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Fatigue: Biomedicine, Health & Behavior

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/rftg20

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To cite this article: Bjørn K. Getz Wold, K. Tveito, A. Angelsen, G. Bringsli, F. Berglund, M. Gustavsen, G. M. Andersen & E. B. Strand (26 Jun 2024): Symptom-based survey diagnoses may serve to identify more homogenous sub-groups of fatigue and postviral diseases, Fatigue: Biomedicine, Health & Behavior, DOI: 10.1080/21641846.2024.2370209

To link to this article: https://doi.org/10.1080/21641846.2024.2370209

Published online: 26 Jun 2024.

FATIGUE: BIOMEDICINE, HEALTH & BEHAVIOR
https://doi.org/10.1080/21641846.2024.2370209

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RESEARCH ARTICLE

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Symptom-based survey diagnoses may serve to identify more homogenous sub-groups of fatigue and postviral diseases

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ABSTRACT

Background and objective: A range of diagnostic criteria are applied for the heterogenous patient group with fatigue or postviral fatigue syndromes with or without Post Exertional Malaise (PEM). We explored whether DePaul Symptom Questionnaires (DSQ) based symptoms reported in an open online survey called MECOV, served to identify more homogenous sub-groups.

Method: Patients living in Norway were invited to participate in an open online survey in 2022. The questionnaire covered diagnostic history, SARS-CoV-2, general health, RAND-36 and DSQ symptoms, treatments and background information.

Results: 2362 patients responded to the survey. 1904 respondents had Fatigue or Postviral disease. 1026 fulfilled CCC criteria with multi-dimensional PEM and 14 h recovery period or ICC criteria for ME. 384 fulfilled IOM/NICE or CCC criteria with only less rigid PEM, while 494 respondents fulfilled only broad fatigue and Fukuda criteria. Self-reported health status, number of treatments tried, and reported effect of activity-based treatments varied significantly across the three groups.

Conclusion: DSQ symptom-based survey diagnoses served to identify more homogenous subgroups of patients with Fatigue or Postviral diseases (ME and CFS) and may serve as a valid supplement to standard medical examinations. Symptoms, treatment, management strategies and further research may gain from being tailored to the three sub-groups.

Acronyms: CBT: Cognitive Behavioral Therapy: CCC: Canadian Consensus Criteria for ME/CFS: CFS: Chronic Fatigue Syndrome: DSQ: DePaul Symptom Questionnaires: DSQ-COVID: DePaul Symptom Questionnaire: Covid: DSQ-PEM: DePaul Symptom Questionnaire: Post-Exertional Malaise: GET: Graded Exercise

ARTICLE HISTORY
Received 8 December 2023
Accepted 14 June 2024

KEYWORDS
Online patient survey; myalgic encephalomyelitis; chronic fatigue syndrome; chronic fatigue; post exertional malaise; Depaul Symptom Questionnaires

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Therapy: ICC: International Consensus Criteria for ME, CFS: IOM: Institute of Medicine: LP: Lightning Process: ME: Myalgic Encephalomyelitis / Encephalopathy: MECOV: Survey for ME and Covid-19: NICE: National Institute for Health and Care Excellence: PEM: Post-Exertional Malaise: RAND-36: The RAND Short Form Health Survey.

Introduction

In 2015, a large meta study commissioned by the US health authorities stated that Chronic Fatigue, Chronic Fatigue Syndrome (CFS) and Myalgic Encephalomyelitis (ME) are 'serious, debilitating conditions that affect millions of people … around the world' [1]. The Institute of Medicine (IOM) report added: 'Diagnosing ME/CFS in the clinical setting remains a challenge. Patients often struggle with their illness for years before receiving a diagnosis' [1]. The report initiated discussions on both diagnostic criteria and recommendations for management, care and treatment of patients with ME/CFS. In 2018, the health authorities in US issued new recommendations for treatment and care for ME/CFS [2]. The National Institute for Health and Care Excellence (NICE) in the U.K. followed a similar path in 2021 [3].

There are a range of diagnostic definitions. The broadly conceived Oxford criteria [4] from 1991 focused on fatigue. The more delineated Fukuda criteria [5] from 1994 included a larger range of symptoms including optional post exertional malaise (PEM), but only required the symptoms to be mild and a little of the time. The more restrictive Canadian Consensus Criteria (CCC) [6] from 2003 required symptoms to be of moderate severity and about half the time, and included PEM due to physical activity as a mandatory symptom. The International Consensus Criteria (ICC) [7] extended the definition of PEM as an exertion-induced worsening of symptoms triggered by excessive activity (physical, mental, or social) as a critically important feature. PEM requiring a 'pathologically slow recovery period – usually 14 hours or longer' [6], is mandatory for CCC and ICC, optional for the Fukuda diagnosis, but not included in the Oxford criteria. The revised diagnostic recommendations of the IOM in US and NICE in U.K. both presented PEM as the cardinal or hallmark symptom of ME/CFS [1,3], but reduced the list of symptoms included. The criteria were followed by a recommendation to avoid activity-based treatments such as Cognitive Behavioral Therapy (CBT) with Graded Exercise Therapy (GET) and Lightning Process (LP). This link between diagnostic criteria and recommendations to avoid certain treatments addressed the core challenge behind this study. Broad diagnostic criteria may identify a large heterogenous group such patients with fatigue. A treatment causing deterioration for patients with PEM, and improvement for fatigue patients who gain from activity, may easily be misinterpreted. Hence the scientific rule of precise identification of patients is especially essential for a heterogenous group as ME/CFS and fatigue.

Several studies have addressed variations in the severity of fatigue in ME/CFS linked to bio-medical factors as cytokine signatures [8], lactate accumulation and corresponding levels of PEM [9], mitochondrial and glycolytic impairments [10], and different brain connectivity due to different risk factors [11]. Different diagnostic criteria for ME/CFS have resulted in different prevalence estimates of fatigue. The National guidelines from 2014/15 in Norway [12] used an estimate of 0.2–0.4 percent referring to a study from

England [13] using Fukuda and CCC criteria. The divergence of estimates is illustrated by a methodological study from 2019 [14], which suggested that 14 out of 15 patients diagnosed with ME/CFS according to the Oxford criteria may not meet the CCC criteria.

Different diagnostic criteria applied in continental European countries

A survey across 17 European countries [15] in 2019 revealed that only five of the countries had national guidelines for diagnosing ME/CFS. Although the Fukuda [5] criteria are recommended most often, the CCC [6], ICC [7] and Oxford criteria [4] are also applied in these countries. The remaining twelve countries – with no national guidelines – apply a diversity of criteria. Based on the work of the European Network on ME/CFS, European diagnosis guidelines were developed in 2021 [16].

Diagnosing patients for care or studies with suspected ME/CFS remains a challenge. One study [17] showed that among a group of patients referred by the family doctor / general practitioner with suspected ME/CFS to the specialist health service for further investigation, an ME diagnosis was confirmed for only a small fraction (13%) of them.

Purpose

The purpose of this study was to assess whether DSQ-based symptom scores can serve to identify subgroups of patients with postviral diseases and fatigue. We addressed patients identifying themselves with Fatigue, Chronic Fatigue, Chronic Fatigue Syndrome (CFS), Myalgic Encephalomyelitis (ME), or Postviral fatigue syndrome. We measured whether they fulfilled the diagnostic criteria for Oxford [4], Fukuda [5], IOM/NICE [1,3], CCC [6], ICC [7], as well as PEM [18] by a symptom-based survey in Norway, called MECOV.

Different treatment recommendations

The recommendation for diagnostic criteria by the Norwegian health authorities was followed by a presentation of treatments for CFS/ME: CBT, GET/training and physical activity, activity and energy regulation, pacing and energy envelope theory either to avoid PEM and stabilize the disease or for partial recovery [12]. On the other hand, the NICE report [3] recommends avoiding specific treatments like CBT and GET. The U.K. and the Norwegian ME-associations carried out coordinated patient-surveys in 2010 and 2012 [19,20] asking for reported effect of various treatments. The MECOV survey includes the various types of treatment and allow for analysis of reported effects across diagnostic group.

A hypothesis that patients with postviral diseases and fatigue may be split in three more homogenous sub-groups

A situation where studies using different diagnostic criteria were followed by different recommendations for treatments, led us to discuss whether it was possible to identify more homogenous subgroups of the large and heterogenous group of patients with a postviral disease or fatigue. The patient representatives in the MECOV study asked us to address how the renewed focus on how both physical, mental and social activities could potentially cause PEM [18] and long recovery could guide the further work.

Given the recent acknowledgement on PEM from Centers for Disease Control and Prevention [2] and NICE [3] we developed our hypothesis that a broad focus on PEM would allow us to identify more homogenous subgroups of patients. The survey data allowed us to test whether health status measured by RAND-36, number of treatments tried, treatment preferences and reported effect of various types of treatment differed between subgroups. The final step in our purpose was to analyse whether any differences between the subgroups could point to recommendations for diagnosis, treatment preferences, and selection criteria suitable for further research.

Methods

Patients were invited to participate in an online survey named MECOV, using a Survey Monkey portal [21] open from June to October 2022. The invitation was published on social media and distributed by patient organizations using the webpage mecov.no. In total, 2362 participants responded to the invitation. Excluding 356 respondents with Long Covid and 102 partial non-responses, 1904 fatigue respondents were included for analysis.

The respondents were allowed to take breaks when answering the questions. We included several screening questions to reduce random partial non-response. Respondents had to actively answer yes or no for suffering from a symptom or trying a treatment before they could continue. The full survey was feasibility-tested in a pilot study. Each respondent who completed the pilot survey was invited for a discussion of their experience and comments by an independent survey specialist or the project leader.

Measures

An introduction to the MECOV questionnaire informed about voluntary, confidential and anonymous participation and asked for the consent of the respondents as required by the EU General Data Protection Regulation following the recommendations by the Norwegian agency ensuring this regulation in research [22].

Modules

Three symptom measurement-modules on fatigue were included in the MECOV questionnaire: DSQ-2 [23], Health Related Quality of Life (RAND-36) [24], and the DSQ-PEM [25], followed by questions on treatment, based upon the two patients surveys in U.K. [19] and Norway [20]. We used the validated translation to Norwegian for DSQ-1 [26], for RAND-36 [27] and the two parallel patient surveys for the treatments [19,20].

We used the symptom measurement in the DSQ-2 [23,28] survey and the DSQ-2 & DSQ-COVID scoring syntaxes[29,30] to identify the diagnostic criteria fulfilled for each respondent. In order to reduce the response-burden we followed the approach used by the DePaul group for the development of the short form DSQ-2 [31], using the load from each symptom for 8 subgroups in a factor analysis. The MECOV questionnaire retained all DSQ-symptoms for three factors (PEM, autonomic, immune). For the other four factors (sleep, pain, neurocognitive, neuroendocrine), half the symptoms were included while ensuring to retain the two symptoms used for the short form DSQ-2

[31] for each factor. This approach allowed us to reduce the number of symptoms with frequency and severity from 54 to 39.

The RAND-36 provides information on health status along eight dimensions. It is validated [24] and allowed for comparison of health status with other diseases and across our sub-groups of fatigue. The MECOV questionnaire included the full RAND-36 set of questions. The RAND-36 scoring syntax [32] allowed us to calculate the score from 0 to 100 for the 8 dimensions.

Three RAND-36 dimensions, role physical, social functioning, and vitality were utilized for both Fukuda – and CCC diagnostic criteria. The remaining five dimensions were applied in the statistical analyses of potential sub-groups in this study.

The DePaul Symptom Questionnaire – Post Exertional Malaise (DSQ-PEM) was developed in collaboration between researchers and patients [18,25]. This questionnaire assessed PEM after physical exertion, mental exertion and social activity exertion within a recovery period of at least 14 h. We term this multi-dimensional PEM.

For each symptom we asked the respondent whether they had the symptom for at least 6 of the last 12 months. We measured frequency on a scale from 1 to 5 (never, a little, some time, most times, and all time) and severity on a scale from 1 to 5 (did not have, mild, moderate, severe, and very severe).

Diagnostic criteria

These modules allowed us to identify the respondents who fulfilled each diagnostic criterion.

Oxford criteria for CFS. The Oxford criteria for CFS from 1991 [4] focused on fatigue and required a severe and disabling fatigue affecting physical and mental functioning for at least half the time with moderate severity for a minimum of 6 months, but not lifelong. Muscle-pain and unrefreshed sleep are recommended included, but not mandatory. They are included in the MECOV algorithms.

Fukuda criteria for CFS. The fulfilment of the Fukuda / Centers for Disease Control and Prevention [5] criteria from 1994 was measured following the DSQ-2 scoring syntax [29] including three RAND-36 dimensions [24]. The Fukuda criteria required that a range of symptoms were experienced at least as mild symptoms at least a little of the time throughout the past 6 months, a reduction in the three RAND-36 dimensions, not lifelong fatigue and at least half the symptom groups. None of these symptom groups, such as PEM, were mandatory.

CCC criteria for ME/CFS. The Canadian clinical working case definition for ME/CFS from 2003 [6], was measured in a similar manner following the DSQ-2 & DSQ-COVID scoring syntaxes [29,30] including the three RAND-36 dimensions [24]. The CCC criteria required that a range of symptoms were experienced at least as moderate symptoms for at least about half the time throughout the past 6 months for a range of 8 symptom groups, a reduction in the three RAND-36 dimensions, and not lifelong fatigue. Most of the symptom groups, such as PEM, were mandatory.

ICC criteria for ME. The International Consensus Criteria for ME from 2011 [7] required at least a 50 percent reduction in activity, and was measured in a similar manner following the DSQ-2 & DSQ-COVID scoring syntaxes [29,30]. The ICC addressed a comprehensive list of symptom groups and required that these were experienced with at least moderate symptoms for at least about half the time throughout the past 6 months, and PEM.

IOM/ NICE criteria for ME/CFS. The IOM/NICE criteria [1,3] were based upon the DSQ-2 & DSQ-COVID scoring syntaxes [29,30], including the three RAND-36 dimensions [24], and not lifelong fatigue. The IOM/NICE criteria addressed a shorter list of symptom groups and required that the symptoms were experienced with at least moderate symptoms for at least about half the time throughout the past 3 months for NICE, and the past 6 months for IOM. PEM is a required symptom.

Post-exertional malaise. Apart from the Oxford criteria, PEM was included as a symptom in the other diagnostic criteria. Both focus and measurement of PEM had however changed. PEM was not mandatory in the Fukuda criteria [5], had a focus on physical effort in the CCC criteria [6], and was presented as the hallmark symptom of the ICC [7] and IOM/NICE criteria [1,3]. PEM was measured in different manners, by a single Likert scale [33], a longer symptom list with a focus on physical efforts [28] or a combination of physical, mental and social activities and the required restitution [18]. We identified multidimensional PEM as patients experiencing exertional malaise after both physical and mental/social efforts above their threshold requiring a long recovery period.

Diagnostic groups – a hypothesis

Based upon the focus on PEM as the hallmark symptom in both the rigid diagnostic ICC criteria [7] and the recent diagnostic criteria IOM / NICE [1,3], the MECOV-team raised the issue of whether sub-groups of patient could be identified following the PEM-approach by Cotler et al. [18]. That hit a nerve in the reference group of patients. As one of them said: 'I may go for a short walk, but if I also have to meet and talk to people it becomes too much. Then I need several days to recover'. The hallmark focus and such comments allowed the MECOV-team to identify three potentially more homogenous sub-groups of patients with fatigue and postviral diseases.

It is essential to stress that this was only a hypothesis. If the hypothesis was valid, we expected the three groups to show different health status as measured by RAND-36, different number of treatments tried, different treatment preferences and different reported effect of various types of treatments. We used the MECOV survey data to test this hypothesis.

The definition and algorithms for these three groups were as follows:

- Group 1: 'Fatigue' with not lifelong fatigue, possibly fulfilling the Oxford and/or the Fukuda criteria, but not CCC, ICC or IOM/NICE criteria.
- Group 2: 'ME with less rigid PEM' fulfilling the CCC and possibly IOM/NICE, but not the ICC, nor the multidimensional PEM.

- Group 3: ME with multi-dimensional PEM' fulfilling all diagnostic criteria from Fukuda to CCC with multi-dimensional PEM and long recovery and/or ICC.

Treatments

The module of treatments builds upon two patient surveys in U.K. [19] in 2010 and Norway [20] in 2012 asking respondents for experienced effect of each treatment tried. A draft list of health sector treatments, alternative treatments and nutritional/ diet treatments was discussed in the focus groups and subsequently adjusted.

The MECOV survey asked respondents to report the experienced effect of twelve non- or low-activity-based treatments, eight activity-based treatments and six nutritional/ diet treatments for all diagnostic groups.

Data analysis methods and tabular presentations

The initial data file from Survey Monkey was transformed for further analysis using Statistical Package for Social Sciences 28 [34]. For means, we applied an Anova test for ordinal variables, presenting F-values and level of significance. We recorded the total number of treatments tried. For the distribution of treatments tried in the various sub-groups we looked at the treatments tried by at least 100 respondents.

Data availability and ethical approval

Anonymous data will be made available upon reasonable request for re-analysis by research institutions six months after publication of this paper. The study applied to the Norwegian centre for research data (now renamed Norwegian agency for shared services in education and research) for ethical approval, and a waiver was granted; data based on a completely anonymous online survey does not require ethical approval [22]. We followed their recommendations for information to participants such as stressing voluntary participation and anonymity.

Results

Sample bias and robustness of covariation and cross-sectional analysis

An open online survey as our study, faces a potential sample bias. We mitigated this by two strategies. Firstly, we compared the distribution of background variables in our sample with other studies of ME/CFS patients [35] and the national population [36] to look for specific bias. In summary, the comparison showed a clear group bias in the sample along chronic female disease dimensions as low income and economic activity, but no group bias along other dimensions.

Our second strategy for controlling a potential bias was to split the sample in two, based upon the time of participation in the study. We asked patient-organizations to invite their communities to participate. We would expect that the first round of respondents was especially concerned respondents, either very satisfied or very unsatisfied with the service from the health sector and the reported effect of any treatment.

Hence, we tested the share fulfilling each diagnostic criteria, number of treatments and reported effect of each treatment across two groups of early response and late response.

This test of a sample bias confirmed that there may be a small bias in the estimation of single variables, but that the cross-sectional analysis was robust across the symptom-based diagnostic groups.

DSQ symptom-based survey diagnoses of fatigue patients

There is a clear pattern in the proportion of respondents fulfilling the various diagnostic criteria. The Oxford criteria limited to fatigue, but strict on severity and frequency covered two of three respondents (64%). The criteria covering a larger range of symptoms, Fukuda, CCC and ICC, identify a decreasing share of respondents from three of four (76%) based on Fukuda not requiring PEM, to a large majority (58%) based on CCC requiring physically based PEM, and around one of three (35%) based upon ICC with a multi-dimensional PEM. The IOM/NICE criteria with a simplified and shorter list of symptoms are fulfilled by three of four (73%) respondents. More than half (59%) of the respondents fulfil the multi-dimensional PEM criteria. As expected, there is only a partial overlap between CCC and multi-dimensional PEM. Less than half (46%) of the respondents fulfil both the CCC criteria and multi-dimensional PEM. Around half the respondents (54%) fulfil either both CCC and PEM, ICC or all three.

We used the information presented in Table 1 of diagnostics group criteria fulfilled in a stepwise approach to identify the three potentially more homogenous sub-groups of fatigue patients based upon how rigid diagnostic and PEM criteria fulfilled:

- Group 1: 'Fatigue' covered 494 respondents (26%), who fulfilled the criteria for fatigue for at least 6 months, but not lifelong. They did not fulfil the IOM/NICE, the CCC, nor the ICC criteria, while some (19%) met the Fukuda criteria and some (26%) the Oxford criteria.
- Group 2: 'ME with less rigid PEM' covered 384 respondents (20%) fulfilling both the Fukuda, the IOM/NICE and the CCC criteria, but neither the multi-dimensional PEM nor the ICC criteria.
- Group 3: 'ME with multi-dimensional PEM' covered approximately half the sample (54%) of respondents (1026). They fulfilled all the diagnosis criteria from Fukuda to CCC with multi-dimensional PEM and/or ICC.

As shown in Table 2a, there was a significant correlation (<0.001) between the level of reduced activity due to symptom severity and the three symptom-based diagnostic groups. The physical functioning and general health dimensions decreased significantly ($p < 0.001$)

Table 1. Fatigue patients fulfilling symptom-based survey diagnostic criteria and combinations.

	Diagnostic criteria						Combinations of diagnostic criteria		
n = 1904*	Oxford	Fukuda	IOM/ NICE	CCC	ICC	DSQ-PEM	CCC & DSQ-PEM and/or ICC	Fukuda, IOM/ NICE and/or CCC, not DSQ-PEM nor ICC	Only fatigue and/or Oxford, Fukuda
Percentages	64	76	73	58	35	59	54	20	26
Number	1210	1454	1381	1110	672	1125	1026	384	494

Source: The MECOV online survey in Norway, June–August 2022, respondents with ME, CFS or fatigue, but not Long Covid.

Table 2. RAND-36 scores and number of treatments tried by diagnostic group.

Table 2a. RAND-36 Health related quality of life scores by diagnostic group

Diagnostic group*	Group 1		Group 2		Group 3			
	Mean (SD)	N	Mean (SD)	n	Mean (SD)	n	F-value	*p*
Physical functioning	41 (24)	531	39 (22)	412	31 (20)	1110	46.18	<0.001
Bodily pain	52 (24)	530	53 (23)	413	43 (19)	1109	51.19	<0.001
General health	35 (17)	411	33 (15)	412	28 (15)	1110	40.56	<0.001
Role-emotional	72 (42)	515	72 (42)	404	72 (42)	1092	0.16	0.852
Mental health	73 (18)	412	74 (15)	413	72 (17)	1110	2.33	0.098

Table 2b. Number of treatments tried by diagnostic group.

Diagnostic group*	Group 1		Group 2		Group 3		F-value	*p*
Number of treatments tried	No (SD)	n	No (SD)	n	No (SD)	n		
	1.85 (3.91)	494	5.05 (5.20)	384	7.13 (5.40)	1026	185.82	<0.001

*Diagnostic groups:
Group 1 Respondents with fatigue and possibly fulfilling Oxford and/or Fukuda criteria.
Group 2 Respondents fulfilling Fukuda, IOM/ NICE and/or CCC criteria, but not DSQ-PEM nor ICC criteria.
Group 3 Respondents fulfilling CCC & DSQ-PEM criteria and/or ICC criteria.

from Group 1 to Group 2 and 3, while the bodily pain dimension increased significantly ($p < 0.001$). The emotional role functioning and mental health dimensions were not correlated.

Treatment patterns, reported effect of treatment types in each diagnostic group

We expected that for more severe respondents the need to try new treatments would lead them to overcome the extra effort. As shown in Table 2b, this was confirmed by a significant ($p < 0.001$) and large increase with the severity of the diagnostic group, respondents in more severe diagnostic groups tried a double (1.85 – > 5.05) or triple number of treatments (1.85 – > 7.13).

To compare the reported effect across the three MECOV diagnostic groups as shown in Table 3, we used a Likert scale with five values from a large deterioration (1), deterioration (2), no effect (3), improvement (4) to large improvement (5). We present the reported effects of all 26 treatments across all diagnostic groups starting with the treatment with the highest share with an improvement (either large improvement or improvement). We present the reported effects in percentages for each diagnostic group for the 21 of 26 treatments tried by at least 100 respondents.

There were three major findings. First, Pacing below the energy threshold (3.70), Adapted diets (3.49), and Low dose naltrexone (3.33), all gave a reported positive impact on the symptoms and disease for all MECOV diagnostic groups. The reported effect of Pacing was significantly ($p = 0.002$) higher in the less severe diagnostic group, but gave a reported positive effect in all groups.

Second, a number of other treatments were reported to give a higher share of respondents an improvement rather than a deterioration: Amino acids, B vitamins / high dose B1 B12, Mindfulness, Physiotherapist, Minerals, Antibiotics, Nevro-/Chiropractor, D vitamins / Fatty acids / Omega3 / Q10, Qigong, Acupuncture, Nutrition with antioxidants, Rehab-centre, Homeopathy. But for all these treatments, the type value reported effect was *no effect*. For the treatments tried by less than 100 respondents, the most common reported effect was *improvement* for Saline infusion and Immunoglobulin. *No effect* was the most common reported effect for Immunomodulatory drugs, Abilify / Attention-deficit hyperactivity disorder drugs, and Antiviral drugs.

Table 3. Reported effect of 26 treatments by diagnostic group.

		Reported effect in percentages 1 – Large deterioration to 5 – Large improvement									
Treatment	Diagnostic group*	Large det. 1	Det. 2	No eff. 3	Imp. 4	Large imp. 5	All	n	Mean	SD	F / sig.
Pacing below threshold	G 1	0	1	18	71	10	100	78	3.90	0.57	F
	G 2	1	1	25	64	9	100	170	3.78	0.67	6.142
	G 3	1	2	31	60	5	100	610	3.65	0.68	*p*
	All	1	2	29	61	6	100	858	3.70	0.67	0.002
Saline infusion – numbers	All	0	0	24	28	6		58	3.69	0.65	
Immuno-globulin – numbers	All	1	3	10	13	6		33	3.61	1.00	
Food mapping and diet	G 1	0	3	53	29	14	100	58	3.53	0.78	F
	G 2	1	2	55	37	6	100	123	3.45	0.67	0.419
	G 3	0	4	46	45	5	100	494	3.50	0.66	*p*
	All	0	3	48	42	6	100	675	3.49	0.67	0.658
Low dose naltrexone	G 1	3	6	53	35	3	100	34	3.29	0.76	F
	G 2	0	14	47	31	9	100	81	3.35	0.82	0.048
	G 3	3	8	49	35	6	100	313	3.33	0.82	*p*
	All	2	9	49	34	6	100	428	3.33	0.81	0.658
Abilify/ Att.-deficit hyperactivity disorder drugs – numbers	All	2	7	23	15	1		48	3.13	0.84	
Amino acids	G 1	0	0	71	24	5	100	21	3.33	0.61	F
	G 2	2	4	68	21	4	100	47	3.21	0.51	0.366
	G 3	0	3	65	30	2	100	169	3.31	0.56	*p*
	All	0	3	66	27	3	100	237	3.30	0.55	0.694
B vitamins high dose B1 B12	G 1	0	1	66	28	5	100	76	3.37	0.58	F
	G 2	0	1	70	28	1	100	142	3.30	0.69	0.575
	G 3	0	1	68	28	3	100	503	3.33	0.57	*p*
	All	0	1	68	28	3	100	721	3.33	0.59	0.564
Mind-fulness	G 1	0	4	58	36	2	100	50	3.36	1.41	F
	G 2	1	2	61	36	1	100	115	3.34	0.30	0.904
	G 3	1	5	69	24	0	100	419	3.17	0.96	*p*
	All	1	5	67	27	1	100	584	3.22	0.88	0.412
Immuno-modulatory drugs – numbers	All	3	2	31	11	4		51	3.22	0.68	
Antiviral drugs – numbers	All	0	3	39	14	4		60	3.32	0.58	
Physio-therapist	G 1	0	10	59	28	3	100	71	3.24	0.58	F
	G 2	5	16	53	24	3	100	152	3.05	0.50	0.167
	G 3	4	15	56	23	2	100	560	3.04	0.49	*p*
	All	3	15	56	24	2	100	783	3.06	0.50	0.846
Minerals Mag-nesium Iodine Selenium	G 1	0	2	72	22	5	100	64	3.30	0.66	F
	G 2	0	1	75	22	2	100	138	3.25	0.84	2.030
	G 3	0	1	72	26	1	100	503	3.27	0.77	*p*
	All	0	1	73	25	1	100	705	3.27	0.78	0.132
Antibiotics	G 1	7	4	64	11	14	100	28	3.21	0.99	F
	G 2	3	9	69	14	6	100	35	3.11	0.76	0.331
	G 3	2	7	63	20	8	100	183	3.23	0.78	*p*
	All	3	7	64	18	8	100	246	3.22	0.80	0.719
Nevro Chiro-practor	G 1	0	0	66	28	7	100	29	3.41	0.63	F
	G 2	4	16	51	27	1	100	73	3.05	0.81	3.235
	G 3	2	9	68	20	1	100	260	3.10	0.64	*p*
	All	2	10	64	22	2	100	362	3.11	0.68	0.041
D vitamins fatty acids Omega3 Q10	G 1	0	0	77	19	3	100	88	3.26	0.51	F
	G 2	0	0	82	17	1	100	188	3.19	0.42	0.731
	G 3	0	0	79	20	1	100	620	3.22	0.46	*p*
	All	0	0	79	19	2	100	896	3.22	0.45	0.482

(*Continued*)

Table 3. Continued.

Treatment	Diagnostic group*	Reported effect in percentages 1 – Large deterioration to 5 – Large improvement: Large det. 1	Det. 2	No eff. 3	Imp. 4	Large imp. 5	All	n	Mean	SD	F / sig.
Qigong	G 1	6	6	50	31	6	100	16	3.25	0.93	F
	G 2	6	3	72	19	0	100	32	3.03	0.69	1.284
	G 3	3	18	62	16	1	100	110	2.95	0.70	*p*
	All	4	14	63	18	1	100	158	2.99	0.73	0.280
Acupuncture	G 1	0	0	80	20	0	100	40	3.20	0.41	F
	G 2	1	1	79	19	0	100	75	3.15	0.48	1.244
	G 3	1	8	72	18	0	100	279	3.08	0.57	*p*
	All	1	6	74	18	0	100	394	3.10	0.54	0.289
Nutrition with antioxi-dants	G 1	0	0	84	16	0	100	25	3.16	0.37	F
	G 2	0	0	84	14	2	100	44	3.18	0.45	0.070
	G 3	1	2	77	19	2	100	178	3.20	0.51	*p*
	All	0	1	79	18	2	100	247	3.19	0.49	0.932
Rehab centre	G 1	14	16	43	23	5	100	44	2.89	1.06	F
	G 2	16	22	45	15	3	100	109	2.67	1.00	5.108
	G 3	20	30	35	14	1	100	425	2.45	0.99	*p*
	All	19	28	38	15	2	100	578	2.53	1.00	0.006
Homeopathy	G 1	0	0	84	16	0	100	19	3.16	0.37	F
	G 2	3	9	75	13	0	100	32	2.97	0.59	1.558
	G 3	2	1	81	15	2	100	133	3.14	0.51	*p*
	All	2	2	80	15	1	100	184	3.11	0.52	0.213
Training to cope with ME	G 1	2	6	69	19	4	100	48	3.17	0.69	F
	G 2	2	17	60	19	3	100	114	3.04	0.73	9.720
	G 3	6	22	60	12	0	100	451	2.79	0.74	*p*
	All	5	19	60	14	1	100	613	2.87	0.75	0.000
Graded exercise training	G 1	23	31	35	12	0	100	26	2.35	0.46	F
	G 2	30	48	20	2	2	100	61	1.98	0.59	4.244
	G 3	35	46	13	6	0	100	245	1.90	0.69	*p*
	All	33	45	16	6	0	100	332	1.95	0.66	0.015
Psychiatrist Psychologist	G 1	0	11	79	9	0	100	53	2.98	0.98	F
	G 2	4	7	79	10	1	100	114	2.97	0.85	3.280
	G 3	7	15	71	6	1	100	417	2.80	0.85	*p*
	All	5	13	73	7	1	100	584	2.85	0.86	0.039
Cognitive therapy and graded exercise training	G 1	12	35	29	18	6	100	17	2.71	1.10	F
	G 2	20	52	20	8	0	100	50	2.16	0.84	4.574
	G 3	28	44	23	5	0	100	217	2.05	0.86	*p*
	All	26	45	23	6	1	100	284	2.11	0.88	0.011
Lightning Process	G 1	21	21	43	7	7	100	14	2.57	1.16	F
	G 2	37	21	37	5	0	100	19	2.11	0.99	1.892
	G 3	40	25	31	3	1	100	72	2.00	0.98	*p*
	All	37	24	33	4	2	100	105	2.10	1.01	0.156

* Diagnostic groups:
G 1 Respondents with fatigue and possibly fulfilling Oxford and/or Fukuda criteria.
G 2 Respondents fulfilling Fukuda, IOM/ NICE and/or CCC criteria, but not DSQ-PEM nor ICC criteria.
G 3 Respondents fulfilling CCC & DSQ-PEM criteria and/or ICC criteria.

Third, each of the three types of activity-based treatments were associated with a deterioration of disease and symptoms for all three MECOV diagnostic groups combined, with strong negative net reported effects (1.95–2.11). There was a clear difference between Group 1 and the two other groups. Even for the respondents in Group 1, there was a reported effect of deterioration or no reported effect (1.95–2.11), but some experienced improvement. Respondents in Group 2 and Group 3 had a different experience. There was a significant difference across the three groups for CBT ($p = 0.011$) and for GET ($p = 0.039$). A mean of around 2 or even below showed that the average reported

experience was a deterioration, with a large deterioration for a substantial share and no reported effect for an equal share. As revealed by the figures, a few patients (5-6%) in Group 2 and Group 3 experienced improvement, but a larger share (31-34%) reported a large deterioration by these treatments.

Discussion

The study confirmed that symptom-based survey diagnoses including extended measures of multi-dimensional PEM with various recovery period may serve to identify 3 more homogenous sub-groups of patients with postviral and fatigue diseases. The three groups included a Group 1 Fatigue patients, a Group 2 ME patients with less rigid, but still physical PEM with a shorter recovery period and a Group 3 ME patients with multi-dimensional PEM and at least 14-hours recovery period. We observed significant differences in health status, treatment pattern and reported effect of treatments. The score in the RAND-36 physical health dimensions were lower in Groups 2 and 3 with a higher symptom burden. The number of reported treatments tried was significantly higher and doubled from Group 1 to Group 2 and with another 50 percent further to Group 3.

The main difference between groups was the reported effect of activity-based treatment. In Group 1 with respondents with less severe symptoms there was *relatively* more reported positive effects with treatments like CBT, GET and LP. While around half (43–53%) of the respondents reported deterioration rather than improvement, it is important to acknowledge that some patients with fatigue without PEM did report an improvement with treatments such as CBT, GET and LP. If such patients are included in a study jointly with patients from Group 2 and 3 with ME with PEM, this may lead to false study results. Such a study may conclude that CBT, GET and LP may have helped some ME-patients to recover, while it actually could have been only patients with fatigue and depression who did recover. The level of reported deterioration was considerably larger and experienced by a large majority in Group 2 (60–77%) and Group 3, (67–80%). Two types of treatment, pacing within the patients' activity threshold and adapted diets reportedly improved symptom severity in all the three groups.

These findings are all in line with patient surveys from U.K. and Norway [19,20,37] for the large heterogenous group of fatigue patients. Pacing within the patients' activity threshold reportedly improved or reduced the symptom severity, while activity-based treatment on average increased the reported symptom severity.

As stated in our overview of diagnostic criteria applied in continental European countries, few studies have identified more homogeneous sub-groups of patients in order to test any differences. One study raised the issue, but due to a too limited measure of PEM, was not able to identify proper sub-groups [38]. Another study have tested a similar split of the large heterogenous group of fatigue patients [35]. This study used the same validated symptom-based survey diagnostic instruments as in our study [18,23,24,30] and identified two more homogenous sub-groups fulfilling either the Fukuda- or the CCC-criteria and measured the PEM score. The study focused on common interventions rather that treatment and did not allow for identification of activity-based interventions.

Overall, we found that other studies had been able to split the heterogenous group of patients with fatigue-diseased in more homogenous sub-groups *or* to measure that

activity-based therapies may cause deterioration rather than improvement. But unfortunately, other studies have not been able to combine these two approaches.

Strength and limitations of data and analysis

The survey modules asking for frequency and seriousness of symptoms are based upon standardized and validated symptom descriptions used to test the fulfilment of diagnostic criteria and various dimensions of PEM [18,23–25,28]. The modules on treatments are developed and discussed in patient communities and tested and analysed in patient surveys in U.K. and Norway [19,20,39].

As for all cross-sectional data it is hard to disentangle causality and relationship between diagnosis and reported effect. Pacing below threshold gave a larger improvement for patients in diagnosis Group 1 that Group 2 and 3. The order of causality may theoretically be that patients in Group 2 and 3 tested pacing below threshold with a positive impact and hence managed to reduce their symptoms and move up to Group 1 before reporting in the survey. Likewise, activity-based treatment tended to give more negative effect for patients in Groups 2 and 3. We may tend to assume this is because such treatment is too hard for patients in these two more severe groups. But theoretically, the order of causality could also be that a patient in group 1 tested activity-based treatment with a negative impact and hence ended up in group 2 or 3 before reporting in the survey. While de do not find any support for this order of causality in recent large meta-studies, as the NICE-study [3], nor this survey, it is still possible. On the other hand, a causal order from diagnostic groups to the effect of different treatments is more in line with findings in recent large meta-studies like NICE [3]. However, only a panel study may validate the causal order.

The analysis of the potential bias in our sample of patients compared with the overall population showed a group bias along chronic female disease dimensions as low income and economic activity as other surveys for patient with fatigue and postviral diseases in Norway [20,35,37], but no group bias along other dimensions. The data showed a strong robustness for cross-sectional analysis across all diagnosis groups. This analysis confirmed that cross-sectional association analysis, such as between diagnostic group and reported effect of treatment, was not likely to be affected by any sample bias.

Conclusion

DSQ symptom-based survey diagnoses of diagnostic criteria and PEM may serve as a valid supplement to the standard medical examination for fatigue patients and can be used to identify sub-groups of patients with fatigue and postviral diseases (ME, CFS). A brief questionnaire to measure the symptom-based survey diagnoses based upon DSQ questionnaires in the national language could be validated, reviewed and adapted in cooperation with patient organizations. The results indicate that the treatment of symptoms should be tailored to the specific sub-group. The modules on symptom-based survey diagnoses may gain from being combined with modules measuring the reported effect of various types of treatment. Based on the answers in the survey, all patients with fatigue or postviral diseases (ME, CFS) are likely to gain from a pacing regime below their activity threshold, nutritional treatment, and adapted diets. The worsening of symptoms

reported with activity-based treatments, indicate that these treatments should not be offered to postviral (ME, CFS) patients. The different reported effect of activity-based treatment across the three groups stressed the need to identify the sub-groups in any study of the large heterogenous groups of patients with postviral diseases (ME, CFS) and fatigue.

Acknowledgements

Leonard A Jason (DePaul University), Nina Langeland (University of Bergen), Kristian Sommerfelt (University of Bergen), the DAM Health Foundation, the survey test group, and the survey participants.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by The DAM foundation / DAMnett: [Damnett project no. 2021/HE2-378466].

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