item, for each T-score

MID, minimal important difference; **MS**, multiple sclerosis

Results 1/4

Table 1. PROMIS Fatigue (MS) 8b T-scores

PROMIS Fatigue (MS) 8b T-scores	UK sample (n=384)	US sample (n=296)
Mean (SD)	58.9 (9.4)	57.7 (10.5)
Median (min, max)	60 (34.1, 80.7)	58.6 (34.1, 80.7)
Ceiling[a], %	1.3	1.4
Floor[a], %	3.4	5.4
T-scores distribution at baseline		
SEM [SD*√(1–reliability)]	2.8	3.3

[a]Estimates for the percentage of participants with the lowest and highest scores for all items (floor and ceiling) are well below the recommended threshold of <15%, indicating minimal floor and ceiling effects

BL, baseline; **SD**, standard deviation; **SEM**, standard error of measurement; **SF**, short form

Results 2/4: Minimal important difference analysis – UK sample

Table 2. Anchor-based analysis of PROMIS Fatigue (MS) MID [UK sample]

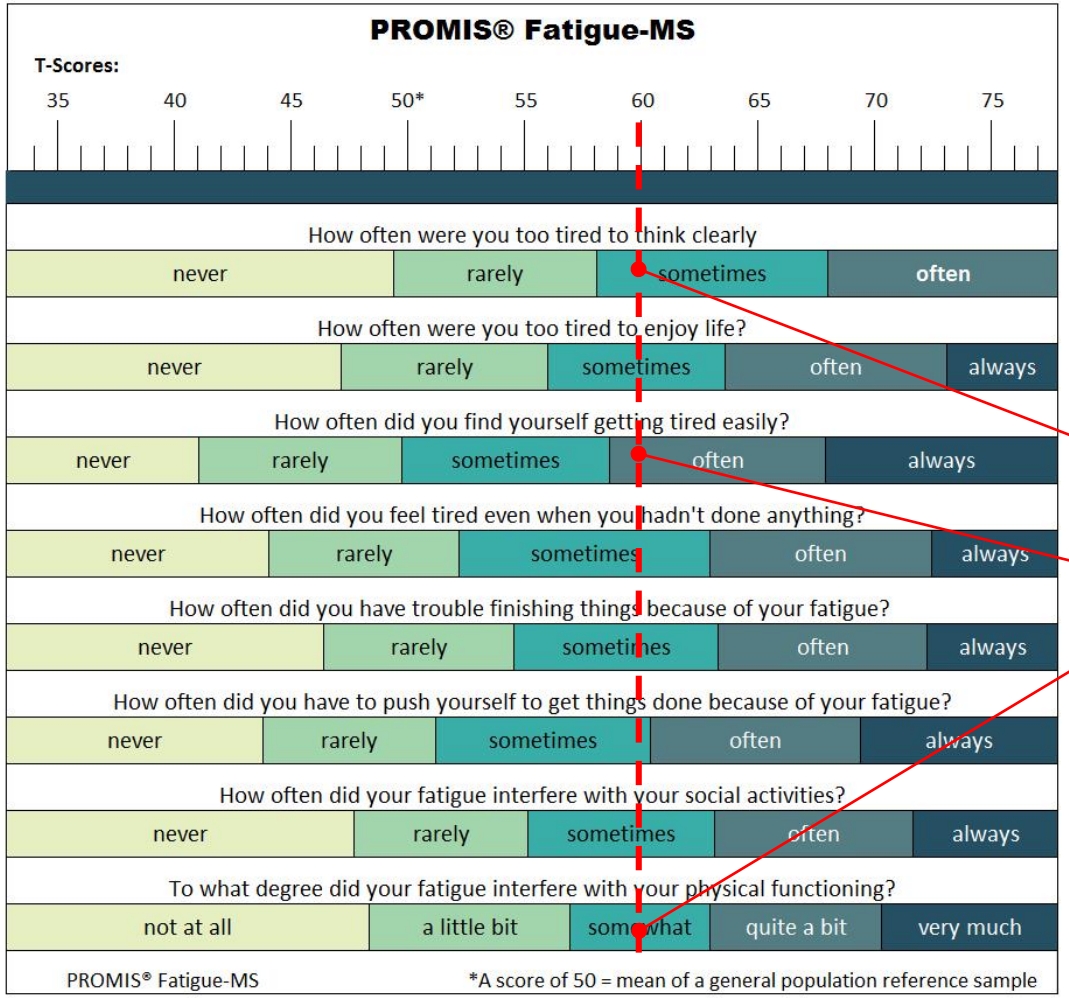
Anchor variable		Δ (Week 52 – baseline)	
	n	**Mean change (SD)**	**ES estimate (95% CI)**
GHS fatigue question (global08r)			
Minimal worsening (1 point decrease)	62	-3.37 (4.62)	-0.39 (-0.74; -0.03)
Minimal improvement (1 point increase)	50	3.86 (4.09)	0.48 (0.08; 0.88)
GHS GPH summary score			
Minimal worsening (4.4–9.4 point decrease)	51	-2.24(4.82)	-0.26 (-0.65; 0.13)
Minimal improvement (4.4–9.4 point increase)	41	3.06 (4.31)	0.36 (-0.08; 0.79)
Fatigue severity scale scores			
Minimal worsening (4.5–9.9 point decrease)	39	-1.17 (6.54)	-0.18 (-0.63; 0.26)
Minimal improvement (4.5–9.9 point increase)	35	3.46 (4.53)	0.4 (-0.08; 0.87)

A score change of 3.4–4.0 points is proposed as MID criteria for minimal improvement or worsening of fatigue

CI, confidence interval; **GHS**, PROMIS Global Health Scale; **GPH**, Global Physical Health Component; **MID**, minimal important difference; **SD**, standard deviation

Results 3/4

Figure 2. A heatmap to facilitate interpretation of PROMIS Fatigue (MS) 8b scores based on fatigue concerns on individual items was developed



The heatmap shows the most likely item level responses, for each PROMIS Fatigue (MS) 8b score

For example, a T-score of 60 represents a fatigue level that, in the last 7 days, was characterized by:

- **Sometimes** being too tired to think clearly
- **Often** getting tired easily, and
- Experiencing fatigue that **Somewhat** interfered with physical functioning

Results 4/4

Table 3. Characteristics of study participants at baseline

Characteristic		UK sample[a]	US sample[a]
		Baseline (n=384)	**Baseline (n=296)**
Age	Mean (SD) Median Range	49.9 (9.8) 51 22–65	44.50 (11.2) 43.5 21.1–65.6
Gender, n (%)	Male Female Non-binary	91 (23.7) 293 (76.3) 0	75 (25.3) 219 (74.0) 2 (0.7)
Time since MS diagnosis, years	Mean (SD) Median Range	10.22 (7.96) 8.0 0–38	9.65(7.51) 8.22 0.12–37.7
Patient-reported WebEDSS	Mean (SD) Median Min-Max Mild (0–4.0), n (%) Moderate (>4–6.5), n (%)	4.59 (1.89) 5.0 0–6.5 168 (43.75) 216 (56.25)	3.41 (1.7) 3.5 0–6.5 202 (68.2) 94 (31.8)
MS phenotype	Relapse-remitting (RR) Secondary progressive (SP) Primary progressive (PP)	260 (67.7) 85 (22.1) 39 (10.2)	280 (94.6) 9 (3.0) 7 (2.4)

At baseline:

- **Study participants had a mean age of 44.5–49.9 years**
- **Patient-reported WebEDSS mean scores were:**
  - 4.59 [UK sample]
  - 3.41 [US sample]
- **The majority of participants had relapsing-remitting MS:**
  - 67.7% [UK sample]
  - 94.6% [US sample]

[a]Analysis sample includes respondents with EDSS ≤6.5, age ≤65 years, and with PPMS, RRMS, or SPMS phenotypes
[b]Baseline characteristics of participants with a week 52 follow-up assessment
WebEDSS, patient-reported Expanded Disability Status Scale available at: https://edss.clinicspeak.com/en/#!/welcome
MS, multiple sclerosis; **SD**, standard deviation

Conclusions

This research adds to the evidence base underpinning the application of the PROMIS-Fatigue (MS) 8b in different settings

- **The proposed MID of 3.4–4 points meets key requirements for establishing meaningful change criteria[1-3] and is consistent with the MID for a similar 7-item PROMIS-Fatigue short form in patients with advanced cancer (i.e. 3.0–5.0)[3]**
- **Availability of MID estimates will be useful when using the PROMIS Fatigue (MS) 8b, especially when evaluating fatigue over time in clinical research as well as in routine clinical practice**
- **The score interpretation guide will aid the integration of the short form's scores into clinical decision-making and facilitate clinician–patient communication**

Please see our other poster at MS Virtual 2020: 8th Joint ACTRIMS–ECTRIMS Meeting
The validity and applicability of a new PROMIS® physical function short form for use in relapsing and progressive multiple sclerosis – Poster P1062

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MID, minimal important difference

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