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Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (MCAM): Design and Implementation of a Prospective/Retrospective Rolling Cohort Study

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Abstract

In the Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (MCAM), we relied on expert clinician diagnoses to enroll patients from 7 specialty clinics in the United States in order to perform a systematic collection of data on measures of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS). Healthy persons and those with other illnesses that share some features with ME/CFS were enrolled in comparison groups. The major objectives were to: 1) use standardized questionnaires to measure illness domains of ME/CFS and to evaluate patient heterogeneity overall and between clinics; 2) describe the course of illness, identify the measures that best correlate with meaningful clinical differences, and assess the performances of questionnaires as patient/person-reported outcome measures; 3) describe prescribed medications, orders for laboratory and other tests, and management tools used by expert clinicians to care for persons with ME/CFS; 4) collect biospecimens for future hypothesis testing and for evaluation of morning cortisol profiles; and 5) identify measures that best distinguish persons with ME/CFS from those in the comparison groups and detect subgroups of

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Preliminary findings were presented at the Food and Drug Administration Scientific Drug Development Workshop, April 26, 2013, Bethesda, Maryland. Aspects of the study design were presented to the Institute of Medicine Diagnostic Criteria for ME/CFS Committee (January 27, 2014, Washington, DC), and descriptive data tables on ME/CFS patients were shared with the Institute of Medicine Committee to assist in their decisions.

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persons with ME/CFS who may have different underlying causes. Enrollment began in 2012 and is planned to continue in multiple stages through 2017. We present the MCAM methods in detail, along with an initial description of the 471 patients with ME/CFS who were enrolled in stage 1.

Keywords

chronic fatigue syndrome; myalgic encephalomyelitis; patient-reported outcome measures; study methods

Chronic fatigue syndrome (CFS) has been known by a variety of names, including postinfectious fatigue, myalgic encephalomyelitis (ME), and, more recently, systemic exertion intolerance disease. The condition, hereafter referred to as ME/CFS, is a chronic multisystem illness characterized by reduced functioning associated with fatigue that is not due to ongoing exertion and not significantly improved by rest. Minimal mental or physical exertion may trigger relapse (termed postexertional malaise). Additional core or common symptoms include unrefreshing sleep, cognitive problems, increased symptoms when standing, and pain; however, patients may experience numerous other symptoms.

ME/CFS is a significant public health problem. Estimates from population-based studies indicate that at least 1 million Americans suffer from ME/CFS (1–3). Patients, their families, their employers, and society all bear significant costs associated with ME/CFS, which are estimated to be $18–$51 billion annually in the United States ($9–$14 billion in direct medical costs and $9–$37 billion in lost productivity) (4–6). Yet, ME/CFS remains poorly understood by the health-care community, and patients face significant barriers to receiving the care that they need (7).

Although a number of biologic abnormalities have been found in some groups of people with ME/CFS, to date, none is sufficiently unique or characteristic to be diagnostic. A number of case definitions based on expert opinion have been used in research and for diagnosis (8–11). Although the case definitions share many features, they differ in the number and type of required symptoms. Because studies of ME/CFS use 1 or more case definitions as entry criteria, developing a data-driven case definition has been challenging. In addition, none of the case definitions provides sufficient detail on methods for operationalizing their applications, so differences in details of how the case definition is applied need to be considered (12). Measures of ME/CFS that are reliable and reflect meaningful clinical differences are needed for diagnosis and would also be important when describing the natural history of the illness, categorizing and measuring changes in response to interventions, and identifying patient populations with similar illness profiles for basic research and clinical trials. Systematically studying patients with ME/CFS identified from multiple specialized clinics would provide a mechanism to evaluate measures of ME/CFS. When the ME/CFS patients are identified by clinicians with recognized expertise in diagnosing and treating the condition, the resulting data could also inform case definition questions. In the present article, we describe the Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (MCAM), a multisite clinical study of ME/CFS that was initiated and funded by the Centers for Disease Control and Prevention (CDC).

MCAM was designed to enroll and follow ME/CFS patients recruited from multiple specialized clinics in order to facilitate systematic collection of data on measures of their illness. A key feature was reliance on the clinical experience of physicians who specialize in the identification and management of ME/CFS patients rather than on a prespecified case definition. Healthy persons and those with other illnesses that share some features with ME/CFS were enrolled in comparison groups. In MCAM, our principal objectives were to:

1. Use standardized questionnaires to measure illness domains of ME/CFS and to evaluate patient heterogeneity overall and between clinics;
2. Describe the course of illness, identify measures that best correlate with meaningful clinical differences, and assess the performances of questionnaires as patient/person-reported outcome measures;
3. Describe prescribed medications, orders for laboratory and other tests, and management tools used by expert clinicians to care for persons with ME/CFS;
4. Collect biospecimens for future hypothesis testing and for evaluation of morning cortisol profiles; and
5. Identify measures that best distinguish persons with ME/CFS from those in the comparison groups and determine subgroups of persons who have ME/CFS with different underlying causes.

In the present article, we provide the reader with detailed information on the design of this multisite clinical investigation of ME/CFS, as well as descriptive information about participants enrolled in stage 1.

METHODS

Study overview

MCAM was initiated in 2012 and is anticipated to continue in multiple stages through 2017. In the first stage (stage 1), investigators enrolled only participants with ME/CFS. In stage 2, researchers collected follow-up information from those enrolled in stage 1 and recruited 2 comparison groups: a group of healthy controls and an ill comparison group comprising patients with other chronic illnesses (e.g., fibromyalgia, rheumatoid arthritis, multiple sclerosis, and cardiovascular disease). Biologic samples were also collected. In subsequent stages, an effort was made to recruit ME/CFS patients who had been ill for a short time (<2 years; i.e., incident cases) and those severely affected by ME/CFS (home-bound). The home-bound ME/CFS patients met the following criteria, which were agreed upon by the study clinicians: 1) bedfast or severely house-bound; 2) activity level less than 10% of prior levels; and 3) unable to come to the office without severe consequences. Beginning with stage 2, we permitted enrollment of new participants in the ME/CFS and control groups to replace those who dropped out or were lost to follow-up. The replacement participants had to complete baseline forms in addition to providing any data or biologic samples that were required for the stage at which they were enrolled. Because enrollment began at different times for the ME/CFS, comparison, incident ME/CFS, and home-bound ME/CFS cohorts, the study is considered to have a rolling cohort design.

Study sites

Recruitment and enrollment were conducted through 7 clinics with specialized expertise in and experience with diagnosis and management of ME/CFS: Mount Sinai Beth Israel, New York, New York; Institute for Neuro Immune Medicine, Miami and Fort Lauderdale, Florida; Bateman Horne Center, Salt Lake City, Utah; Hunter-Hopkins Center, Charlotte, North Carolina; Open Medicine Clinic, Mountain View, California; Richard Podell N. Medical, Summit, New Jersey; and Sierra Internal Medicine, Incline Village, Nevada. Five clinics (Bateman Horne Center, Hunter-Hopkins Center, Open Medicine Clinic, Richard N. Podell Medical, and Sierra Internal Medicine) participated through the coordination of the Open Medicine Institute Consortium (Mountain View, California). The present study was approved by the institutional review boards of the CDC, Open Medicine Institute Consortium, Mount Sinai Beth Israel, and Institute for Neuro Immune Medicine.

Enrolled study groups

All participants were enrolled after providing informed consent. ME/CFS patients were those between 18 and 70 years of age who had been diagnosed with CFS, ME, or postinfectious fatigue or who were managed as were other ME/CFS patients in the clinical practice. Each clinician determined patient eligibility using his or her clinical expertise with the condition; patients were not required to fit a specific case definition. The exclusion criteria were onset of illness at an age older than 62 years, human immunodeficiency virus infection, current pregnancy, or dementia. The study was conducted in English, and participants had to be able to read written forms and computer screens at an eighth grade level; however, no formal testing of reading ability was performed.

Participants enrolled as healthy controls were individuals between 18 and 70 years of age who were in good health and had no history of ME/CFS and no other active illnesses. They were enrolled on an approximately 1:1 basis with ME/CFS patients and were matched on sex and age (±5 years). Participants enrolled into the ill comparison group were those between 18 and 70 years of age who had physician-diagnosed fibromyalgia (without ME/CFS), rheumatoid arthritis, Lyme disease, or cardiovascular disease, with a minimum of 50 participants enrolled for each diagnosis. Clinics recruited participants in the comparison groups in a variety of ways, including by posting flyers in the clinics, distributing flyers in the communities, and recruiting from other primary care or specialty clinics in the same institutions or networks.

Clinic staff or study coordinators telephoned patients who were identified by the clinician or through clinical record as potentially eligible for study participation to explain the study to them and to obtain verbal consent for eligibility screening and medical record data abstractions before the clinic visit. Those who were eligible and interested in participating provided signed informed consent via a web-based system (OpenMedNet, Open Medicine Institute) or a paper form at the next clinic visit. Each participant was given a unique study identification number that was used in coding of all data and samples. The linkage of study identification number to personal identifiers was maintained by each clinic and not shared with the CDC. Access to identifiable patient records was limited to the study staff at each clinic and, for those clinics participating through the Open Medicine Institute Consortium,

the Open Medicine Institute coordinating center. No identifying information was recorded on any materials shared with the CDC.

Medical record abstraction

To minimize the burden of the study on the participants, authorized study personnel reviewed participant medical records to abstract information. Forms were developed to standardize collection of data on basic demographic characteristics (age, sex, race, ethnicity, marital status, employment, insurance status, and educational level); history of ME/CFS (date of diagnosis, age at diagnosis, symptoms, and date of symptom onset); medical history (major illnesses before and after 21 years of age, surgeries, major injuries and hospitalizations and age at those events, allergies and sensitivities, and review of organ systems); family history (mother, father, siblings, and children); medication use (prescription and over-the-counter drugs; supplements; herbal, homeopathic and health food preparations; dose and dosing schedule of each; date initiated; and reason for taking); infection and immunization history; and laboratory and test results at the first and most recent visits to the clinic (e.g., complete blood count with differential, blood chemistry, C-reactive protein concentration, antinuclear antibody level, rheumatoid factor level, thyroid-stimulating hormone level, free thyroxine concentration, urinalysis, electrocardiogram, sleep study, and tilt test). In addition, the clinic intake form was copied, stripped of patient identifiers, and scanned to make a portable document format (PDF) copy for data transfer. Data abstractions forms (other than clinical intake forms) are included in the Web Appendix (available at http://aje.oxfordjournals.org/). The study was designed not only to retrospectively abstract participants' medical records before their study enrollment but also to prospectively collect detailed clinical and epidemiologic data.

Measures of ME/CFS illness domains

Standardized questionnaires were used to collect data on symptoms and to measure fatigue, function, pain, sleep, anxiety, depression, quality of life, and illness impact (11, 13–32). The questionnaires are listed in Table 1, with forms and scoring available from the references cited. Anxiety and depression scales were self-administered by participants in the clinic and completed during the visit. All other forms were provided to the patients to complete as they were able, either online or on paper. The study allowed some flexibility in the timeline for completing these forms because the severity of each patient's illness could vary from day to day. Instead, the dates and times at which each form was started and completed were noted. Family members or clinic personnel provided assistance to patients if necessary. Forms were to be completed within 2 weeks of the visit to clinic.

The complete set of forms was collected at the enrollment visit; however, for follow-up, only interim changes in medical history, family history, and medication use were recorded. Likewise, the Brief Pain Inventory (long form) (24) and questionnaires on depression and anxiety were omitted at follow-up, and the CDC Symptom Inventory for chronic fatigue syndrome (13) and questions from DePaul Symptom Questionnaire (11) were shortened to reduce the burden on study participants. Some other forms were modified to adapt to the differing needs of cohorts, such as home-bound patients.

Flow of clinic visit used for study enrollment

Clinic personnel obtained informed consent (if not given previously) and reviewed questionnaires completed by patients at home (Table 1) to check for completeness and to resolve any contradictory or missing information. Clinic staff reviewed the abstracted information on medical history, family history, and medication use with the participants to verify the data and add any missing information. Participants were also asked to complete the 3 forms reserved for completion at the clinic (28–32), and clinic staff were available to provide assistance. Each patient underwent a complete physical examination if one had not been performed within 1 year. To increase standardization of the physical examination, a study form was used to record the results (Web Appendix). The remainder of the clinic visit was devoted to the patient's routine clinical care.

Follow-up clinic visits

Follow-up visits kept the same general flow as the enrollment visit. Patients completed the questionnaires at home within 1 week of the clinic visit, and some of the questionnaires were omitted. Biologic samples collected at home (saliva) were given to clinic personnel, and blood samples were drawn. (Biologic samples were collected at the first visit for all participants enrolled in stage 2 and subsequent stages.) The remainder of the clinic visit was devoted to the patient's routine clinical care. Follow-up is planned annually (10–14 months) to coincide with return clinic appointments. The number of follow-up visits for each participant will vary depending on the stage at first enrollment. Persons enrolled at stage 1 would have a maximum of 5 follow-up visits.

Biologic samples

To assure quality and comparability of biologic samples, a standard operating procedure for collection, labeling, storage, and handling was developed by the CDC's Molecular Epidemiology Laboratory. Laboratory staff reviewed the standard operating procedure with study personnel at each clinic to be sure that the steps were clear. Each clinic had the written standard operating procedure readily available onsite to guide collection. The CDC provided components for the saliva collection kits, blood collection tubes, and shipping supplies to the clinics.

Saliva—Participants were asked to collect 4 saliva samples at home to allow measurement of cortisol and α-amylase awakening response (immediately after awakening while still in bed and 30, 45, and 60 minutes after awakening). Clinic personnel mailed saliva collection kits to patients approximately 2 weeks before their clinic visits. Each kit included written instructions for collection, 4 individually wrapped SalivaBio Oral Swabs (Salimetrics, Carlsbad, California), 4 swab storage tubes, 1 specimen transport bag, 1 cold pack, 1 thermal bag, and a saliva collection form (to record time at which the participant went to sleep, the usual time at which she or he went to sleep, the times of saliva collection, and quality of sleep during the night before collection). The clinic called each patient after his or her kit was received to review all parts of the kit, describe the process for collecting samples, and answer any questions. Patients were asked to collect samples on awakening in the morning before the day of the clinic visit. Collection could be performed as many as 3 days before the

clinic visit to avoid cortisol changes due to stressful travel days. Patients placed saliva samples in specimen transport bag, added the saliva collection form to outer pouch of the transport bag, and sealed the bag. The bagged samples were placed in the thermal bag and kept in a refrigerator until the day of the clinic visit, when the chilled cold pack was added to thermal bag to keep contents cool during travel. When patients came to the clinic, study personnel reviewed the specimens, correlated numbers with information on the saliva collection form, resolved any missing or contradictory information, and noted any problems or concerns on the form. Saliva samples were stored at −20°C at the clinics until shipped to the CDC laboratory on dry ice.

Blood—Study personnel collected whole blood via venipuncture at the antecubital fossa, first completely filling 1 Tempus blood RNA tube (ThermoFisher Scientific/Applied Biosystems, Foster City, California) and then filling a PAX-gene blood DNA tube (Qiagen, Valencia, California). Immediately after each tube of blood was collected, it was vigorously shaken by hand for 10–20 seconds and placed upright in a wire rack at room temperature for 2 hours. Blood samples in collection tubes were then stored at −20°C (upright in wire rack) until shipped to the CDC.

Sample size consideration

In stage 1, we aimed to enroll 450 patients in a 1-year timeframe using a standardized approach. Sample size was primarily constrained by budgets and the feasibility of the study management at each clinical site. On the basis of previous ME/CFS clinical studies, we anticipated a follow-up rate of 75%, resulting in a total of 338 patients for whom we would collect complete data (≥80% of valid data via instruments/forms) and who would be eligible for the follow-up of ME/CFS subjects at stage 2. Based on an effect size of 0.4, a minimum of 130 subjects were needed in the ill comparison group to achieve 90% power to detect the 2-point difference in mean Multidimensional Fatigue Inventory sub-scale scores (16) and in the groups with ME/CFS and other illness to detect the 12-point differences in mean 36-Item Short Form Survey subscale scores (14, 15). A healthy control group of equal size was recruited for group comparisons of ME/CFS illness domain measures.

Data management

Coded data were delivered to the CDC's Epidemiology, Data Management, and Analysis team via a secure file transfer protocol (FTP) site. Data formats included electronic data files or PDF files of scanned data collection forms/instruments. After completing quality control assessments of data collection and any additional required data entry, the team merged data into 1 master database for centralized storage, cleaning, data processing, and analysis. The team developed a standard protocol for data entry and data cleaning/editing, including checking out-of-range values, outliers, and missing data. Clinic personnel were contacted to attempt to resolve any missing or discordant data.

For data collected at multiple time points, such as awakening salivary cortisol and α-amylase measures, quality control was performed by 1) using a subject matter expert review guide developed from previous CDC studies of ME/CFS and 2) applying statistical approaches, including descriptive statistics summaries and data visualization (e.g., lasagna

plots or heat maps). For instrument data, the scale scores were generated using the triangular validation approach: Scores were calculated by 2 independent programmers using different software and compared by a third person. (Programming codes developed for scoring are available upon request.) During the scoring process, internal consistency and skip patterns were checked. Overall, the internal consistency coefficients were equal to or greater than the reported values from the original source documents for each scale.

RESULTS

Stage 1 was completed in September 2013, with 471 study participants completing at least 80% of each instrument and form. This exceeded target enrollment by 5%. Each of the 7 clinics contributed 10%–16% of enrolled patients. Demographic characteristics of the ME/CFS patients are shown in Table 2. Overall, the mean age of patients was 48.2 years; 73.9% were female, and 94.7% were white. Nearly all were insured (94.4%), but 74.9% were not working. Of those who were currently unemployed, 69.6% reported that they were disabled, and only 16.9% were currently receiving unemployment benefits. Regardless of current employment status, 72.6% of patients reported missing work or school because of their illness. The majority (77.0%) had a college education or more, and 56.1% were married. Patients had a mean body mass index (weight in kilograms divided by height in meters squared) of 26.6. The mean age at onset of illness was 38.4 years, and the mean duration of illness at the time of enrollment was 14.3 years. Overall, 65.4% of patients described a sudden onset of illness.

The proportions of patients who reported each symptom evaluated using the CDC Symptom Inventory are shown in Figure 1. Fatigue, postexertional malaise, and unrefreshing sleep were the 3 most-reported symptoms. As shown in Table 3, the mean number of reported CFS symptoms (from the 1994 case definition) was almost 6 (out of a possible 8), and the mean score (frequency × severity) for these symptoms was 55. Table 3 also summarizes the mean scores for each subscale of the 36-Item Short Form Survey and Multidimensional Fatigue Inventory, providing an indication of the extent of functional impairment and fatigue in this study sample at baseline. The 36-Item Short Form Survey subscales were transformed to a scale of 0–100, with lower scores indicating less function (more impairment). The mean scores on the Physical Role Functioning and Vitality subscales were the lowest, whereas those on the Emotional Role Functioning and Mental Health subscales were highest. The Multidimensional Fatigue Inventory subscales are scored from 0 to 20, with higher scores indicating more severe fatigue. Among the ME/CFS patients, general fatigue and physical fatigue were the 2 subscales with highest scores, and reduced motivation had the lowest score. For each measure, the scores were distributed broadly over a wide range, which indicates a large variation. As an example, the distribution of scores on the 36-Item Short Form Survey is shown in Figure 2, with the average values for the healthy controls enrolled to date shown as a comparison.

Collection of biospecimens was initiated in stage 2, with overall success. To date, more than 90% of participants have provided blood and saliva samples. We chose collection methods that required minimal processing and handling at the clinics. The saliva collection required

frequent communication between the participants and clinic personnel for explanation of kit components and reminders before the clinic visit.

DISCUSSION

In the present article, we provide detailed information on the design of our multisite clinical investigation of ME/CFS. All data abstraction forms, questionnaires, and scoring methods are provided in the Web Appendix as a resource for other investigators. As future studies use and evaluate these data collection tools, we anticipate that a systematic approach to data collection and agreement on common data elements will emerge that will facilitate data sharing initiatives.

The Chronic Fatigue Initiative (CFI) Study shares some similarities with MCAM, but in the former, eligibility was determined based on case definition, and smaller numbers of patients with ME/CFS were enrolled (33). Inclusion of multiple clinics is important to increase geographic representation and identify differences between clinical practices. The success of the multisite infrastructure established with the partnership of study clinicians is indicated by the fact that enrollment data were collected on 471 ME/CFS patients, which exceeded the target by 5%. The rolling cohort design will allow collection of follow-up data, as well as enrollment of comparison groups (ill and healthy) and hard-to-reach ME/CFS patients (near onset and severely ill).

The data on frequency and severity of symptoms, extent of functioning, and fatigue of the patients enrolled in stage 1 demonstrate characteristic features of ME/CFS. As measured using the CDC Symptom Inventory, fatigue, postexertional malaise, and unrefreshing sleep are the most frequently reported symptoms. The 36-Item Short Form Survey and Multidimensional Fatigue Inventory subscale scores of ME/CFS patients document profound impairment from this illness and also show the relative preservation of emotional functioning and mental health. Scores on these and other instruments will be used to compare patients among clinics and to compare patients with the healthy and ill comparison groups that are being enrolled in subsequent stages of the study. A standardized approach to measuring ME/CFS will allow the extent of patient heterogeneity to be described and could contribute to being able to more reproducibly evaluate the similarities and differences in study populations that affect the ability to replicate findings.

Evaluating the performance of the patient-reported outcome measures will be helpful in developing recommendations for their use as outcome measures in clinical trials of ME/CFS. Finally, the full range of phenotypic measures combined with biologic data (routine laboratory data and morning cortisol data) can allow us to begin the process of subgrouping patients. The DNA and RNA isolated from whole blood and the saliva will form the basis of a biorepository linked to epidemiologic data that can be used to address hypothesis-driven questions on etiology.

The most significant limitation of the present study is a consequence of its most significant strength. The partnering ME/CFS clinics are highly specialized (tertiary care) clinics where patients with more resources (economic and social) are more likely to be seen. For example,

uninsured patients, members of minority groups, and those with less education have not been well represented in the study sample to date. The study was conducted in English and required participants to read documents that were at an eighth grade reading level. Therefore, the study sample might not represent all ME/CFS patients.

The strength of this study's design lies in the expertise of the clinicians who recruited patients. The clinicians each have 10 to more than 30 years of experience with diagnosing and caring for ME/CFS patients. This allows the participants' self-reported measures of the major domains of illness (activity limitation, fatigue, sleep, pain, range of symptoms, and severity) to be evaluated based on expert clinical diagnosis, which is the best option in the absence of a gold standard. Using the same process to collect data on ill and healthy comparison groups will allow us to identify those measures with greatest specificity for ME/CFS diagnosis. Data on how expert physicians use pharmacologic and nonpharmacologic management and laboratory evaluations to care for their ME/CFS patients can be useful to describe current expert practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (MCAM) Study Group included the following: *Centers for Disease Control and Prevention/Division of High-Consequence Pathogens and Pathology/Chronic Viral Diseases Branch, Atlanta, Georgia*: Elizabeth Unger (principal investigator), Jin-Mann Sally Lin (co- principal investigator), Jaeyon Bae, Felicia Blocker, Roumiana Boneva, Kathleen Bonner, Dana Brimmer, Jordan Burns, Charlotte Campbell, Judith Chuang, Monica Cornelius, Irina Dimulescu, Vince Emanuele, Alyx Groth, Brian Gurbaxani, Ashley Hagaman, Kyle Hasenstab, Colleen Haynes, Britany Helton, Joyce Ho, James F. Jones, Maung Maung Khin, Daisy Lee, Timothy McLoed, Lisa Oakley, Alex Pao, Meredith Philyaw, Esther Piervil, Troy Querec, Ashish Rai, Mangalathu Rajeevan, Jendai Richards, Daniel Robertson, Hao Tian, Blair Turner, and Amanda Williams; *Bateman Horne Center, Salt Lake City, Utah*: Lucinda Bateman (principal investigator), Ali Allen, Jennifer Bland, and Veronica Parkinson; *Hunter-Hopkins Center, Charlotte, North Carolina*: Charles Lapp (principal investigator) and Wendy Springs; *Institute for Neuro Immune Medicine, Miami, Florida*: Nancy Klimas (principal investigator), Elizabeth Balbin, Ayled Barreda, Jeffry Cournoyer, Melissa Fernandez, Luis Gustavo Jara, and Precious Leaks-Gutierrez; *Mount Sinai Beth Israel, New York, New York*: Benjamin Natelson (principal investigator), Michelle Blate, Gudrun Lange, and Diana Vu; *Open Medicine Clinic, Mountain View, California*: Andreas Kogelnik (principal investigator), Bela Chheda, Joan Danver, David Kaufman, Macy Pa, Catt Phan, and Sophia Taleghani; *Richard N. Podell Medical, Summit, New Jersey*: Richard N. Podell (principal investigator), Trisha Fitzpatrick, and Beverly Licata; and *Sierra Internal Medicine, Incline Village, Nevada*: Daniel Peterson (principal investigator), Elena Lascu, Gunnar Gottschalk, and Janet Smith.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abbreviations

CDC	Centers for Disease Control and Prevention
CFS	chronic fatigue syndrome
MCAM	Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
ME	myalgic encephalomyelitis

References

1. Jason LA, Richman JA, Rademaker AW, et al. A community-based study of chronic fatigue syndrome. Arch Intern Med. 1999; 159(18):2129–2137. [PubMed: 10527290]
2. Reyes M, Nisenbaum R, Hoaglin DC, et al. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. Arch Intern Med. 2003; 163(13):1530–1536. [PubMed: 12860574]
3. Reeves WC, Jones JF, Maloney E, et al. Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Popul Health Metr. 2007; 5:5. [PubMed: 17559660]
4. Lin JM, Resch SC, Brimmer DJ, et al. The economic impact of chronic fatigue syndrome in Georgia: direct and indirect costs. Cost Eff Resour Alloc. 2011; 9(1):1. [PubMed: 21251294]
5. Reynolds KJ, Vernon SD, Bouchery E, et al. The economic impact of chronic fatigue syndrome. Cost Eff Resour Alloc. 2004; 2(1):4. [PubMed: 15210053]
6. Jason LA, Benton MC, Valentine L, et al. The economic impact of ME/CFS: individual and societal costs. Dyn Med. 2008; 7:6. [PubMed: 18397528]
7. Lin JM, Brimmer DJ, Boneva RS, et al. Barriers to healthcare utilization in fatiguing illness: a population-based study in Georgia. BMC Health Serv Res. 2009; 9:13. [PubMed: 19154587]
8. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994; 121(12):953–959. [PubMed: 7978722]
9. Carruthers BM, Jain AK, De Meirleir KL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. J Chronic Fatigue Syndr. 2003; 11(1):7–115.
10. Carruthers BM, van de Sande MI, De Meirleir KL, et al. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med. 2011; 270(4):327–338. [PubMed: 21777306]
11. Jason LA, Evans M, Porter N, et al. The development of a revised Canadian Myalgic Encephalomyelitis Chronic Fatigue Syndrome case definition. Am J Biochem Biotechnol. 2010; 6(2):120–135.
12. Unger ER, Lin JM, Tian H, et al. Methods of applying the 1994 case definition of chronic fatigue syndrome - impact on classification and observed illness characteristics. Popul Health Metr. 2016; 14:5. [PubMed: 26973437]
13. Wagner D, Nisenbaum R, Heim C, et al. Psychometric properties of the CDC Symptom Inventory for assessment of chronic fatigue syndrome. Popul Health Metr. 2005; 3:8. [PubMed: 16042777]
14. Ware JE Jr. SF-36 health survey update. Spine (Phila Pa 1976). 2000; 25(24):3130–3139. [PubMed: 11124729]
15. Ware JE Jr, Sherbourne CD. The MOS36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992; 30(6):473–483. [PubMed: 1593914]
16. Smets EM, Garssen B, Bonke B, et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995; 39(3):315–325. [PubMed: 7636775]
17. Garcia SF, Cella D, Clauser SB, et al. Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. J Clin Oncol. 2007; 25(32):5106–5112. [PubMed: 17991929]
18. Lai JS, Cella D, Choi S, et al. How item banks and their application can influence measurement practice in rehabilitation medicine: a PROMIS fatigue item bank example. Arch Phys Med Rehabil. 2011; 92(10 suppl):S20–S27. [PubMed: 21958919]
19. Buysse DJ, Yu L, Moul DE, et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. Sleep. 2010; 33(6):781–792. [PubMed: 20550019]
20. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. Med Care. 2007; 45(5 suppl 1):S3–S11.

21. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol. 2010; 63(11):1179–1194. [PubMed: 20685078]
22. Revicki DA, Chen WH, Harnam N, et al. Development and psychometric analysis of the PROMIS pain behavior item bank. Pain. 2009; 146(1–2):158–169. [PubMed: 19683873]
23. Amtmann D, Cook KF, Jensen MP, et al. Development of a PROMIS item bank to measure pain interference. Pain. 2010; 150(1):173–182. [PubMed: 20554116]
24. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994; 23(2):129–138. [PubMed: 8080219]
25. Centers for Disease Control and Prevention. [Accessed August 30, 2016] CDC HRQOL-14 "Healthy Days Measure". http://www.cdc.gov/hrqol/hrqol14_measure.htm Updated May 26, 2016
26. Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol. 2005; 23(5 suppl 39):S154–S162. [PubMed: 16273800]
27. Bennett RM, Friend R, Jones KD, et al. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Res Ther. 2009; 11(4):R120. [PubMed: 19664287]
28. Corson K, Gerrity MS, Dobscha SK. Screening for depression and suicidality in a VA primary care setting: 2 items are better than 1 item. Am J Manag Care. 2004; 10(11 Pt 2):839–845. [PubMed: 15609737]
29. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med. 2002; 64(2):258–266. [PubMed: 11914441]
30. Kroenke K, Spitzer RL, Williams JB, et al. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med. 2007; 146(5):317–325. [PubMed: 17339617]
31. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006; 166(10):1092–1097. [PubMed: 16717171]
32. Zung WW, Richards CB, Short MJ. Self-rating depression scale in an outpatient clinic. Further validation of the SDS. Arch Gen Psychiatry. 1965; 13(6):508–515. [PubMed: 4378854]
33. Klimas NG, Ironson G, Carter A, et al. Findings from a clinical and laboratory database developed for discovery of pathogenic mechanisms in myalgic encephalomyelitis/chronic fatigue syndrome. Fatigue. 2015; 3(2):75–96.
34. Centers for Disease Control and Prevention. [Accessed August 30, 2016] CDC Public Health Grand Rounds. Chronic Fatigue Syndrome: Advancing Research and Clinical Education. https://www.cdc.gov/cdcgrandrounds/pdf/archives/2016/feb2016.pdf Published February 16, 2016

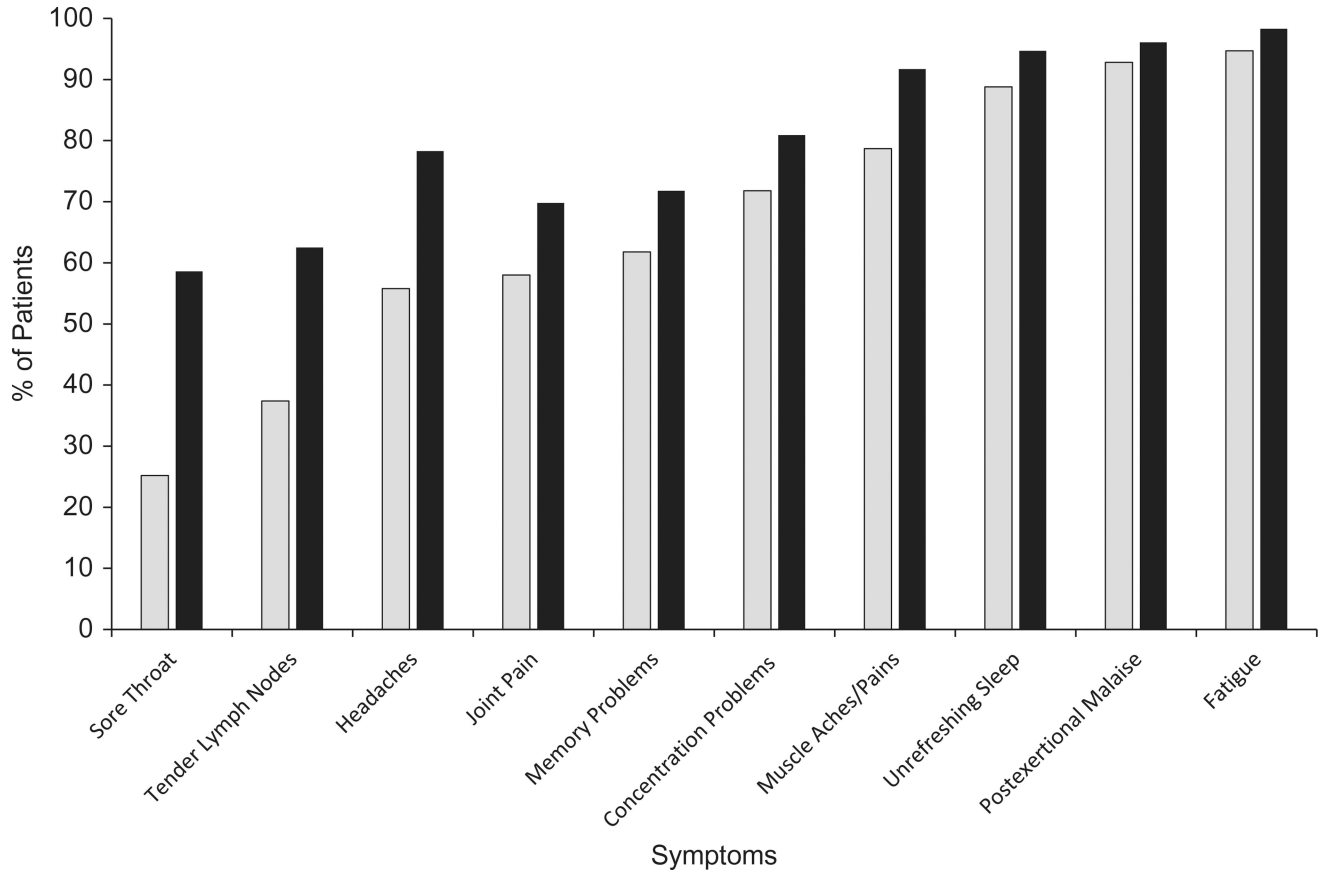

Figure 1.

Percentages of patients with specific symptoms (based on the CDC Symptom Inventory for chronic fatigue syndrome) in stage 1, Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2012–2013. The CDC Symptom Inventory asks about symptoms experienced in the past month. Symptoms that have been present for less than 6 months were assigned a score of 0 and were not included. A frequency of 1 indicates a little of the time, and a frequency of 2 indicates some of the time. A severity of 1 indicates very mild or mild, and a severity of 2.5 indicates moderate. The gray bars indicate the percentages of patients who reported the specified symptom with both frequency and severity of 2 or greater. The black bars indicate the percentages of patients reporting that symptom with frequency and severity of 1 or greater. Symptoms are listed by increasing percentages of patients who reported symptoms with a frequency and a severity of at least 2.

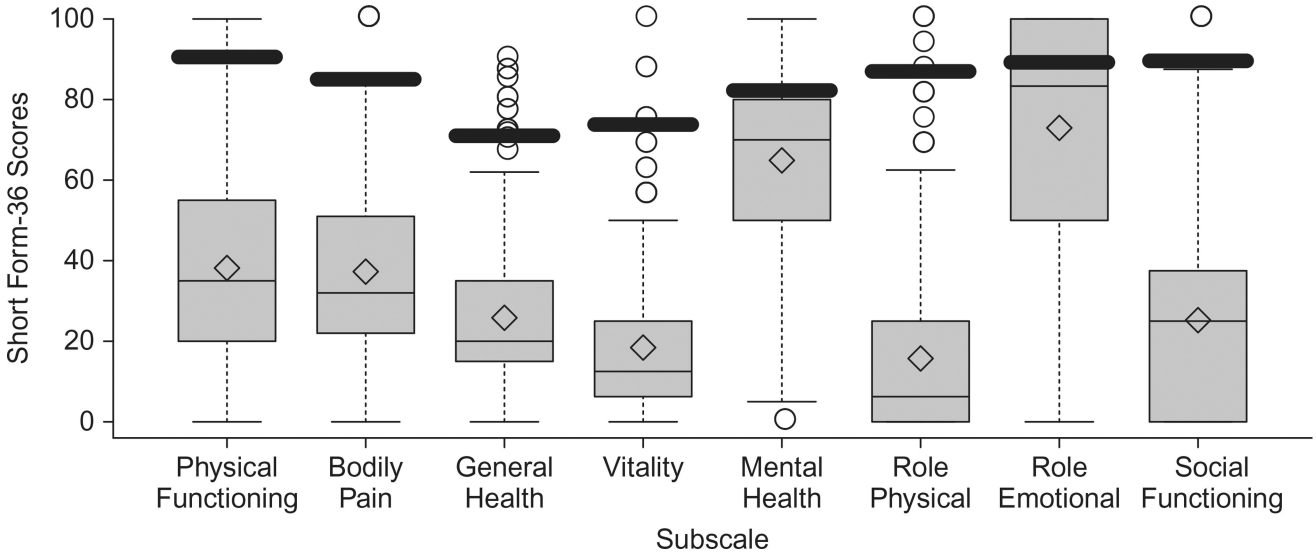

Figure 2.

Distribution of 36-Item Short Form Survey Subscale (Short Form-36) scores in patients with myalgic encephalomyelitis/chronic fatigue syndrome in stage 1, Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2012–2013. The boxplots display the 5-number summary: minimum, first quartile, median, third quartile, and maximum. The central rectangle spans from the first quartile to the third quartile (the interquartile range), a segment inside the rectangle shows the median, and the dotted lines (sometimes referred to as whiskers) are extended to the extrema of the distribution in the data set. The mean value in each boxplot is indicated by a diamond. The circles indicate outliers, and the thick black bars indicate the means among the 213 healthy controls with data as of September 2015 (collected 2013–2015). Lower scores indicate more disability. Adapted from the Centers for Disease Control and Prevention (34).

Table 1

Questionnaires Used in the Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Questionnaire	Recall Period	Description	Reference
CDC Symptom Inventory	Past month	Assessment of the occurrence, frequency, and intensity of symptoms common in CFS and other fatiguing illnesses	13
Medical Outcomes Study 36-Item Short Form Survey	Past 4 weeks	General indicator of function and wellbeing in 8 areas (physical activities, social activities, usual role activities, bodily pain, general mental health, limitations due to emotional problems, vitality (energy and fatigue), and general health perception)	14, 15
Multidimensional Fatigue Inventory	"Lately" (less than a week)	Self-reported measure of fatigue covering dimensions of general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity	16
DePaul Symptom Questionnaire (partial)	Past 6 months	Assessment of the occurrence, frequency, and intensity of symptoms common in CFS and other fatiguing illnesses; only items not covered in other questionnaires are included	11
PROMIS Fatigue Short Form V1.0	Past 7 days	Seven self-reported items selected to represent content in the PROMIS fatigue item bank; measures of fatigue were designed for use in wide variety of illnesses	17, 18
PROMIS Sleep Disturbance 8-Item Short Form	Past 7 days	Eight self-reported items to assess perception of sleep quality, sleep depth, and restoration associated with sleep over the past 7 days, including questions about difficulties getting to sleep, staying asleep, adequacy of sleep and satisfaction with sleep	19–21
PROMIS Sleep-Related Impairment Short Form V1.0	Past 7 days	Eight self-reported items to assess perception of alertness, sleepiness, and tiredness during usual waking hours and functional impairment associated with sleep problems or impaired alertness over the past 7 days	19–23
PROMIS Pain Behavior Short Form	Past 7 days	Seven self-reported measures of external manifestations of pain over the past 7 days, including observable displays (sighing, crying), pain severity behavior (resting, guarding, facial expressions, asking for help), and verbal reports of pain	20–22
PROMIS Pain Interference Short Form	Past 7 days	Six self-reported measures of the consequences of pain on social, cognitive, emotional, physical, and recreational activities, as well as on sleep and enjoyment of life, over the past 7 days	20, 21, 23
Brief Pain Inventory (long form)	In the past week	Measures intensity of pain and interference with activities; records location of pain and pain descriptor	24
Health-Related Quality of Life	Past 30 days	Four questions to assess perceived sense of well-being, self-rated health, recent number of days when mental or physical health was not good, and days when activity was limited because of health	25
Illness Impact Questionnaire[a]	Past 7 days	Adapted from Fibromyalgia Impact Questionnaire Revised; assesses pain, fatigue, stiffness, poor sleep, depression, poor memory, anxiety, tenderness, poor balance, and environment sensitivity, with subscales for symptoms, function, and overall impact	26, 27
Patient Health Questionnaire depression scale[b]	Past 2 weeks	Comparable to Patient Health Questionnaire-9 in diagnosing depressive disorders; omits suicidal ideation	28, 29
Generalized Anxiety Disorder 7-Item Scale[b]	Past 2 weeks	Seven items developed to diagnose generalized anxiety and screens for panic, social anxiety, and posttraumatic stress disorder. Score cutpoints for mild, moderate, and severe anxiety developed	30, 31
Self-Rating Depression Scale[b]	Recently	Quantifies the severity of current major depression in 20 items	32

Abbreviations: CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome; PROMIS, Patient Reported Outcome Measurement Information System.

[a] We adapted the Fibromyalgia Impact Questionnaire by replacing “fibromyalgia” with “illness” throughout the questionnaire.

[b] Only administered at the clinic.

Table 2

Demographic Characteristics of Patients in Stage 1, Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2012–2013

Characteristic	No.	%
Age, years[a]		
18–29	53	11.3
30–39	57	12.1
40–49	104	22.1
50–59	177	37.6
≥60	80	17.0
Female sex	384	73.9
Race		
White	442	94.7
Black/African-American	6	1.3
All others	19	4.1
Marital status		
Married/committed	259	56.1
Previously married	76	16.5
Never married	127	27.5
Employment		
Full-time	66	14.2
Part-time	51	10.9
Not working	349	74.9
Had insurance	435	94.4
Educational level		
Less than high school	4	0.9
High school	101	22.1
College	181	39.6
Postcollege	171	37.4

[a]The mean age was 48.24 (standard error, 0.59) years.

Table 3

Measures of Illness in Patients in Stage 1, Multi-Site Clinical Assessment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome, 2012–2013

Scale and Subscale	Score, mean (SE)
SF-36 Physical Functioning[a]	37.98 (1.39)
SF-36 Physical Role Functioning[a]	4.00 (0.91)
SF-36 Bodily Pain[a]	39.14 (1.42)
SF-36 General Health Perceptions[a]	25.24 (0.96)
SF-36 Vitality[a]	17.53 (1.04)
SF-36 Social Role Functioning[a]	26.32 (1.40)
SF-36 Emotional Role Functioning[a]	72.73 (2.49)
SF-36 Mental Health[a]	67.19 (1.24)
MFI-20 General Fatigue[b]	18.27 (0.14)
MFI-20 Physical Fatigue[b]	17.44 (0.17)
MFI-20 Reduced Activity[b]	16.08 (0.21)
MFI-20 Reduced Motivation[b]	11.81 (0.25)
MFI-20 Mental Fatigue[b]	14.56 (0.24)
CDC Symptom Inventory: no. of CFS symptoms[c]	5.89 (0.11)
CDC Symptom Inventory: CFS symptom score[d]	55.02 (1.38)

Abbreviations: CFS, chronic fatigue syndrome; MFI-20, Multidimensional Fatigue Inventory; SF-36, 36-Item Short Form Survey.

[a]SF-36 scores range from 0–100, with higher scores indicating better health.

[b]MFI-20 scores range from 4–20, with higher scores indicate a higher level of fatigue.

[c]The score for number of CFS symptoms ranges from 0–8, with higher scores indicating more symptoms lasting for 6 months or longer.

[d]The 8 CFS symptom score ranges from 0–128, with higher scores indicating higher severity of symptoms.