Assessing fibromyalgia-related fatigue: content validity and psychometric performance of the Fatigue Visual Analogue Scale in adult patients with fibromyalgia

B.K. Crawford[1], E.C. Piault[1], C. Lai[2], R.M. Bennett[3]

[1]Mapi Values, Tokyo, Japan;
[2]Jazz Pharmaceuticals, Inc.;
[3]Oregon Health & Sciences University, Oregon, USA.

Bruce K. Crawford, MA, MpH
Elisabeth C. Piault, Pharm D, MA
Chinglin Lai, PhD
Robert M. Bennett, MD

Please address correspondence and reprint requests to:
Bruce Crawford,
General Manager, Asia,
Mapi Values,
Arco Tower 12F,
1-8-1 Shimomeguro, Meguro,
Tokyo 153-0064, Japan.
E-mail: bruce.crawford@mapivalues.com

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ABSTRACT

Objectives. *To document 1) the content validity and 2) measure improvements in fatigue, using the Fatigue Visual Analogue Scale (VAS) assessment tool in patients with fibromyalgia.*

Methods. *The relevance and comprehensiveness of the Fatigue VAS were tested through a qualitative analysis of 20 subjects' verbatim transcripts from semi-structured qualitative interviews. Data from two randomised, controlled trials in fibromyalgia (n=1121) were used to conduct correlation analyses with the Fatigue and Tiredness items from the Fibromyalgia Impact Questionnaire (FIQ) and the Short Form-36 Vitality scale. Known-groups and cross classification analyses were conducted to demonstrate the ability to measure improvement in fatigue using the Fatigue VAS.*

Results. *All subjects spontaneously reported that fatigue was an important symptom to capture in fibromyalgia. The Fatigue VAS was well understood by most subjects (n=18/20). High correlations (Pearson r>0.75) and good agreement (k>0.66) were found between the Fatigue VAS and the FIQ tiredness items no. 16 and 17 and SF-36™ Vitality scale. In both clinical trials there was a substantial separation of approximately 20 points on the mean change in the Fatigue VAS score between responders (>30% improvement in pain VAS) and non-responders.*

Conclusion. *Previous studies have confirmed that fatigue is a major component of the fibromyalgia experience. This current study reports that fibromyalgia patients spontaneously rated fatigue as a highly significant feature of their illness, and supports the use of the Fatigue VAS as a valid questionnaire in fibromyalgia clinical trials.*

Introduction

Fibromyalgia is a chronic musculoskeletal disorder with an estimated 2–3% prevalence rate in the United States and 2.9% prevalence in Europe (1); it is the second most common disorder observed by rheumatologists after osteoarthritis. Fibromyalgia is estimated to be approximately seven times more common in women than men, and its prevalence increases with age, with the highest prevalence among those 60–79 years of age (2).

Fibromyalgia is a complex disease with a hallmark symptom of widespread pain (3, 4). Fibromyalgia-related pain is often associated with fatigue, typically referred to as lack of energy or tiredness. Fatigue is reported by subjects to be one of the worst fibromyalgia symptoms that can lead to a substantial impact on daily life, limiting subjects' ability to perform daily activities and negatively affecting emotional well-being (2, 5, 6). Fatigue is one of the core symptoms along with pain and tenderness that the Outcome Measures in Rheumatology (OMERACT) consensus group recommended to be studied in all fibromyalgia clinical trials (7, 8). Over the past decade, a number of clinical research studies (7, 9-19) have focused on fatigue as a key endpoint to evaluate treatment benefit using fibromyalgia- or fatigue-specific multidimensional self-completed instruments, including the Fibromyalgia Impact Questionnaire (FIQ) (20-22), the Multidimensional Fatigue Inventory (17, 23-25), the Fatigue Severity Scale (25-27) or its modified version (28), the Multidimensional Assessment of Fatigue (29), the Fatigue Impact Scale (30), the Fibromyalgia Assessment Status (31), the Brief Fatigue Inventory (32), the Patient-Centered Outcomes Questionnaire (9), and the Arthritis Self-Management Program (18, 7, 29, 33-35). Generic instruments such as the 36-item Short Form Health Survey (SF-36™) (7, 29, 34) and global assessment of fatigue through a Visual

Analogue Scale (20, 36, 37) (VAS) (11, 16, 19) have also been reported. Only a few of these measures document patients' involvement in item generation or testing (38).

Measuring fatigue related to fibromyalgia is challenging; clinicians, scientists and regulatory reviewers are still debating whether the term "fatigue" itself would be spontaneously understood by fibromyalgia patients (39) or pertains to the clinical jargon (40). Several conceptual models of fatigue, like for those for pain, have been suggested. These include, but are not limited to, simple models relying on patients' global assessment of the severity of fatigue, or all-encompassing models including physical, emotional, and cognitive components. There is a need for a clearer understanding of fatigue from a patient's viewpoint. The present qualitative study, using a patient-centric approach, provided an opportunity for patients to describe their condition in terms that are meaningful to both patients and clinicians. In the present study, feedback regarding the understandability of the term "fatigue" was tested through the use of the Fatigue Visual Analogue Scale, a self-completed instrument developed according to the format of the gold standard in pain assessment, the global assessment of pain severity using a 0–100 point VAS. In a second study, data from two randomised, controlled trials of a pharmacological treatment in fibromyalgia patients were analysed to further aid our understanding of fibromyalgia-related fatigue by documenting the relationships between changes over time in fatigue and other fibromyalgia symptoms including pain, tiredness, and sleep.

Materials and methods

Three clinical sites in the US recruited patients to ensure geographical diversity: Pennsylvania, Texas, and California. All subjects had a clinician-confirmed diagnosis of fibromyalgia using American College of Rheumatology (ACR) criteria. Face-to-face in-depth interviews were conducted following the principles of grounded theory. With grounded theory the concepts emerge from patients' input, allowing the voice of the patient to be heard rather than applying *a priori* concepts driven by researchers' preconceived notions or biases (41-43). The interviews aimed to demonstrate that "fatigue" is a relevant and understandable concept to evaluate in patients with fibromyalgia. Interviews included a concept elicitation exercise to document patients' descriptions of fibromyalgia-related fatigue, in which subjects were asked to describe the symptoms they experience in relation to fibromyalgia, without presuming that subjects would spontaneously use the term "fatigue." Then, interviewers clarified concepts that could be related to fatigue, including "tired" or "lack of energy," through inductive probing. The second part of the interview involved a cognitive debriefing testing. The patients were provided with the Fatigue VAS and through a "think-aloud" exercise with retrospective probing, the patients' familiarity of the term "fatigue", as well as their decision-making process when rating the symptom, were documented. Each interview lasted approximately 60 minutes and was conducted by a trained interviewer using a semi-structured interview guide. All interviews were audio-recorded with prior consent from the subjects, and subjects were compensated for their participation in the study. To ensure the integrity of the research, the word "fatigue" was not mentioned during the recruiting process. Consequently, participating subjects were not screened for their fatigue severity, but subjects had to document a severity of pain greater than or equal to 5 on a Pain Numerical Rating Scale (NRS) (10=worst imaginable pain) at the time of screening. As pain and fatigue have shown high correlations, it was expected that each subject had a recent experience of fatigue at the time of the interview.

Interviews were transcribed verbatim, and data were organised using ATLAS.ti Version 6.0 (44), a qualitative software package. Coding is an iterative process; hence, the code scheme was modified and became richer as the analysis progressed (45). Coding was performed by two independent coders and reviewed by a senior team member to ensure consistency in the interpretation of subjective data across coders and transcripts. Any coding discrepancies were resolved with the entire team. Codes reflected concepts that could be related to fatigue, including related sensations or impacts. Additional codes were used to document patients' feedback on the Fatigue VAS. Only spontaneously elicited concepts were considered in this analysis, so that the subjects' experiences were captured without influence from the interviewer. Data analysis was performed concurrently with data collection, and detailed information from a representative number of cases was analysed.The sample size was capped when no further unique concepts emerged from successive interviews (concept saturation). Once saturation was reached, the sample size was considered adequate (43).

The data for the quantitative study were collected within two randomised, double-blind, placebo-controlled, parallel-group, 14-week studies of patients with ACR-defined fibromyalgia (n=548 trial 1, n=573 trial 2). The sample size for those studies was powered for the primary endpoint of the clinical trials (proportion of subjects who had at least 30% reduction in pain severity from baseline to study endpoint). In validation studies, sample sizes are typically determined based on planned analyses rather than anticipated effect size and power (40, 46, 47), Validation analyses were conducted on the intent-to-treat (ITT) population, which included all randomised subjects.

In addition to the Fatigue VAS, the following measures were part of the trials: Pain VAS, FIQ (48), Functional Outcomes of Sleep Questionnaire (FOSQ), SF-36™ v2, Patient Global Impression of Change (PGIc), and Clinical Global Impression of Change (CGIc).

The Fatigue VAS and the Pain VAS are global assessments of subjects' current severity levels of fatigue and pain, respectively, using a horizontal line (VAS) anchored by "0=No fatigue/pain" and "100=Worst imaginable fatigue/pain". Subjects were instructed to record their level of fatigue and pain in the morning, afternoon, and evening using a personal digital assistant-like device that allowed electronic data capture. Both scales had already been

used in clinical trials with subjects with fibromyalgia to support treatment efficacy endpoints.

The FIQ is a questionnaire that evaluates the functional and symptom impact of fibromyalgia, based on recollection over the previous 7 days (55). It is composed of 10 items, each rated on a 0–10 scale, and the total FIQ score, derived from addition of the 10 items, reflects the total impact of fibromyalgia, with scoring being rated on a 0–100 scale (higher score indicating a greater impact) (49). Two items of the FIQ "*How tired have you been*" and "*How have you felt when you get up in the morning*" were of particular interest as comparators for the Fatigue VAS.

The FOSQ (50) is a questionnaire that evaluates the impact of daytime sleepiness and tiredness on daily activities. It is composed of 30 questions subdivided into 5 subscales (activity, vigilance, intimacy, productivity and social outcomes). Each subscale is rated on a 0–4 scale (no difficulty, a little, moderate or extreme difficulty), to give a total score ranging from 5 to 20, with lower scores indicating greater dysfunction. The FOSQ does not specify any time for answer recollection.

The SF-36™ v2 is a widely used and well-validated questionnaire that provides information on various aspects of health-related quality of life, based on recollection over the previous 4 weeks. The vitality scale asks 4 questions related to fatigue (*Did you feel full of pep? Did you have a lot of energy? Did you feel worn out? Did you feel tired?)*.

Subjects and clinicians rated their impression of change in fibromyalgia severity and in subject's overall condition since baseline (*i.e.* prior to first dose of study medication) using a 7-point scale anchored on 1="very much better/ improved" and 7= "very much worse."

Ethics

The qualitative study protocol and corresponding study documents were approved by a centralised Institutional Review Board (IRB), Copernicus Group IRB, in July 2009. The quantitative study procedures were in accordance with the Helsinki Declaration of 1975/83.

Statistics

The relationships of change scores between the Fatigue VAS and other patient-completed scales capturing fibromyalgia-specific and fatigue-related symptoms were examined in each study. Moderate (r Pearson range 0.50 to 0.70) to high (r range 0.70 to 0.90) (51) correlations were expected to show that the Fatigue VAS tracks closely with simpler and more concise measures of the same/similar concept. The Fatigue VAS was then evaluated for its ability to discriminate among known groups of subjects grouped by a combined responder status, defined by ≥30% reduction after 14 weeks on both the FIQ scores and the Pain VAS. Responders were also categorised based on their scores on the PGIc ("Very much better" or "Much better"), the CGIc ("Very much improved" or "Much improved"), the FOSQ (change score ≥ minimal important difference defined by standard error of the mean) and the SF-36™ Vitality subscale (>5 and >10 (52-60) points improvement). Observation of a meaningful pattern of mean differences using Student *t*-tests across the defined subgroups supported the validity of the Fatigue VAS. In addition, the level of agreement between responder definitions using the Fatigue VAS and the responder definitions using the comparison scales were documented using Cohen's kappa (range from 0.00–1.00, with larger values indicating better reliability or agreement) (61).

A treatment group analysis on the Fatigue VAS was performed as part of the clinical analyses (62). To help aid in the interpretation of these results, cumulative response distributions were plotted by treatment group for change from baseline to end of study (Visit 11) in the Fatigue VAS Scale, FIQ item 16 ("*How tired have you been"),* and item 17 ("*How have you felt when you get up in the morning*"). The cumulative response distribution shows the percentage of subjects (y-axis) attaining a change from baseline less than or equal to the value on the x-axis. A separation between the curves with treatment moving in the "improved" direction with relation to the comparator curve indicated a superior response to treatment. These analyses were performed using the baseline observation carried forward data to be consistent with the clinical efficacy analyses.

All of the analyses were performed using Statistical Analysis System software (SAS), Version 9.1.3.

For interval or ordinal variables, group comparisons were performed using ANCOVA. If the distribution of the dependent variable did not appear to be normal upon visual inspection, or if the dependent variable had fewer than seven discrete score categories, then group comparisons were performed using a Kruskal-Wallis test (three or more groups) or a Mann-Whitney-Wilcoxon test (two groups). Nominal categorical variables were compared between groups by a Chi-square test (or whenever cells with fewer than five participants were present, by the Fisher exact test).

Analyses of correlations used Pearson correlation coefficients for both interval and multi-item ordinal scales. When the variables under examination did not meet normality assumptions, Spearman's rank correlation coefficient was used. For correlation of an interval or ordinal variable with a dichotomous variable, point-biserial correlation was used.

The statistical significance testing was two-sided at the 0.050 level, unless otherwise indicated.

Results

Concept elicitation interviews

Twenty subjects including 15 (75%) female subjects participated in the qualitative study. The average age of the subjects was 54 years (range: 30–70). Most subjects were White/Caucasian (n=14, 70%), and most had received either a college degree (n=8, 40%) or reported completing "some college" (n=8, 40%). Using survey-like questions at the end of the interview to prevent bias, all subjects reported that muscular or joint pain and tiredness were the primary symptoms that prompted them to seek treatment for their fibromyalgia; most of the subjects (n=15, 75%) reported taking a pain medication Table I).

All the subjects spontaneously used the term "tiredness" to characterise one of

their symptoms associated with fibromyalgia; other terms included "lack of energy," (n=17), "exhaustion," (n=15), "fatigue" (n=10), and "lack of strength/ feeling weak" (n=10) (Fig. 1). Subjects who spontaneously used the term "fatigue" described it as a "feeling of tiredness" (n=6), "lacking energy" (n=5), "feeling worn out" (n=2), "feeling weak" (n=2), "feeling wiped out" (n=1), "feeling groggy" (n=1), and "feeling drained" (n=1) (note that the terms could be used concomitantly). Furthermore, subjects often used metaphors ("walking in knee high water") and insisted on the debilitating impact of the sensation on their body (*e.g.* pain, heaviness, tightness) (n=4). Subjects' definition of "tired" or "exhaustion" yielded similar concepts and terminology. The terms "fatigue" and "tired" were the same for eight subjects; yet for others "fatigue" conveyed a higher severity level than "tired" (with exhausted suggested at the end [high level] of the continuum), not relieved by rest and of lasting duration. Subjects asserted that fatigue was not limited to a physical sensation (muscle tightness (n=5) and body heaviness (n=4)); but also had emotional (feeling depressed (n=1) or feeling down (n=1)) and cognitive manifestations (difficulties concentrating (n=4), feeling foggy (n=4), and decreased alertness (n=3)). Impacts were multifaceted, including limitation of activities of daily living (*e.g.* housework (n=7), shopping (n=3), self-care (n=2), driving (n=2)). Social activities such as going out with friends (n=3), being social (n=2), and interactions with family (n=1) were also mentioned as impacted.

Any new concepts, defined as a concept that had not been elicited in prior interviews but was important to the patient and was clinically relevant, including sensations related to fibromyalgia-related fatigue and impacts, were recorded. Figure 2 demonstrates that no new concepts were elicited after the third set of five interviews indicating that concept saturation was achieved hence, supporting the adequacy of a sample of 20 subjects.

Fatigue VAS cognitive interviews

Nearly all subjects (n=18) understood the question "please indicate your current level of fatigue" as a rating of the severity of their fatigue. One subject reported seeing "fatigue" for the first time and another misread "fatigue" as "function." The latter, however, correctly defined the concept being measured when prompted to do so (fatigue meant "*Tired (…) No energy*").

Subjects (n=10) who had not spontaneously mentioned fatigue during the concept elicitation part of the interview, were invited to provide a definition of this concept while completing the VAS. Eight subjects referred to feeling "tired"; two of them emphasised that "fatigue" was conveying a higher severity than "tired". Consistent with previous feedback, subjects referred to their lack of energy (n=4), feeling exhausted

Table I. Qualitative Research: demographic and medical information (n=20).

	n=20 (%)
Age Mean (SD) [range]	53.6 (12.75) [30–70]
Gender: Female	15 (75.0)
Race/Ethnicity	
Asian	1 (5.0)
Black/African American	3 (15.0)
Native American or Alaskan Native	2 (10.0)
White/Caucasian	14 (70.0)
Education	
Some high school	3 (15.0)
Diploma/GED	3 (15.0)
Some college but no degree	5 (25.0)
Certificate	3 (15.0)
College degree (*e.g.* BA, BS)	5 (25.0)
Graduate or professional degree	3 (15.0)
Symptoms *	N (%)
Pain (muscular or joint)	20 (100.0)
Tiredness	20 (100.0)
Disrupted sleep	17 (85.0)
Headaches	8 (40.0)
Restless legs	10 (50.0)
Numbness or tingling	11 (55.0)
Impaired memory	12 (60.0)
Leg cramps	8 (40.0)
Impaired concentration	8 (40.0)
Nervousness	4 (20.0)
Depression	5 (25.0)
Other	5 (25.0)
Prescription pain medication *	
Received pain medication	15 (75.0)
Lyrica	1 (5.0)
Neurontin	2 (10.0)
Ultram	2 (10.0)
Narcotics	2 (10.0)
NSAIDS	10 (50.0)
Non-prescription pain medications	11 (55.0)
Problems with sleep *	
No problem with sleep	1 (5.0)
Trouble falling asleep	13 (65.0)
Waking up several times during sleep	14 (70.0)
Having abnormal behaviour during sleep	3 (15.0)
Having an increased need to sleep	12 (60.0)
Waking up in the morning feeling unrested	17 (85.0)
Sleep medication *	
Received sleep medication	16 (80.0)
zolpidem	5 (25.0)
sodium oxybate	1 (5.0)
Other sleep medication	1 (5.0)

* Subjects were able to mark multiple selections; results are not mutually exclusive.

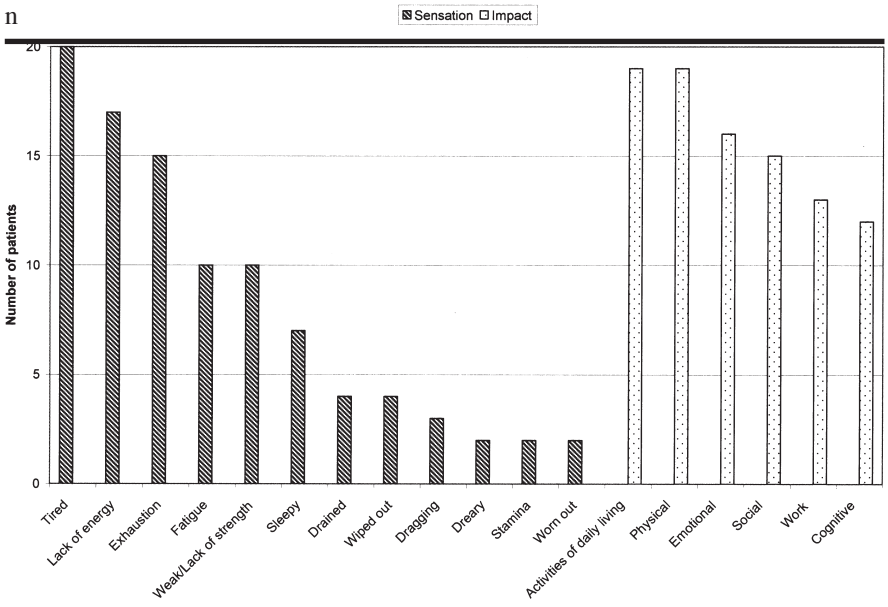

Fig. 1. Qualitative study: sensations and impact related to fatigue in fibromyalgia spontaneously elicited* (n=20).
*Number of patients spontaneously using each term in concept elicitation interviews.

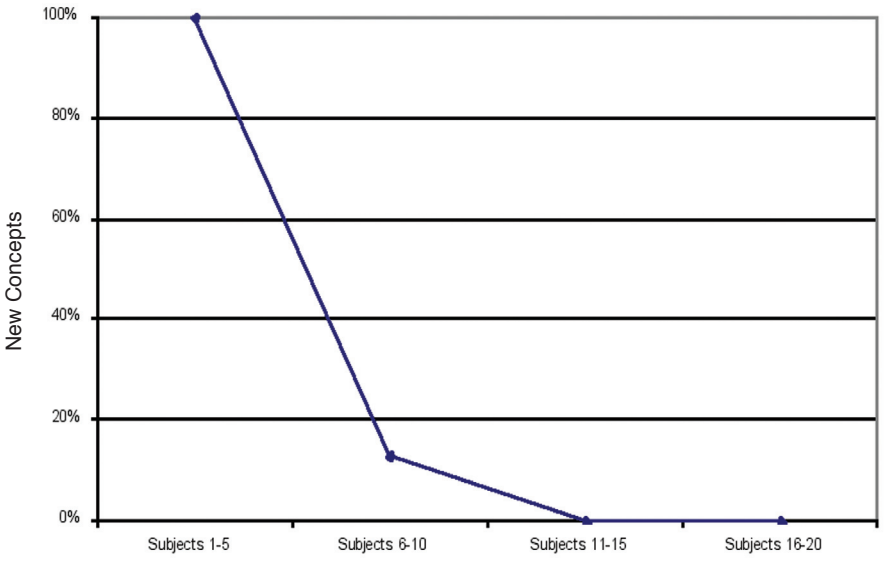

Fig. 2. Qualitative study: emergence of new concepts* (n=20).
*Percentage of new concepts elicited in each group of interviews

(n=2), feeling sleepy (n=1), or feeling listless (n=1) when describing the concept. Overall, twelve subjects reported that "fatigue" was an appropriate term to represent the sensation they experienced as a result of fibromyalgia.

Through the think-aloud exercise while answering the Fatigue VAS, patients demonstrated referring to the severity of their tiredness but also to emotional and physical sensations when selecting a response option, as indicated in the following exemplary quotes:

"Please indicate your current level of fatigue… I'm sore. I'm starting to get frustrated. I've noticed I have less energy. I'm more fatigued than I was when I came in. So I would say I'm probably at a five right now."

"I would think about how much my joints were affecting me throughout the day. I would think how my muscles had felt throughout the day. How my energy level was. My current level of fatigue right now is probably three quarters of the way from no fatigue to worst imaginable fatigue."

Quantitative study

In the two ITT populations (n=1,121), most subjects were female (90%) and White/Caucasian (91%). The average age of the subjects was 47 years (range: 18–80). The median time since onset of first fibromyalgia symptoms was 8.0 years (range: 0–51 years), and the median time since first diagnosis of fibromyalgia was 3.0 years (range: 0–48 years). The average subject-reported fatigue and pain VAS scores at baseline were 72.86 and 71.84, respectively (range: 7.5–100.0, 45.0–100.0, with a higher score representing a more severe symptom) (Tables II and III).

Fatigue, tiredness and vitality appeared to be related concepts, as high correlations were displayed between the Fatigue VAS, the FIQ item 16 ("*How tired have you been*") r~0.80, the FIQ item 17 ("*How have you felt when you get up in the morning*") r~0.75, and the SF-36™ . Vitality scale r~-0.60 (Table IV).

When responders were defined through the FIQ, the SF-36™ . Vitality scale or the FOSQ scales, there was a substantial separation of approximately 20 points when assessing mean changes of Fatigue VAS between responders (mean change from -28.10 to -48.49) and non-responders (mean change from -5.60 to -26.29) in both trials. All responder groups had significantly higher improvements in Fatigue VAS compared to non-responder groups ($p<0.01$). The improvements in the non-responder groups were likely due to the use of conservative responder classifications. The comparators that capture fibromyalgia-related symptoms (*i.e.* Pain VAS, FIQ total score, FIQ Pain, FIQ item 16 and item 17) yielded the smallest Fatigue VAS improvements in the non-responder groups (mean change from -5.60 to -8.79) (Fig. 3). It should be noted that the Fatigue VAS asked about the current level of fatigue 3 times a day, via an electronic diary; the FIQ asks about tiredness over the last 7 days; the SF-36™ asks about vitality over the last 4 weeks; and the FOSQ does not specify a recollection period. Considering this difference in the fatigue reporting "timeline", the strong correlation of the 4 scales is all the more impressive.

Table II. Clinical trials: demographic and medical information (n=1,121).

	Fatigue VAS in Trial 1 n=548 (%)	Fatigue VAS in Trial 2 n=573 (%)
Age Mean (SD) [range]	47.0 (11.26) [18–79]	46.6 (10.72) [19–80]
Gender: Female	500 (91.2)	513 (89.5)
Race/Ethnicity		
Am. Indian or Alaska Native	6 (1.1)	3 (0.5)
Asian	7 (1.3)	4 (0.7)
Black/African American	33 (6.0)	39 (6.8)
White/Caucasian	498 (90.9)	524 (91.4)
Other	4 (0.7)	3 (0.5)
Time since first fibromyalgia symptoms		
Mean (SD) [range]	9.7 (8.49) [0–47]	9.7 (8.75) [0–51]
Median	7.0	8.0
Time since first fibromyalgia diagnosis		
Mean (SD) [range]	5.9 (6.75) [0–39]	4.9 (5.61) [0–48]
Median	4.0	3.0

Table III. Clinical trials: baseline fatigue and pain VAS scores (n=1,121).

	Fatigue VAS in Trial 1 n=548			Fatigue VAS in Trial 2 n=573		
	Placebo	Sodium oxybate 4.5g	Sodium oxybate 6g	Placebo	Sodium oxybate 4.5 g	Sodium oxybate 6g
Fatigue VAS						
Mean	73.55	72.88	74.56	73.48	71.14	71.53
(SD)	(13.31)	(13.92)	(13.81)	(15.03)	(15.44)	(17.23)
Range	36.5–99.2	30.9–99.3	39.0–100.0	7.5–100.0	23.1–100.0	8.6–99.9
Median	73.9	73.6	75.2	74.3	72.2	73.8
Pain VAS						
Mean	71.58	71.87	72.30	72.57	70.52	72.22
(SD)	(12.95)	(12.69)	(13.42)	(12.90)	(13.03)	(13.98)
Range	48.4–99.8	45.1–99.7	48.0–99.9	50.1–100.0	45.0–100.0	45.4–100.0
Median	70.7	71.0	71.4	72.8	69.5	72.2

Table IV. Correlations between the Fatigue VAS change from baseline and the Comparison Scales change from baseline.

	Fatigue VAS in Trial 1 n=548	Fatigue VAS in Trial 2 n=573
High correlations		
Pain VAS	0.90	0.84
FIQ item 16 (“How tired have you been”)	0.87	0.84
FIQ Total score	0.80	0.79
FIQ Pain	0.79	0.73
FIQ item 17 (“How have you felt when you get up in the morning”)	0.76	0.79
FIQ Stiffness	0.73	0.67
Moderate correlations		
FIQ Difficulty with work	0.68	0.68
FIQ Did not feel good	0.61	0.50
SF-36™ Vitality scale	-0.61	-0.62
Low correlation		
FIQ Physical impairment	0.46	0.47
FIQ Anxiety	0.36	0.35
FIQ Work missed	0.32	0.30
FIQ Depression	0.30	0.29
FOSQ Social outcome	-0.24	-0.34
FOSQ Intimate relationships	-0.32	-0.19
FOSQ General productivity	-0.36	-0.42
FOSQ Vigilance	-0.37	-0.42
FOSQ Total score	-0.40	-0.43
FOSQ Activity level	-0.42	-0.46

The Fatigue VAS “responders” demonstrated good agreement with “responders” defined by the most related measures (Table V). Kappa coefficients ranged from 0.61 to 0.80, except for the SF-36™. Vitality and the FOSQ total score, which were moderate and fair, respectively. The good concordance between the Fatigue VAS and the most related concepts in the classification of responders supports the validity and responsiveness of the Fatigue VAS.

The interpretation of the significant findings of the Fatigue VAS from the clinical efficacy analyses was facilitated by developing cumulative distribution curves. The Fatigue VAS and the FIQ item 16 produced similar separation between active and placebo treatment groups (Figs. 4–9).

Evaluation of the cumulative distribution indicated an improvement of -10 points to -40 points in favour of a treatment benefit in the Fatigue VAS and an improvement of between -1 point and -5 points (on a 0–10 scale) in favour of a treatment benefit in the FIQ item 16. These results were replicated with both trials, reflecting similar response patterns with fatigue and tiredness.

Discussion

Herein we report on the content validity of the Fatigue VAS and its ability to measure improvements in fatigue. A qualitative study conducted with 20 subjects with a clinician-confirmed diagnosis of fibromyalgia was designed to elicit subjects’ spontaneous descriptions of fibromyalgia-related fatigue.

Half of the subjects spontaneously used the word “fatigue,” and most of the subjects demonstrated familiarity with this concept when completing the Fatigue VAS. Subjects’ descriptions of fatigue were conveyed through a rich and diverse vocabulary, and its manifestation and impact were fairly consistent across patients. Subjects were queried to obtain a definition of each fatigue-related term they were using. This method of in-depth clarifying continued until no new descriptors could be elicited. While this process of continual probing proved to be extremely thorough, subjects might have begun overanalysing their experience in an

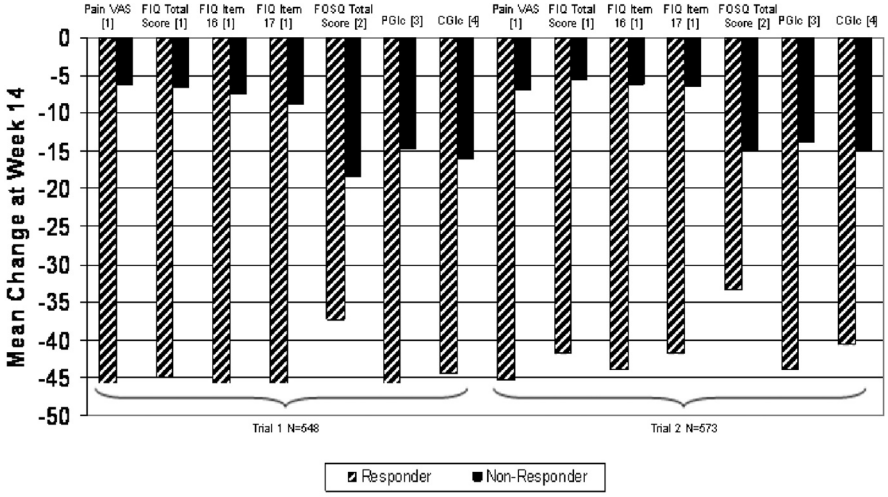

Fig. 3. Known-groups analysis of Fatigue VAS with other scales at Week 14*.
*Mean change in score for responders *versus* non-responders as defined:
[1] A responder is defined as >=30% score reduction from baseline at Week 14.
[2] A responder is defined as change score >= MID (defined by SEM).
[3] A responder is defined as having a response of "Very much better" or "Much better".
[4] A responder is defined as having a response of "Very much improved" or "Much improved".

Table V. Cross classification analysis of responder definitions between Fatigue VAS and other scales.

	Cohen's kappa	
	Trial 1 n=548	Trial 2 n=573
Pain VAS[1]	0.75	0.75
FIQ Total score[1]	0.67	0.68
FIQ Physical impairment[1]	0.34	0.36
FIQ Did not feel good[1]	0.45	0.41
FIQ Work missed[1]	0.31	0.16
FIQ Difficulty with work[1]	0.54	0.56
FIQ Pain[1]	0.70	0.62
FIQ item 16 ("How tired have you been")[1]	0.74	0.68
FIQ item 17 ("How have you felt when you get up in the morning")[1]	0.66	0.69
FIQ Stiffness[1]	0.60	0.61
FIQ Anxiety[1]	0.29	0.35
FIQ Depression[1]	0.29	0.21
FOSQ Total score[2]	0.27	0.28
FOSQ General productivity[2]	0.20	0.27
FOSQ Social outcome[2]	0.12	0.19
FOSQ Activity level[2]	0.28	0.28
FOSQ Vigilance[2]	0.29	0.27
FOSQ Intimate relationships[2]	0.30	0.10
SF-36™ Vitality scale[3]	0.43	0.42
SF-36™ Vitality scale[4]	0.38	0.48
PGIc[5]	0.48	0.44
CGIc[6]	0.42	0.41

[1]A responder for Pain VAS or FIQ scale is defined as a subject with a score reduction of ≥30% from baseline to visit 11.
[2]A responder for FOSQ scale is defined as improvement ≥MID from baseline to visit 11.
[3]A responder for SF-36™ Vitality Scale is defined as 10 points improvement (MID) from baseline to visit 11.
[4]A responder for SF-36™ Vitality Scale is defined as 5 points improvement (MID) from baseline to visit 11
[5]A responder for PGIc is defined as a response of "Very much better" or "Much better" from baseline to visit 11.
[6]A responder for PGIc is defined as a response of "Very much improved" or "Much improved" from baseline to visit 11.

effort to distinguish between overlapping sensations. In addition, although the education level of the sample was heterogeneous, the authors did not control for time since diagnosis of fibromyalgia nor documented patients' knowledge about their condition. Patients might have been aware of the term "fatigue" through patient-directed educational materials or discussion with formal (physician) or informal (support group) sources.

To avoid recall bias, subjects were not asked to compare their current level of fibromyalgia-related sensation of fatigue with their "normal" tiredness (*i.e.*, before being diagnosed with fibromyalgia); instead, researchers focused on their present experience.

Visual analogue scales (VAS) alongside numerical rating scales and Verbal Rating Scales are the most common ways to measure pain intensity (63) as they are sensitive to treatment effect and distinct from measures of other subjective components of pain such as pain sensations or impact. The Fatigue VAS was developed according to the format of the Pain-VAS that supports the primary endpoint in the two phase III, randomised, placebo-controlled trials considered in the quantitative study. Analyses using the Pain VAS and the Fatigue VAS yielded high correlations (r=0.90) and good agreement (k=0.75).

Fatigue and tiredness are clearly related concepts, as evidenced by correlations higher than 0.80 between Fatigue VAS and FIQ "*How tired have you been*" and "*How have you felt when you get up in the morning*". A recently revised version of the FIQ, the FIQR, refers to "fatigue" in terms of "energy", with the question *"please rate your level of energy"* and the 2 anchors "lots of energy" and "no energy*"* (64). The FIQR "energy" item had a correlation of 0.45 with the "vitality" scale of the SF-36™ and a correlation of 0.61 with the "tiredness" item of the original FIQ, thus providing further evidence that fibromyalgia patients tend to use the terms *"tiredness"*, *"fatigue"* and *"lack of energy"* interchangeably. Interestingly, the recall periods of the various questionnaires, which range from thrice daily (Fatigue VAS), to once a week (FIQ and FIQR)

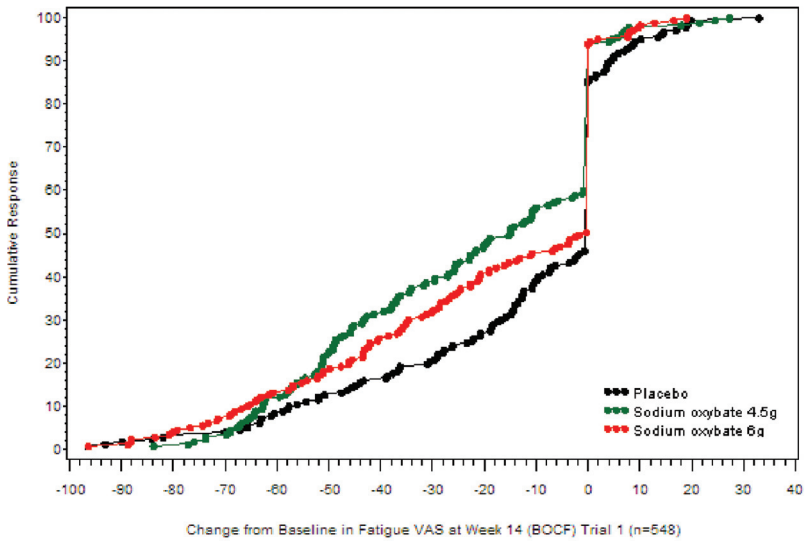

Fig. 4. Cumulative response curves change from baseline in Fatigue VAS (Trial 1, n=548).

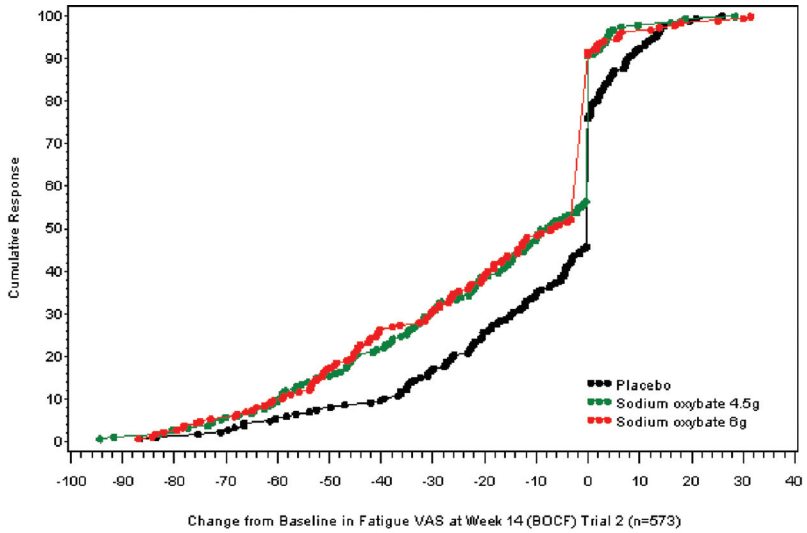

Fig. 5. Cumulative response curves change from baseline in Fatigue VAS (Trial 2, n=573).

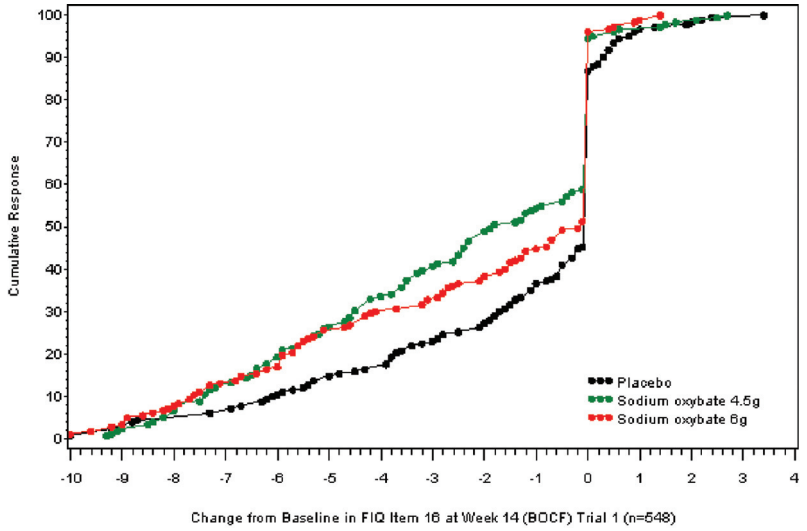

Fig. 6. Cumulative response curves change from baseline in FIQ item 16 ("How tired have you been") (Trial 1, n=548).

and 4 weeks (SF-36™), did not have a significant effect on the reported levels of fatigue; suggesting that fatigue is a pervasive problem for fibromyalgia patients that has little diurnal or quotidian variation.

Furthermore, an analysis of 2 fibromyalgia drug studies demonstrated that changes in the Fatigue VAS clearly discriminated between placebo and treatment groups as well as between treatment responders and non-responders. Although these quantitative analyses were exploratory; replication of the findings in two distinct trials helps to substantiate the validity of these findings.

Overall, these results substantiate the face validity and construct validity of the Fatigue VAS and support its use as a valid endpoint in fibromyalgia clinical trials.

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Contributions of Authors:

- Design and conduct of research study (qualitative): BC, EP, CL
- Analysis and interpretation of the data (qualitative and quantitative): BC, RB, EP, CL
- Preparation, review, and approval of the manuscript: BC, RB, EP, CL

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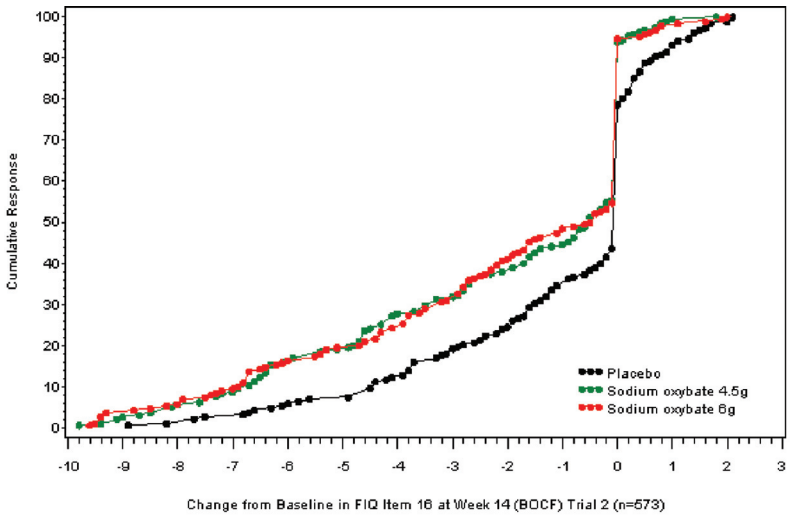

Fig. 7. Cumulative response curves change from baseline in FIQ item 16 ("How tired have you been") (Trial 2, n=573).

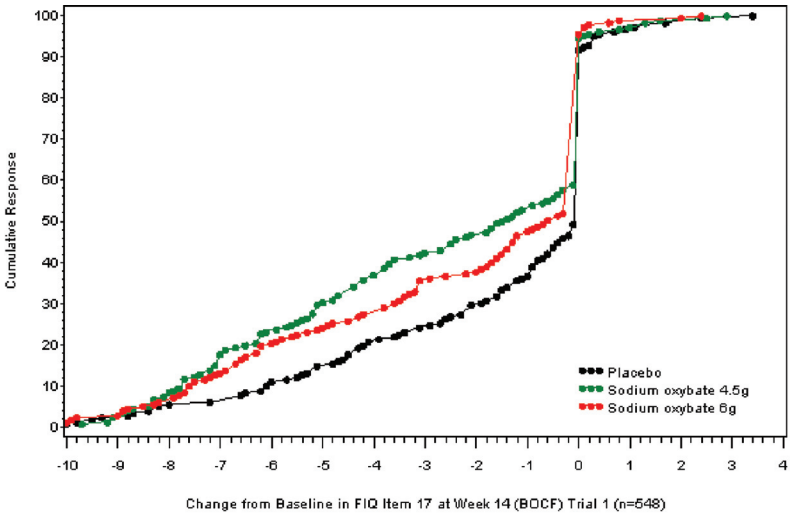

Fig. 8. Cumulative response curves change from baseline in FIQ item 17 ("How have you felt when you get up in the morning") (Trial 1, n=548).

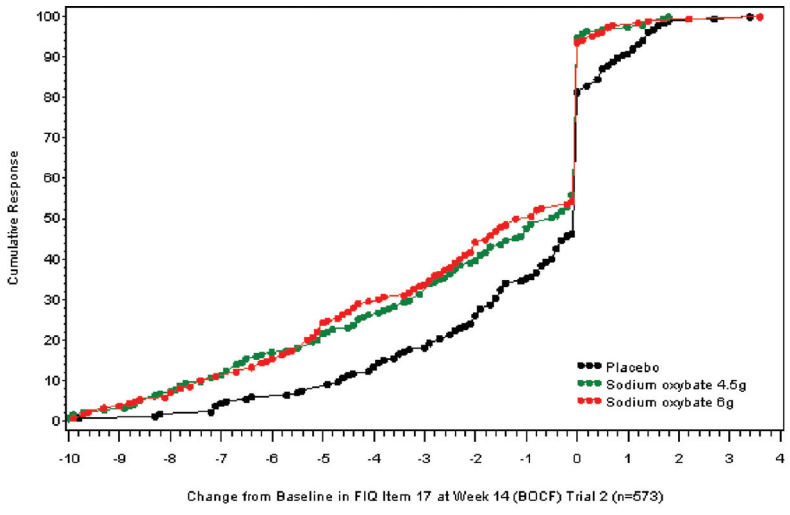

Fig. 9. Cumulative response curves change from baseline in FIQ item 17 ("How have you felt when you get up in the morning") (Trial 2, n=573).

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