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Identification of Ambiguities in the 1994 Chronic Fatigue Syndrome Research Case Definition and Recommendations for Resolution

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Running Head: CFS Case Definition

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Abstract

Background. Chronic fatigue syndrome (CFS) is defined by symptoms and disability, has no confirmatory physical signs or characteristic laboratory abnormalities, and the etiology and pathophysiology remain unknown. Difficulties with accurate case ascertainment contribute to this ignorance.

Methods. Experienced investigators from around the world who are involved in CFS research met for a series of three day workshops in 2000, 2001 and 2002 intended to identify the problems in application of the current CFS case definition. The investigators were divided into focus groups and each group was charged with a topic. The investigators in each focus group relied on their own clinical and scientific knowledge, brainstorming within each group and with all investigators when focus group summaries were presented. Relevant literature was selected and reviewed independent of the workshops. The relevant literature was circulated via list-serves and resolved as being relevant by group consensus. Focus group reports were analyzed by WCR and compiled into the recommendations presented here.

Results. Ambiguities in the current CFS research definition that contribute to inconsistent case identification were identified. Recommendations for use of the definition, standardization of classification instruments and study design issues are presented that are intended to improve the precision of case ascertainment. The International CFS Study Group also identified ambiguities associated with exclusionary and comorbid conditions and reviewed the standardized, internationally applicable instruments used to measure symptoms, fatigue intensity and associated disability.

Conclusion. This paper provides an approach to guide systematic, and hopefully reproducible, application of the current case definition, so that case ascertainment would be more uniform across sites. Ultimately, an operational CFS case definition will need to be based on empirical studies designed to delineate the possibly distinct biological pathways that result in chronic fatigue.

Background

Chronic fatigue syndrome is a complex illness defined by unexplained disabling fatigue and a combination of non-specific accompanying symptoms. Similar disorders have been described for at least two centuries and have been variously named neurasthenia, myalgic encephalomyelitis, Akureyri disease, post-viral fatigue, and chronic mononucleosis [1]. The first formal case definition, published in the United States in 1988 [2], suggested the name “chronic fatigue syndrome” or CFS, which was retained in subsequent Australian [3] and British [4] case definitions. In 1994, an international collaborative group that included authors of the previous case definitions published the current CFS research case definition [5].

Although, the 1994 case definition comprises the current international standard for classification of research subjects as CFS, there are substantial differences between the earlier definitions and it is important to understand this when interpreting results of research studies. CFS is identified by symptoms and disability and by excluding illnesses that could explain them. There are no confirmatory physical signs or characteristic laboratory abnormalities. The etiology and pathophysiology of the syndrome remain unknown, and there is a lack of consensus in the findings of many well-conducted studies both within and between centers [6]. Difficulties with accurate case ascertainment are a major contributor to this problem. Much of the difficulty reflects conceptual and operational problems inherent in classifying an illness defined by symptoms and reported disability [7].

The objective of this article is to identify ambiguities in the current CFS case definition that contribute to inconsistent case identification and to recommend revisions for improving the precision of case ascertainment for research studies. This document is the product of three structured meetings of international experts in CFS, representing epidemiology, infectious diseases, endocrinology, immunology, neurology, psychology, psychiatry, biostatistics, and patient advocacy. While recognizing the need for a more consistently applied definition, the group resolved the need for empirical studies designed to delineate the different syndromes contained in unexplained fatigue. While intended to apply primarily to the research setting, many of our recommendations will be useful for health care providers (and the patient community they serve) because they suggest standardized instruments to record and to measure the key symptom domains and the disability associated with CFS.

Methods

From May of 2000 to May of 2002, the Centers for Disease Control and Prevention (CDC) sponsored a series of three-day workshops to discuss issues related to the current CFS research definition. Each workshop was attended by approximately 20 invited participants that represented an international mix of scientists, clinicians and medical researchers and approximately 10 CDC staff members. During the first workshop, focus groups were formed to address standardization and utilization of instruments used to classify CFS. Each focus group then prepared a summary report. The process that each focus group used included reliance on clinical and scientific knowledge, brainstorming, consensus building and literature reviews. Each focus group report was presented to all workshop participants for further discussion and was modified if necessary. Interval periods between workshops were used for independent review of relevant literature. The papers were circulated via list-serves and resolved as relevant by group consensus either on-line or during the subsequent workshop. Workshop summaries and focus group reports were analyzed and compiled into the recommendations presented here. Where recommendations for specific evaluation instruments were made, wherever possible we favored those that were freely available in the public domain and validated across various language and cultural groups.

Results

Exclusionary and Comorbid Conditions

The 1994 CFS case definition [5] recommends that patients with severe chronic fatigue undergo a clinical evaluation to identify underlying, contributing, and comorbid conditions that require treatment. The lists of exclusionary diagnoses used to screen subjects for enrollment into CFS studies provided by the 1994 case definition were not exhaustive, but rather were examples to guide investigators in their decisions. To increase the uniformity of decisions about exclusionary conditions, we have further clarified exclusionary criteria and give more exhaustive recommendations of conditions that should be excluded.

Examples of permanent medical exclusions include the following: 1) organ failure (e.g., emphysema, cirrhosis, cardiac failure, chronic renal failure); 2) chronic infections (e.g., AIDS, hepatitis B or C); 3) rheumatic and chronic inflammatory diseases (e.g., systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, inflammatory bowel disease, chronic pancreatitis); 4) major neurologic diseases (e.g., multiple sclerosis, neuromuscular diseases, epilepsy or other diseases requiring ongoing medication that could cause fatigue, stroke, head injury with residual neurologic deficits); 5) diseases requiring systemic treatment (e.g., organ or bone marrow transplantation, systemic chemotherapy, radiation of brain, thorax, abdomen, or pelvis); 6) major endocrine diseases (e.g., hypopituitarism, adrenal insufficiency); 7) primary sleep disorders (e.g., sleep apnea, narcolepsy).

Temporary medical exclusions include treatable conditions that require evaluation over time to determine the extent to which they contribute to the fatiguing illness. These encompass four general categories: 1) conditions discovered at onset or initial evaluation (e.g., effects of medications, sleep deprivation, untreated hypothyroidism, untreated or unstable diabetes mellitus, active infection); 2) conditions that resolve (e.g., pregnancy until 3 months post-partum, breast feeding, major surgeries until 6 months post-operation, minor surgery until 3 months post-operation, and major infections such as sepsis or pneumonia until 3 months post-resolution; sleep disorders such as restless leg syndrome and periodic limb movement should be considered temporary exclusions for research criteria, if they are severe, but not if the degree of the sleep problem is insufficient to explain the severity of the fatigue); 3) major conditions whose resolution may be unclear for at least 5 years (e.g., myocardial infarction, heart failure); and 4) morbid obesity (body mass index [BMI] > 40). The 1994 CFS case definition specified a BMI >45. While both cut-off values are arbitrary, a BMI > 40 defines morbid obesity and is a more inclusive contributing factor to explain chronic fatigue.

Permanent psychiatric exclusions include lifetime diagnoses of bipolar affective disorders, schizophrenia of any subtype, delusional disorders of any subtype, dementias of any subtype, organic brain disorders, and alcohol or substance abuse within 2 years before onset of the fatiguing illness. The 1994 case definition stated that any past or current diagnosis of major depressive disorder with psychotic or melancholic features, anorexia nervosa, or bulimia permanently excluded a subject from the classification of CFS. Because these illnesses may resolve with little or no likelihood of recurrence and only active disease or disease requiring prophylactic medication would contribute to confusion with evaluation of CFS symptoms, we now recommend that if these conditions have been resolved for more than 5 years before the onset of the current chronically fatiguing illness, they should not be considered exclusionary.

Reliable detection of psychiatric illness requires a structured interview conducted during clinical evaluation of persons suspected to have CFS. We recommend the Composite International Diagnostic Instrument (CIDI) [8]. The CIDI is a computerized structured psychiatric interview that can be administered by general medical personnel and is supported by the World Health Organization (WHO) (for further information see <http://www.who.int/msa/cidi/> or <http://www.who.int/msa/cidi/listofcontacts.htm>). The CIDI has been widely used in large epidemiologic studies and therefore allows for national comparisons of psychiatric prevalence rate. Alternatively, the Structured Clinical Interview for DSM-IV Axis 1 (SCID) [9] may be utilized. However, trained interviewers (i.e., psychiatrists, clinical psychologists, psychiatric social workers, psychiatric nurse practitioners or research nurses with experience in psychiatric assessments) must administer the SCID. Both paper and pencil and computer assisted versions of the SCID are available (for further information see <http://cpmcnet.columbia.edu/dept/scid/>). The SCID is better suited for clinical studies. However, because of the difference in how they are administered, the SCID and CIDI often do not produce comparable results. These differences must be considered in evaluating study results and comparing studies. Any study must specify

which psychiatric instrument was used and discuss its strengths and weaknesses when interpreting results.

Definition and Evaluation of Fatigue

Several instruments that measure fatigue have been used in studies of CFS. The instruments have considerable overlap and each has advantages and disadvantages. We recommend that research studies of CFS consider using the more extensive Checklist Individual Strength, but shorter instruments such as the Chalder and Krupp scales are also appropriate. The Checklist Individual Strength (CIS) [10] is a 20-item inventory with 4 subscales: fatigue severity, concentration, reduced motivation and, physical activity. The fatigue severity subscale measures both general and physical fatigue and a score above 36 represents severe fatigue. The CIS focuses on fatigue over the preceding two weeks. Considerable normative data have been collected with reference to both CFS and post cancer patients and it has been used in epidemiological studies [11-13].

The Chalder Fatigue Scale [14] is a 14-item instrument with a 4-choice format that measures fatigue intensity and separates mental and physical fatigue. The Chalder scale has been used in large community samples and has published receiver-operating characteristics [15].

The Krupp Fatigue Severity Scale [16] includes 9 items rated on 7-point scales and is sensitive to different aspects and gradations of fatigue severity. Most items in the Krupp scale are related to behavioral consequences of fatigue.

Patients with similar fatigue intensity may have widely divergent levels of disability.

Assessment of CFS patients must also evaluate functional disability associated with the overall illness. Research studies should stratify CFS subjects according to the level of disability, but consensus as to which scales are most relevant has not been achieved. Four scales should be considered in this context; two are questionnaires of functional disability and two measure daily activity. We recommend that research studies use either the Medical Outcomes Survey Short Form-36, or if disability is a major focus of the study (e.g., treatment trials), then we recommend the more detailed Sickness Impact Profile.

The Medical Outcomes Survey Short Form-36 (MOS SF-36) is a well-validated instrument that measures the effects of the entire illness (i.e., fatigue and accompanying symptoms) on physical activity, social activity, usual role activities, bodily pain, general mental health, vitality, and general health perceptions [17]. Considerable normative data are available for many illnesses including CFS [18, 19].

The Sickness Impact Profile (SIP) [20] measures functional disability in different areas of daily functioning. Eight subscales of the 12 available are generally used in CFS: alertness behavior, sleep, homemaking, leisure activities, work, mobility, social interactions, and ambulation. Like the MOS SF-36, the SIP measures the consequences of the entire illness. However, the SIP records disability in concrete activities, which makes it less dependent on subjective impression.

The Activity record (ACTRE) is a self-administered 2-day diary of physical activity that has been used to obtain a profile of functioning and dysfunction [21]. To objectively record physical activity, study subjects can be monitored by actigraphy. Actigraphy data can be collected over

days or weeks, and the intensity of activity patterns can be analyzed [22-25]. Comparisons of physical activity measured by actigraphy and by self-report show only a weak correlation [23].

Definition and Evaluation of Accompanying Symptoms.

The 1994 case definition defines CFS by the presence of debilitating fatigue accompanied by at least 4 of 8 designated symptoms. Accompanying symptoms must have persisted or recurred during 6 or more consecutive months of illness and cannot have predated the fatigue. Designated accompanying symptoms include the following: post-exertional malaise lasting more than 24 hours; unrefreshing sleep; impaired short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; headaches of a new type, pattern, or severity; muscle pain; multi-joint pain without swelling or redness; sore throat; and tender cervical/axillary lymph nodes. It is important to stress that these are symptoms not signs. Signs such as inflamed tonsils or swollen lymph nodes should prompt the search for alternative diagnoses.

These symptoms are non-specific and variable in both nature and severity over time. They were selected on the basis of consensus clinical opinion and were not identified empirically. We recommend that research studies use the SPHERE (discussed below) to query subjects (cases and controls) about the occurrence, duration, and severity of the 8 case defining symptoms and other potentially accompanying symptoms.

Impact of the cumulative symptom complex should be the primary determinant in the classification of CFS. The MOS SF-36 and SIP (discussed above) measure overall disability. The remainder of this section discusses recommended standardized instruments to measure sleep, cognition, and pain. The information derived from these instruments will allow the identification of subgroups of subjects classified as CFS according to their clinical characteristics and disability (6).

The Group was not aware of an internationally standardized and validated instrument that measures the cumulated symptom complex of CFS. We recommend that investigators use the Somatic and Psychological Health Report (SPHERE) as a screening instrument for potential participants in research studies of CFS. The SPHERE is a 36-item instrument that identifies severe and disabling fatigue and measures accompanying symptoms and somatic distress by combining questions from the General Health Questionnaire (GHQ-30) and the CIDI. The SPHERE allows for concurrent measurement of depression, anxiety, somatization disorder and fatigue as independent constructs, hence its utility as a screening instrument in studies of CFS [26]. It has been used extensively in studies of primary care patients [27], and patients with post-infective and post-cancer fatigue [28]. However, it does not address fatigue in the same detail as other scales nor is it an acceptable substitute for standardized psychiatric screening instruments.

However, the SPHERE does not assess the entire symptom complex in detail and screens only for depression and anxiety and not for exclusionary psychiatric conditions. Therefore investigators should consider using the publicly available Centers for Disease Control and

Prevention Symptom Checklist (<http://www.cdc.gov/ncidod/diseases/cfs/index.htm>). This checklist has not been formally validated but it has been used in several population-based studies so that comparative data is available. The use of a common instrument to assess the accumulated symptom complex of CFS would lead to standardization and validation.

To measure sleep, cognition, and pain we recommend the following standardized instruments.

Sleep disturbance

Systematic evaluation with objective sleep studies is not practical (or necessary) in most CFS studies, and we recommend two instruments for use in CFS research studies. The Pittsburgh Sleep Questionnaire was developed to measure sleep quality in psychiatric research [29]. The Sleep Assessment Questionnaire (SAQ), a 17-item instrument developed by Moldofsky and collaborators, measures seven factors: insomnia/hypersomnia, restlessness, sleep schedules, excessive daytime sleeping, sleep apnea, restless leg/motility, and non-restorative sleep [30-32]. The SAQ has been validated against data obtained from polysomnography. The instrument and substantial support, including scoring and data maintenance, are available via the internet (<http://sleepmed.to>). However, the instrument is proprietary and a fee is charged for its use. Of note, sleep scales that measure somnolence rather than unrefreshing sleep are not adequate for studies of CFS. These include visual analogue scales such as the Epworth and Stanford Sleepiness Scales [33, 34].

Neurocognitive functioning

Impaired short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities is a case defining symptom and is reported by most persons with CFS. The deficit appears to be global but non-specific deficit most notably in the areas of attention and information processing. Newly emerging technology (e.g., functional neuroimaging) may complement and eventually replace traditional neurocognitive function tests. However, the Group did not recommend specific imaging measurements at this time.

Three alternatives to traditional neuropsychological testing should be considered in the CFS research setting. The Cambridge Neuropsychological Test Automated Battery (CANTAB) is currently the most practical single tool to assess cognition in CFS research studies [35, 36]. The CANTAB includes tests of memory, attention, and executive function and is administered via a touch-sensitive computer screen. The CANTAB allows a decomposition of complex tasks commonly used in clinical assessment into their cognitive components. Tests include versions of the Wisconsin Card-Sorting Test, the Tower of London, and the Delayed Matching-to-Sample Test. The CANTAB is non-verbal and largely language and culture independent. It has been standardized and validated in the elderly [37, 38], and in patients with depression [39], other mood disorders [40], schizophrenia [41], Alzheimer's disease [42], and CFS [43]. Unfortunately, the CANTAB is proprietary and relatively expensive.

The Australian Group (Ute Vollmer-Conna and Jim Lemon, personal communication) has developed the Rozelle Test Battery (RTB), that, similar to the CANTAB, is administered on laptop computers. Like the CANTAB, the RTB consists of mostly non-verbal tests, thus minimizing language and culture biases. Six tests from the RTB comprise the RTB-Fatigue battery and were selected to detect subtle cognitive impairment in the domains likely to be affected in CFS (attention, working memory, information processing, and mental flexibility) and were selected to allow repeated trials. Tests included in the RTB-Fatigue were derived from public domain standardized neurocognitive instruments and include versions of the Symbol Digit test, the Stroop Color-Word test, the Tower of London, a Spatial Memory Search test, a Concurrent Attention task, and a Task Shifting test. The RTB-Fatigue has been used in studies of CFS [44]. Finally, the hardware, operating system, and programming environment were selected to provide an inexpensive, flexible testing system that does not rely upon specialized or proprietary technology.

Recently, a Cognitive Function Index (CFI) for CFS has been developed on a sample of 189 CFS subjects and 61 demographically matched controls by investigators at the New Jersey Medical School (Gudrun Lange and Benjamin Natelson personal communication). The CFI score is comprised of two demographic factors (age and education) and seven cognitive factors derived from a restricted set of scores on standard neuropsychological assessment instruments. Items are either non-verbal or available in English, Spanish, and German. The CFI score represents a weighted average of the nine factors and appears to discriminate between CFS patients and controls (Benjamin Natelson personal communication). Items include the California Verbal Learning Test, the Rey-Osterrieth Complex Figure Test, the computerized NES continuous performance test, the Trail Making Test A and B, the grooved pegboard test, and the WAIS-III Vocabulary and Digit Span subtests. For more information concerning the CFI contact the investigators (<http://www.umdnj.edu/cfsweb/CFS/cfshome.html>).

Pain

If characterization of pain is necessary, we recommend using the McGill Pain Questionnaire. The McGill Pain Questionnaire (MPQ) is well validated, relatively inexpensive, available in several languages, and in a short form [45]. The 4 components of the MPQ include 1) a human figure drawing on which patients are asked to mark the location of their pain; 2) a series of 78 adjectives divided into 20 groups from which patients identify their experience by circling word descriptors; 3) questions about prior pain experience, pain location, and information on the use of pain medication; and 4) a present pain intensity index. The short form (MPQ-SF) does not assess areas of bodily involvement and, if used in CFS research studies, should be supplemented by pain diagrams.

Discussion

Clinical evaluation of persons with a fatiguing illness requires a thorough history that assesses physical and psychological symptoms, social factors, and medications and supplements that could contribute to fatigue; a thorough physical examination, a mental status examination; and, a minimum battery of laboratory tests. The presence of a medical or psychiatric condition that may explain the chronic fatigue state excludes the classification as CFS in research studies because overlapping pathophysiology may confound findings specific to CFS. The concept of “exclusionary conditions” makes sense only in research settings in which such distinction is required for clarity. In clinical settings, exclusionary conditions provide a list of differential or comorbid diagnoses that should be considered in patients with debilitating fatigue. This is important because appropriate intervention for these disorders could improve quality of life. In the clinical setting, patients with exclusionary conditions may be diagnosed and managed as having CFS on the basis of the physician’s medical opinion as to whether the exclusionary condition is likely to be a major contributor to the patient’s fatigue.

For the research definition of CFS, some exclusionary medical diagnoses may be considered permanent if no intervention will adequately resolve the condition. By contrast, some medical conditions will resolve or are adequately managed with treatment and should therefore be considered temporary exclusions. Research studies should stratify those individuals with apparently resolved medical conditions that otherwise meet the CFS case definition.

The 1994 case definition excluded psychiatric conditions that prevent a subject from accurately reporting symptoms and those with fatigue as a reasonably anticipated symptom. Consistent application of these exclusionary criteria has proven difficult because there was no recommendation as to how these conditions should be accurately and rapidly detected. In addition, opinions have evolved as to the best way to approach psychiatric diagnoses that may arise as result of, or co-morbid with, CFS. The following guidelines include recommendations for exclusionary psychiatric conditions and for stratification of study subjects.

The 1994 CFS case definition stipulates that patients have the following: 1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue (of least 6 months duration) that is of new or definite onset (i.e., has not been lifelong), 2) is not the result of ongoing exertion; 3) is not substantially alleviated by rest; and 4) results in substantial reduction in previous levels of occupational, educational, social, or personal activities [5]. These descriptors of fatigue are difficult to apply in practice [46]. The stipulation that the fatigue is “of new or definite onset” (i.e., has not been life long) was intended to exclude subjects with personality or somatization disorders that are characterized by a “lifelong pattern of presentations to medical attention with unexplained symptoms” [47]. We recommend that somatization disorder be identified and serve as a stratification diagnosis. Only subjects who recount having always felt fatigued should be excluded as having “lifelong” fatigue.

The stipulation that the fatigue be unrelated to ongoing exertion was intended to distinguish the unexplained fatigue in persons with CFS from that due to ongoing physical demands. However, CFS patients have an exaggerated fatigue response to previously well-tolerated activities and many report their fatigue is unusually sensitive to physical or mental exertion. Indeed, post-exertional malaise lasting more than 24 hours is one of the accompanying symptoms that define CFS. Therefore, this requirement should be interpreted as referring to exhaustion unrelated to an excessively demanding schedule that would induce fatigue in an otherwise healthy adult.

The requirement that rest should not substantially alleviate the fatigue is also unclear. It was intended to exclude the type of fatigue associated with overwork that resolves when the excessive demands end. Most persons with CFS experience some alleviation of fatigue and accompanying symptoms if they rest, but this relief does not allow for recovery of pre-illness physical and mental stamina. Some CFS patients use resting as a strategy to avoid over-exertion and the attendant exacerbation of symptoms. Therapeutic use of rest or a partial response to rest should not exclude a subject's illness from classification as CFS.

Finally, reliance on an affirmation that the fatigue substantially limits performance of daily activities is insufficient because "substantial" limitation is undefined, and independent confirmation of the reported level of disability is rarely sought. Fatigue is highly subjective, multidimensional, and variable during the course of disease. Ambiguities in the nature and severity of fatigue could be reduced by assessing fatigue and associated symptoms in a standardized manner. Measures of fatigue should encompass both its intensity and associated disability [48].

The 1994 case definition defines CFS by the presence of debilitating fatigue accompanied by at least four of eight designated symptoms. These symptoms are non-specific and variable in both nature and severity over time. They were selected on the basis of consensus clinical opinion and were not identified empirically. Accompanying symptoms must have persisted or recurred during six or more consecutive months of illness and cannot have predated the fatigue. Designated accompanying symptoms include the following: post-exertional malaise lasting more than 24 hours; unrefreshing sleep; impaired short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; headaches of a new type, pattern, or severity; muscle pain; multi-joint pain without swelling or redness; sore throat; and tender cervical/axillary lymph nodes. It is important to stress that these are symptoms not signs. Signs such as inflamed tonsils or swollen lymph nodes should prompt the search for alternative diagnoses.

Most CFS patients report unrefreshing sleep. However, narcolepsy and clinically significant obstructive sleep apnea are considered exclusionary diagnoses. It is unclear whether as yet-undefined sleep pathologies should be considered as co-morbid features of CFS or as common pathogenic pathways. Unrefreshing sleep accompanies a variety of sleep disorders and may explain some fatiguing illnesses [29]. Thus, assessment of sleep must detect treatable primary sleep disorders and evaluate sleep-related symptoms that may be part of CFS.

CFS patients typically complain of difficulties with concentration, memory, and thinking, yet neuropsychological testing does not generally confirm the reported cognitive dysfunction [49, 50]. The available data point to a more global, but non-specific performance deficit possibly related to impaired attention and slowed processing speed [51]. Investigators should use the report of cognitive impairment by the individual or a reliable informant as an initial screening tool. Measurement of cognitive function is complex, time consuming, and cannot be currently recommended for use in classifying CFS in research studies. However, studies exploring the cognitive dimension of CFS should be high priority.

Five of the eight CFS-defining symptoms reflect pain (headaches of a new type, pattern, or severity, muscle pain, and multi-joint pain without swelling or redness, sore throat, tender cervical/axillary lymph nodes). Pain may be a result of, responsible for, or associated with, both fatigue and sleep disturbances. Assessment of chronic pain (such as that reported by patients with CFS) includes a clinical history, physical examination, and psychiatric screening, all of which are discussed above. The SPHERE records sufficient information on the frequency and extent of chronic pain for most CFS research studies. However, pain may be the primary determinant of disability for some CFS patients. Chronic widespread pain may be a stratifying factor in the analyses.

Conclusion

The intent of this article was to guide systematic and reproducible application of the current case definition so that case ascertainment will be more uniform across research study sites. As part of this guide, we have recommended several standardized and validated instruments be used in assessments of fatigue, disability, and symptoms. If done, research studies on patients with CFS are more likely to be comparable. We have offered suggestions and examples to further clarify permanent medical and temporary exclusions including the best way to approach psychiatric diagnoses that may arise as result of, or are co-morbid with, CFS. Since fatigue is highly subjective, multidimensional, and variable during the course of disease, we have recommended approaches for standardized assessment of the nature and severity of fatigue. Finally, given that both the 1994 case definition and these recommendations for the better application of that definition were derived by expert consensus, the International CFS Study Group recommended a study of patients with chronic unexplained fatigue from which a definition of CFS can be empirically derived. The study should encompass different regions and cultures and utilize the instruments discussed here. To test the validity and reliability of the CFS case definition as revised, prospective studies of subjects at high risk for CFS should be undertaken.

Competing Interests. WCR, AL, SDV, LAJ, GB, BE, RN and ERU declare no competing interests. NK has protocol agreements with pharmaceutical industry to assess the affects of various drugs on CFS, does paid and unpaid consultancy work and receives paid and unpaid speaking invitations. PDW does both paid and unpaid consultancy work for Universities, the United Kingdom government, the United States Centers for Disease Control and Prevention, legal claimants and defendants, and insurance companies.

Author's Contributions. WCR, AL and SDV contributed equally to the conception, critique and process for attempting to improve the utilization of the CFS research case definition. WCR wrote the initial and final draft. AL, SDV, NK, LAJ, GB, BE, PDW, RN and ERU assisted with the drafting and finalization of this manuscript. WCR, AL, SDV, NK, LAJ, GB, BE, PDW, RN and ERU contributed to the manuscript through the summary of their work that resulted from a series of working group meetings on CFS classification and assessment.

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