Chronic Fatigue Syndrome: A Review

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Objective: Chronic fatigue syndrome is an illness characterized by disabling fatigue of at least 6 months, accompanied by several other symptoms. This review summarizes the current state of knowledge about chronic fatigue syndrome.

Method: The case definition, prevalence, clinical presentation, evaluation, and prognosis of chronic fatigue syndrome are discussed. Research on the pathophysiology and treatment of chronic fatigue syndrome is reviewed.

Results: Chronic fatigue syndrome is diagnosed on the basis of symptoms. Patients with chronic fatigue syndrome experience significant functional impairment. Pathophysiological abnormalities exist across many domains, suggesting that chronic fatigue syndrome is a heterogeneous condition of complex and multifactorial etiology. Evidence also is beginning to emerge that chronic fatigue syndrome may be familial. Although chronic fatigue syndrome has significant symptom overlap and comorbidity with psychiatric disorders, several lines of research suggest that the illness may be distinct from psychiatric disorders. Patients' perceptions, attributions, and coping skills, however, may help perpetuate the illness. Treatment for chronic fatigue syndrome is symptom-based and includes pharmacological and behavioral strategies. Cognitive behavior therapy and graded exercise can be effective in treating the fatigue and associated symptoms and disability.

Conclusions: Chronic fatigue syndrome is unlikely to be caused or maintained by a single agent. Findings to date suggest that physiological and psychological factors work together to predispose an individual to the illness and to precipitate and perpetuate the illness. The assessment and treatment of chronic fatigue syndrome should be multidimensional and tailored to the needs of the individual patient.

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Fatigue is a common symptom in the community, with up to half of the general population reporting fatigue in large surveys (1, 2). It also is reported by at least 20% of patients seeking medical care (3–7). Typically the fatigue is transient, self-limiting, and explained by prevailing circumstances. However, a minority of persons experience persistent and debilitating fatigue. When the fatigue cannot be explained by a medical condition such as anemia or hypothyroidism, it may represent chronic fatigue syndrome.

Chronic fatigue syndrome is an illness characterized by profound disabling fatigue lasting at least 6 months and accompanied by numerous rheumatological, infectious, and neuropsychiatric symptoms (8). As the name implies, chronic fatigue syndrome is a symptom-based or clinical diagnosis without distinguishing physical examination or routine laboratory findings. Infectious, immunological, neuroendocrine, sleep, and psychiatric mechanisms have been investigated; however, a unifying etiology for chronic fatigue syndrome has yet to emerge. It seems likely that chronic fatigue syndrome is a heterogeneous disease with different pathophysiological disturbances that manifest with similar symptoms. Regardless of the pathogenesis, persons with chronic fatigue syndrome, like those with other chronic diseases, have a substantially impaired functional status that results in significant personal and economic morbidity (9, 10). This article presents an overview of the issues of chronic fatigue syndrome diagnosis, prevalence, pathogenesis, evaluation, treatment, and prognosis, with an emphasis on psychiatric factors involved in chronic fatigue syndrome.

Case Definition

Syndromes characterized by persistent fatigue, pain, sleep difficulties, and cognitive impairment have been common in clinical practice for decades and perhaps centuries. In the 1980s, interest in fatiguing illnesses was rekindled by reports of outbreaks of a chronic debilitating illness that was associated with various virological and immunological abnormalities (11). Subsequently, the United States Centers for Disease Control and Prevention (CDC) named this illness "chronic fatigue syndrome" (12) and developed a case definition that was created primarily to standardize the patient population for research studies (13). The case definition facilitated a systematic and comprehensive approach to defining the etiology and pathophysiology of the syndrome by removing the implication of a causative agent such as Epstein-Barr virus. Similar definitions for chronic fatigue syndrome also were developed in England and Australia (14, 15).

A 1994 revision of the CDC case definition (8) constitutes the current criteria for chronic fatigue syndrome and the most widely used definition internationally. This definition requires at least 6 months of persistent fatigue that substantially reduces the person's level of activity. In addition, four or more of the following symptoms must occur with fatigue in a 6-month period: impaired memory or concentration, sore throat, tender glands, aching or stiff muscles, multijoint pain, new headaches, unrefreshing sleep, and postexertional fatigue. Medical conditions that may explain the prolonged fatigue as well as a number of psychiatric diagnoses (i.e., eating disorders, psychotic disorders, bipolar disorder, melancholic depression, and substance abuse within 2 years of the onset of fatigue) exclude a patient from the diagnosis of chronic fatigue syndrome. Those who do not meet the fatigue severity or symptom criteria can be given a diagnosis of idiopathic chronic fatigue. A notable feature of the CDC case definition is that many nonpsychotic psychiatric disorders are not exclusionary for the diagnosis of chronic fatigue syndrome. In addition, like psychiatric diagnoses, chronic fatigue syndrome is defined on the basis of expert consensus, and its diagnosis is made on the basis of symptom criteria.

Epidemiology

Estimates of the prevalence of chronic fatigue syndrome have varied depending on which definition was used, the type of population that was surveyed, and the study methods (16). Estimates for the prevalence of current chronic fatigue syndrome range from 0.007% to 2.8% in the general adult population (17–19) and from 0.006% to 3.0% in primary care or general practice (3, 20–22). Chronic fatigue syndrome also occurs in children and adolescents but apparently at a lower rate (23).

Early reports from tertiary clinics suggested that chronic fatigue syndrome affected primarily young, white, successful women (15). Indeed, most persons who receive a diagnosis of chronic fatigue syndrome are 30–40 years of age, and most surveys support a female preponderance (17, 18). However, community surveys have found that white individuals have a lower risk of chronic fatigue syndrome, compared with Latinos (17), African Americans (18, 22), and Native Americans (18). These disparate findings suggest that the increased prevalence of chronic fatigue syndrome among whites in clinic populations is most likely the result of a bias attributable to health care access and utilization.

Clinical Presentation

As the name indicates, fatigue is the hallmark of chronic fatigue syndrome. Patients often report excellent pre-illness physical fitness and energy (24) and an abrupt onset of fatigue, typically with a flu-like illness (25, 26). After illness onset, however, patients indicate that physical exertion tends to exacerbate the fatigue. Many patients with chronic fatigue syndrome also often experience anorexia, nausea, drenching night sweats, dizziness, and intolerance to alcohol and other pharmaceuticals that affect the central nervous system (27). Finally, those with chronic fatigue syndrome have significant functional impairment. Nearly all patients with chronic fatigue syndrome note a decrease in social relationships in addition to other unwanted consequences of illness (14); about one-third are unable to work, and another one-third can only work part-time (9). Recent findings from community-based studies suggest that women, members of minority groups, and nonworking individuals with chronic fatigue syndrome may experience greater functional disability and symptom severity than men, whites, and working individuals (28). Fortunately, the diagnosis of chronic fatigue syndrome is not associated with increased mortality.

Overlapping Conditions

The symptoms of chronic fatigue, as well as chronic fatigue syndrome itself, often co-occur with other so-called functional illnesses such as fibromyalgia, multiple chemical sensitivities, irritable bowel syndrome, and temporomandibular joint disorder (29, 30). Chronic fatigue syndrome has been best studied in relation to fibromyalgia, a syndrome of characteristic tender points and chronic diffuse body pain (31). Despite the contrasting definitions of the two disorders, 20%–70% of patients with fibromyalgia also meet the criteria for chronic fatigue syndrome (32–34), and conversely, 35%–70% of those with chronic fatigue syndrome–like illnesses have concurrent fibromyalgia (32, 35).

The overlap in case definition, reported symptoms, patient characteristics, and treatments for these functional somatic syndromes has led some researchers to suggest that these conditions are arbitrarily classified and should be considered as different manifestations of the same biomedical and psychosocial processes (36). Indeed, variable expressions of a common pathophysiology may explain the extensive overlap among these conditions (37). In addition, research on the etiology of one of these conditions could help further understanding of other conditions. In the clinical setting, an appreciation of the coexistence of these disorders will help physicians and patients to consider additional treatment options and achieve more satisfactory overall care.

Pathophysiology

Despite more than a decade of research, the etiology of chronic fatigue syndrome remains elusive. Many theories for the pathophysiology of chronic fatigue syndrome have been suggested, with earlier theories focusing on the prominence of symptoms that suggested an acute viral illness or a psychiatric disorder. Subsequent investiga-

tions have documented abnormalities in rather disparate domains, including brain structure and function, neuroendocrine responses, sleep architecture, immune function, virological studies, exercise capacity, and divergent psychological profiles (38). Despite the demonstration of abnormalities across these and other domains, such findings remain largely isolated observations, with the interactions and relationships among them unexplored. In addition, some more recent investigations have focused on understanding the heritability of chronic fatigue and chronic fatigue syndrome. It is possible that chronic fatigue syndrome is a heterogeneous syndrome with different pathophysiological anomalies manifesting with the same or similar symptoms. Many investigators have postulated that chronic fatigue syndrome is a condition of complex and multifactorial etiology. Indeed, some elements may predispose an individual to develop chronic fatigue syndrome, others may precipitate the illness, and still others perpetuate the disorder (38, 39).

Genetic Studies

To understand the relative importance of genetic and environmental influences on the development of a disorder, investigators often attempt to demonstrate its heritability and familiality using family, adoption, or twin studies. To our knowledge, no adoption studies of chronic fatigue syndrome have been conducted. One family history study of chronic fatigue syndrome, three twin studies of prolonged fatigue, and one twin study of chronic fatigue syndrome have been published.

In the family history study of chronic fatigue syndrome, results based on subjects' reports of illness in family members suggested that relatives of patients with chronic fatigue syndrome had significantly higher rates of chronic fatigue syndrome than relatives of medical comparison subjects (40). Two investigations involving twins aged 50 years and older from the volunteer Australian Twin Registry found that fatigue of at least 1 month's duration was moderately heritable (41, 42). The intrapair correlation (i.e., the correlation within twin pairs) for monozygotic twins was more than 2.5 times greater than the intrapair correlation for dizygotic pairs. Similarly, according to parental reports of fatigue, disabling prolonged fatigue lasting at least 1 month in childhood was familial among twins from a British twin registry (43). The intrapair correlations for monozygotic and dizygotic twins were 0.75 and 0.47, respectively. The model that best explained these results included additive genetic and nonshared environmental effects.

In the only twin study of chronic fatigue syndrome, data from a chronic fatigue twin registry were used to examine evidence for a familial clustering and genetic predisposition to chronic fatigue in female twins (44). Concordance rates were higher between monozygotic than between dizygotic twins across three definitions of fatigue: fatigue of at least 6 months' duration (42% versus 30%), chronic fatigue unexplained by other medical conditions (39% versus 21%), and chronic fatigue syndrome–like illness identified on the basis of self-reported symptoms and medical and psychiatric exclusion criteria consistent with the CDC criteria for chronic fatigue syndrome (38% versus 11%). Biometrical genetic modeling suggested that additive genetic factors and common environmental effects each accounted for more than 40% of the variance in liability for chronic fatigue syndrome–like illness. These results should be interpreted cautiously because of the potential for differential ascertainment bias by zygosity in volunteer twin subjects. Nonetheless, the findings suggest a familial predisposition for chronic fatigue of varying intensities, with both genetic and environmental contributions.

Taken together, the family and twin data suggest that prolonged fatigue and chronic fatigue syndrome–like illness may be familial and that genetic effects could be important. However, these results cannot be applied to a broader population because of several factors, such as the restricted age range of the twins included in the studies, the use of brief measures of fatigue, and the classification of chronic fatigue syndrome on the basis of self-report only. As with other conditions such as cardiovascular disease (45) and major depression (46), large population-based twin studies and family interview studies are necessary to further clarify the heritability of chronic fatigue syndrome.

Central Nervous System Abnormalities

Several symptoms reported by chronic fatigue syndrome patients—including fatigue; impaired concentration, attention, and memory; and headache—suggest that the central nervous system may be involved in the pathophysiology of the syndrome. Indeed, researchers have investigated a central nervous system (CNS) link to chronic fatigue syndrome by means of structural and functional neuroimaging, cognitive testing, neuropeptide assays, and autonomic assessment.

Neuroimaging studies. Neuroimaging research in chronic fatigue syndrome has primarily entailed magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT). Some MRI studies have detected significantly more abnormalities in the subcortical white matter of chronic fatigue syndrome subjects, compared to healthy or trauma comparison subjects (47–49), while in other MRI studies the results for subjects with chronic fatigue syndrome did not differ from those for healthy or depressed subjects (50–52). In addition, MRI abnormalities have not been associated with neurocognitive performance (53). Other studies using SPECT scans have found that chronic fatigue syndrome patients have lower levels of regional cerebral blood flow throughout the brain, compared to healthy subjects (50, 54). CNS perfusion abnormalities, typically hypoperfusion, also have been found more often on

SPECT scans in chronic fatigue syndrome patients than in healthy or depressed comparison subjects, although no specific anatomic pattern has emerged and the effect of comorbid major depression is difficult to ascertain (51, 54). Conversely, a recent rigorously controlled study detected no difference in cerebral blood flow between twins with chronic fatigue syndrome and their healthy co-twins (55). Overall, MRI and SPECT studies are generally consistent in demonstrating some abnormalities in chronic fatigue syndrome patients. However, the functional significance and clinical utility of these findings remain uncertain and await further clarification (52).

Neuropsychological studies. Cognitive problems are some of the most disruptive and disabling symptoms of chronic fatigue syndrome (56). Although as many as 85% of patients complain of impairments in attention, concentration, and memory abilities (57, 58), formal neuropsychological studies have not yielded consistent results. As a recent review of neuropsychological studies in chronic fatigue syndrome confirmed, the weight of the evidence suggests a modest but significant deficit in information processing, impaired working memory, and poor learning of information (59). These impairments could account for the poorer performance of subjects with chronic fatigue syndrome on complex attention and information-processing tasks (60). Coexisting psychological distress or psychiatric disorder also may contribute to neurocognitive deficits. In general, however, persons with chronic fatigue syndrome appear to possess normal cognitive and global intellectual abilities (60, 61).

Neuroendocrine studies. A recent comprehensive review of neuroendocrine studies (62) reported that abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis and serotonin pathways have been identified in chronic fatigue syndrome patients, suggesting an altered physiological response to stress (63). About one-third of patients with chronic fatigue syndrome have been shown to exhibit hypocortisolism (62), which appears to originate from a CNS source rather than a primary adrenal site (64, 65). It is interesting to note that a recent study of a family with 32 members who had chronic fatigue syndrome reportedly identified a genetic mutation that affects the ability to produce globulin, a protein essential for the transport of cortisol in the blood (66).

In addition, studies have demonstrated abnormalities of CNS serotonin physiology in patients with chronic fatigue syndrome (62). More specifically, administration of serotonin agonists causes a significant increase in serum prolactin levels in chronic fatigue syndrome patients, relative to depressed and healthy comparison subjects, suggesting a CNS up-regulation of the serotonergic system. In contrast, patients with clinical depression demonstrate an opposite pattern of hypercortisolism and have a suppressed serotonin-mediated prolactin response (67, 68). The studies of abnormalities in HPA function, hormonal stress responses, and serotonin neurotransmission in chronic fatigue syndrome patients have generated the most reproducible and robust findings reported to date.

Autonomic activity studies. Autonomic dysfunction, demonstrated by tilt-table testing and manifested by hypotension with bradycardia (vasovagal reaction) or hypotension with tachycardia (vasodepressor reaction) upon vertical tilting, has been inconsistently implicated in the pathophysiology of chronic fatigue syndrome (69–73). However, the precise nature and extent of autonomic system involvement in chronic fatigue syndrome are still undetermined. While anecdotal reports suggest chronic fatigue syndrome patients with symptoms indicative of neurally mediated hypotension often improve with fluid, salt, or fludrocortisone therapy (74), these improvements have not been demonstrated in large, well-controlled trials (75, 76). This type of therapy also is unlikely to be useful for all patients with chronic fatigue syndrome (75).

Immune System Abnormalities

Despite many studies of the immune system, only a few abnormalities have been consistently reported in chronic fatigue syndrome patients. These include increased expression of activation markers on the cell surface of T lymphocytes (77, 78), especially increased numbers of CD8+ cytotoxic T cells that bear certain antigenic markers (79), and deficiencies in natural killer cell function (80–84). Other findings include higher frequencies of various autoantibodies (85, 86). Although collectively these results point to chronic low-level immune system activation, whether these abnormalities have any relationship to the symptoms of chronic fatigue syndrome remains unclear. Some findings suggest that the degree of cellular immune activation could be associated with the severity of the physical symptoms, cognitive complaints, and perceived impairment associated with chronic fatigue syndrome (87). However, others have shown that clinical improvement in chronic fatigue syndrome was not associated with changes in lymphocyte subsets or activation (88). At this time, there are no immunological tests that are diagnostic for chronic fatigue syndrome (89).

Infectious Agents

Epstein-Barr virus, human herpesvirus 6, group B coxsackie virus, human T-cell lymphotrophic virus II, hepatitis C, enteroviruses, and retroviruses, among others, have been proposed as etiological agents in chronic fatigue syndrome (90). Research is focusing on a potential marker for viral infection (91). Even so, there has been no consistent evidence to date that chronic fatigue syndrome results from a specific infection (92). In fact, some patients have no clinical or laboratory evidence of viral infection (93), and antiviral agents such as acyclovir or interferon α have not been beneficial in the treatment of chronic fatigue syndrome (94, 95). Therefore, it is improbable that a single infectious agent causes chronic fatigue syndrome.

Rather, a heterogeneous group of infections may trigger or perpetuate the symptoms of chronic fatigue syndrome.

Sleep Disruption

Chronic fatigue syndrome patients report more difficulty falling asleep, more interrupted sleep, and more daytime napping than healthy or chronically ill comparison subjects (96–98); however, polysomnography has yielded variable results. Some studies of chronic fatigue syndrome have revealed a characteristic "alpha intrusion" during non-REM sleep (99) and decrease in stage 4 sleep (100), while other studies have not (96, 98, 101). Thus, in contrast to findings with major depression (102), the results of polysomnography in chronic fatigue syndrome have not shown a consistent or diagnostic sleep disturbance. It is interesting to note that sleep disruption does not appear to correlate with fatigue severity (98) or degree of functional status impairment (100). Finally, some individuals with the symptoms of chronic fatigue syndrome who are assessed with polysomnography are discovered to have a sleep disorder such as sleep apnea (98, 103). Such conditions are readily treatable and, if they are severe, exclude a diagnosis of chronic fatigue syndrome. Some investigators believe sleep disorders are the most commonly overlooked medical diagnoses among chronic fatigue syndrome patients (101), underscoring the importance of distinguishing fatigue from sleepiness.

Exercise Studies

Patients with chronic fatigue syndrome often complain of exercise intolerance. Many patients report that even minor efforts at physical activity lead to significant worsening of fatigue and other symptoms. In addition, some evidence suggests that many chronic fatigue syndrome patients cope with their illness by resting or avoiding physical activity (104–106). A study that used objective actigraphic monitoring of physical activity patterns found that chronic fatigue syndrome subjects were overall less active than neighborhood comparison subjects and took longer rest periods after activity peaks but that only about one-fourth were pervasively inactive (107). Thus, subjectively and possibly objectively, chronic fatigue syndrome patients have reduced physical activity, which could exacerbate or perpetuate fatigue.

Consequently, several studies have focused on chronic fatigue syndrome patients' strength, level of conditioning, and physiological response to exercise, with mixed results. A number of studies have provided evidence for a model in which physical deconditioning helps to maintain physical disability (108). These studies have demonstrated an increase in lactic acid in response to exercise (109) and reductions in capacity for oxygen transport (110), number of muscle mitochondria (111), and physical fitness and exercise capacity (112–114). Other studies, however, have found normal or near-normal aerobic capacity (115, 116) and muscle function (117, 118) and postexercise lactate concentrations comparable to those in sedentary comparison subjects (116).

Given the same level of laboratory-documented physical activity, many chronic fatigue syndrome patients do not achieve their age-predicted maximal heart rate (119, 120). They perceive the requisite effort and resulting fatigue as significantly higher (118), yet the degree of measurable effort is significantly lower (117) than in sedentary comparison subjects. These observations are more consistent with submaximal exertion than with physical deconditioning, possibly as a result of perceptual shifts in assessing bodily sensations. While these findings do not clarify the role of exercise capacity in chronic fatigue syndrome, they do suggest that the perception of increased effort, decreased activity, and the ensuing physical deconditioning can perpetuate the symptoms of chronic fatigue syndrome.

Psychiatric Disorders

Because a consistent physiological marker or physical finding for chronic fatigue syndrome has not been identified, some researchers have postulated that chronic fatigue syndrome is primarily a psychiatric disorder (121, 122). Several researchers believe that chronic fatigue syndrome and related disorders are manifestations of a psychiatric condition such as somatization disorder (123), hypochondriasis (124), major depression (125, 126), or atypical depression (127). Indeed, persons with chronic fatigue syndrome have an increased prevalence of current and lifetime mood disorders, primarily major depression, compared to other chronically ill subjects or healthy comparison subjects; 25% and 50%–75% of patients have a current or a lifetime history of major depression, respectively (128–132). Generalized anxiety disorder and somatoform disorder also occur at a higher rate in chronic fatigue syndrome subjects than in the general population (128, 133–135). In most (130–132), but not all cases (3, 136), the mood or anxiety disorder precedes the onset of chronic fatigue syndrome.

Of special note is the issue of how psychiatric prevalence in chronic fatigue syndrome is determined. The Diagnostic Interview Schedule (137), a highly structured interview designed to be administered by lay interviewers, is the instrument most commonly used to ascertain psychopathology in chronic fatigue syndrome. Thus, by rigidly attributing unexplained symptoms such as fatigue to psychiatric causes, it may overestimate the prevalence of psychiatric disorders in chronic fatigue syndrome patients. Several studies that have used the Structured Clinical Interview for DSM-III-R (138), a semistructured interview that is administered by a trained clinician, have found that its use results in lower rates of psychiatric disorders in chronic fatigue syndrome (15, 136, 139).

Somatization disorder. Compared to a prevalence of 0.03% for somatization disorder in the community (140), the prevalence in chronic fatigue syndrome is high, with

rates up to 28% (121, 130, 131, 134–136, 141–143). The evaluation of somatization disorder in chronic fatigue syndrome, however, is strongly affected by the attributions made regarding the patient's symptoms. Although the distinctions between physical and psychiatric illnesses often are not useful or accurate, their differentiation is in part the basis for a diagnosis of somatization. Thus, whether the multiorgan and poorly understood symptoms typical of chronic fatigue syndrome are considered to be medically or psychiatrically based influences the frequency of somatization disorder (141). Indeed, when the symptoms of chronic fatigue syndrome are considered to result from physical and not psychiatric causes, the rate of somatization disorder is dramatically reduced in patients with chronic fatigue syndrome (141). Thus, the diagnosis of somatization disorder is, to a considerable degree, dependent on the examiner's attributions of chronic fatigue syndrome symptoms (144) and is of limited use in understanding chronic fatigue syndrome.

Anxiety disorders. Anxiety disorders are common in the general population, with lifetime rates of 3.5% and 5.1% for panic disorder and generalized anxiety disorder, respectively (145). Panic disorder and generalized anxiety disorder are also common comorbid conditions among those with chronic fatigue syndrome, although chronic fatigue syndrome is characterized differently across studies. Lifetime prevalence rates for panic disorder in chronic fatigue syndrome are estimated to range from 17% to 25%, and rates for generalized anxiety disorder from 2% to 30% (133, 134, 146). This literature points to an overlap between chronic fatigue syndrome and anxiety. This overlap, along with some neurobiological similarities between chronic fatigue syndrome and generalized anxiety disorder—including decreased cerebral blood flow, sympathetic overactivity, and sleep abnormalities (147)—argues for further investigation of the relationship between chronic fatigue syndrome and anxiety disorders. The simple comorbidity of chronic fatigue syndrome and anxiety disorders, however, does not suggest that chronic fatigue syndrome is a physical manifestation of an anxiety disorder.

Major depression. Persons with chronic fatigue syndrome have high rates of current and lifetime major depression, which has been taken as evidence that chronic fatigue syndrome is an atypical manifestation of major depression. On the other hand, the high rates of depression in chronic fatigue syndrome could be a result of overlapping symptoms, an emotional response to disabling fatigue, viral or immune changes, or alterations in brain physiology (144). In fact, several lines of research have suggested that chronic fatigue syndrome and major depression are possibly distinct entities. First, while some symptoms of chronic fatigue syndrome are also symptoms of major depression, many others—such as sore throat, adenopathy, arthralgias, and postexertional fatigue—are not typical of psychiatric disorders. Second, the pattern of symptoms differs significantly, with chronic fatigue syndrome patients generally not endorsing the classic depressive symptoms of anhedonia, guilt, and lack of motivation (128, 148, 149) but more closely resembling patients with multiple sclerosis (149). Third, severe major depression may be associated with a central up-regulation of the HPA axis, resulting in mild hypercortisolism (67, 68); conversely, in chronic fatigue syndrome, a central down-regulation is observed (64). Fourth, the typical sleep abnormalities of major depression—reduced REM latency and increased REM density (102)—are not usually present in chronic fatigue syndrome. Fifth, therapeutic doses of antidepressants have not been overwhelmingly effective in treating the symptoms of chronic fatigue syndrome (150). Sixth, many patients with chronic fatigue syndrome have no evidence of major depression at any point in their lives. Finally, simple comorbidity of chronic fatigue syndrome and depression does not address their temporal relationship; depressive symptoms could precede or occur in response to the illness. In this regard, anxiety and depression are the most common emotional responses to a medical illness (151).

Although the data thus far suggest that chronic fatigue syndrome and psychiatric disorders (especially major depression) are distinct, the relationship between chronic fatigue syndrome and psychiatric diagnoses remains an area of controversy. The fundamental issue is one of diagnostic labeling for symptom-based disorders in the absence of marked physiological findings or a clear etiology. Historically, this issue may have been resolved by distinguishing between "medical or physical" and "psychiatric" conditions. While a comprehensive discussion of diagnostic labeling is beyond the scope of this article, there are many debates regarding the utility and appropriateness of making this distinction (152). In addition, the success of pharmacological agents in the treatment of psychiatric disorders has blurred this distinction, perhaps suggesting that there is no distinction to be made (153). More recently, a multiaxial model of diagnosis has been proposed that would take into account the biological, psychological, and social factors involved in any particular diagnosis and the associated impairment (154). While the debate about chronic fatigue syndrome as a "medical" or "psychiatric" condition undoubtedly will continue, it is unlikely that major depression, for example, will prove to be the sole or primary cause of chronic fatigue syndrome. Clinically, however, since many patients with chronic fatigue syndrome suffer from major depression and anxiety disorders, efforts should be made to assess and treat these conditions as well as the symptoms of chronic fatigue syndrome.

Attribution, Perception, and Coping

Attributions about the causes of an illness or its symptoms are important in determining a patient's response to the illness (155). Patients with chronic fatigue syndrome often attribute their illness to physical causes and minimize psychological or personal contributions (148, 156, 157). For example, compared to patients with diabetes, rheumatoid arthritis, and chronic pain, those with chronic fatigue syndrome attributed their symptoms more often to "a virus" or "pollution" and less often acknowledged a role for their own behavior (56). Such causal attributions have been related to an increase in symptoms (158) and functional impairment (159, 160) and to worse subjective and objective outcomes over time (161). It is noteworthy that relatives also tend to attribute the patients' symptoms to somatic causes (157), and their beliefs and attributions about chronic fatigue syndrome, as well as solicitous behavior, may inadvertently reinforce patients' illness behavior (162). Although it has been suggested that somatic attributions may be a risk factor for the development of chronic fatigue syndrome (157), at the very least, they probably exacerbate the illness and lead to greater disability.

Perception of bodily sensations and symptoms can affect the interpretation of somatic experiences and illness (163). Subjectively, patients with chronic fatigue syndrome and those with chronic pain scored significantly higher than healthy comparison subjects on a measure of somatic perceptual distortions, suggesting that both groups view themselves as seriously ill (164). Perceptions regarding immune functioning have been strongly related to mood and feelings of fatigue but were unrelated to objective measures of immunity such as serum antibodies or blood lymphocytes (165). Moreover, perception of the symptoms of chronic fatigue syndrome has been shown to be a strong predictor of vitality and physical and social functioning (166, 167).

Objective findings from exercise and pain testing in chronic fatigue syndrome patients have been suggestive of perceptual distortions in assessing bodily sensations. In addition to the exercise studies cited earlier, other studies have assessed pain threshold and tolerance by using pressure dolorimetry and the cold pressor test in healthy subjects and those with chronic fatigue syndrome and major depression (168). Subjects with chronic fatigue syndrome and depression had significantly more pain complaints than comparison subjects, but the groups did not differ in pressure or cold pain threshold or tolerance. These findings are consistent with the increased perceptual sensitivity (low threshold and tolerance) to heat, pressure, and cold pain demonstrated in fibromyalgia (169–171), a closely related disorder. Overall, studies of perception suggest that, regardless of the etiology of chronic fatigue syndrome, the ways in which chronic fatigue syndrome patients perceive themselves, label their symptoms, and appraise stressors may perpetuate or exacerbate their physical and psychosocial dysfunction.

Individuals with chronic fatigue syndrome employ a variety of strategies to cope with the debilitating consequences of fatigue. Overall, several studies suggest that patients with chronic fatigue syndrome use significantly more escape/avoidance strategies, compared with healthy subjects (172), age- and gender-matched primary care patients without chronic fatigue (173), or their nonfatigued twins (174). Avoidance strategies, in turn, have been associated with greater fatigue, impairment, and other psychosocial disturbances in chronic fatigue syndrome (175, 176). Thus, while not a cause of chronic fatigue syndrome, maladaptive coping strategies can perpetuate the illness.

Clinical Evaluation

To date, no single test has been sufficiently sensitive or specific enough to constitute a diagnostic test for chronic fatigue syndrome. The clinical evaluation of chronically fatigued patients is aimed at detecting underlying medical or psychiatric causes of fatigue, many of which are specified in the CDC case definition (8). To accomplish this, the National Institutes of Health has recommended that patients with chronic fatigue be evaluated with a battery of standard laboratory tests and a complete physical examination (26). Nonetheless, laboratory tests and physical examination are generally unremarkable in chronic fatigue syndrome (177). The most common abnormality is the presence of musculoskeletal tenderness at various sites that is consistent with fibromyalgia, which occurs in as many as 70% of chronic fatigue syndrome patients (35).

While most nonpsychotic psychiatric disorders are not exclusionary for the diagnosis of chronic fatigue syndrome, the assessment of comorbid psychiatric disorders is imperative in the adequate management of patients with chronic fatigue syndrome. Indeed, major depression is the most significant factor in the differential diagnosis of chronic fatigue syndrome. Other personality and psychosocial factors should also be considered. Although many chronic fatigue syndrome patients do not have current psychiatric disorders, maladaptive coping styles, or other psychopathology, assessing the presence of these issues as part of the routine clinical evaluation can be the first step in treating both chronic fatigue syndrome and other symptoms.

Treatment

Because of the unclear etiology, diagnostic uncertainty, and the resultant heterogeneity of the chronic fatigue syndrome population, there are no firmly established treatment recommendations for chronic fatigue syndrome. In practice, therapy, whether pharmacological or nonphar-

TABLE 1. Controlled or Case-Control Studies of Treatment for Chronic Fatigue Syndrome, by Therapy Category

Therapy Category and Study	Year	Comparisons	Results
Immunological and antiviral			
Straus et al. (94)	1988	Acyclovir versus placebo	Inconclusive
Lloyd et al. (178)	1990	Immunoglobulin G (IgG) versus placebo	IgG > placebo
Strayer et al. (179)	1994	Ampligen versus placebo	Ampligen > placebo
Steinberg et al. (180)	1996	Terfenadine versus placebo	No difference
Peterson et al. (181)	1990	IgG versus placebo	No difference
Vollmer-Conna et al. (182)	1997	IgG versus placebo	No difference
See and Tilles (183)	1996	Interferon-α2a versus placebo	No difference
Brook et al. (184)	1993	Interferon-α2b versus no treatment	Inconclusive
De Vinci et al. (185)	1996	Dialyzable extract from immune lymphocytes versus placebo	No difference
Andersson et al. (186)	1998	Staphylococcus toxoid vaccine versus placebo	Inconclusive
Immunological and nonpharmacological therapy			
Lloyd et al. (187)	1993	Dialyzable leukocyte extract and cognitive behavior therapy versus either treatment alone versus placebo	Combination treatment > either treatment alone or placebo for effects on quality of life
Pharmacological			
Peterson et al. (75)	1998	Fludrocortisone versus placebo	No difference
Rowe et al. (76)	2001	Fludrocortisone versus placebo	No difference
Vercoulen et al. (150)	1996	Fluoxetine versus placebo	No difference
McKenzie et al. (188, 189)	1998, 2000	Hydrocortisone versus placebo	No difference
Moorkens et al. (190)	1998	Growth hormone versus placebo	No difference
Snorrason et al. (191)	1996	Galanthamine versus placebo	No difference
Forsyth et al. (192)	1999	Nicotinamide adenine diucleotide versus placebo	Inconclusive
Natelson et al. (193)	1996	Phenelzine versus placebo	No difference
Hickie et al. (194)	2000	Moclobemide versus placebo	Inconclusive
Cleare et al. (195)	1999	Hydrocortisone versus placebo	Hydrocortisone > placebo
Natelson et al. (196)	1998	Selegiline versus placebo	Selegiline > placebo
Pharmacological and physical			
Wearden et al. (197)	1998	Fluoxetine and graded exercise versus placebo	Fluoxetine improved depression; exercise improved health perception and fatigue
Physical			
Fulcher and White (198)	1997	Graded exercise therapy versus flexibility/relaxation	Exercise > flexibility/relaxation
Powell et al. (199)	2001	Maximum exercise education, minimum exercise education, or educational telephone intervention versus standardized medical care	All education groups > standardized medical care
Field et al. (200)	1997	Massage versus sham transcutaneous electrical nerve stimulation	Massage > sham transcutaneous electrical nerve stimulation
Perrin et al. (201)	1998	Osteopathic therapy versus normal care	Osteopathic therapy > normal care
Multidimensional			
Friedberg and Krupp (202)	1994	Cognitive behavior therapy versus no treatment	Cognitive behavior therapy > no treatment
Deale et al. (203, 204)	1997, 1998	Cognitive behavior therapy versus relaxation	Cognitive behavior therapy > relaxation
Sharpe et al. (205, 206)	1996, 1998	Cognitive behavior therapy and medical care versus medical care only	Combination treatment > medical care only
Chisholm et al. (207)	2001	Cognitive behavior therapy versus counseling	No difference
Ridsdale et al. (208)	2001	Cognitive behavior therapy versus counseling	No difference
Prins et al. (209)	2001	Cognitive behavior therapy versus guided support groups versus natural course	Cognitive behavior therapy > guided support groups; cognitive behavior therapy > natural course
Shlaes and Jason (210)	1996	Buddy and mentor versus waiting list comparison condition	Buddy/mentor > waiting list comparison condition
Marlin et al. (211)	1998	Medical management, psychiatric treatment, and cognitive behavior therapy versus assessment only	Inconclusive
Nutritional supplements and other products			
Cox et al. (212)	1991	Magnesium sulfate versus placebo	Treatment > placebo
Warren et al. (213)	1999	Essential fatty acid versus placebo	No difference
Kaslow et al. (214)	1989	Liver extract containing folic acid and cyanocobalamin versus placebo	No difference
Awdry (215, 216)	1996, 1996	Homeopathy versus placebo	Inconclusive

macological, has been generally directed toward relieving symptoms and improving function. Table 1 summarizes the findings of controlled trials and case-control treatment studies with at least 10 subjects with chronic fatigue syndrome diagnosed according to an established definition. These treatment studies have evaluated immunological substances, pharmacological products, nutritional supplements, physical therapies, and multidimensional

treatments. With the exception of findings for physical and multidimensional treatments (i.e., behavioral interventions), the results of these controlled treatment studies have been negative or inconclusive (217).

Pharmacological Treatments

With the exception of one placebo-controlled trial of immunoglobulin G (IgG) (178) and a randomized, placebo-controlled, double-blind study of a ribonucleic acid (179), immunological and antiviral substances have not been shown to be effective in the treatment of fatigue and other symptoms in chronic fatigue syndrome (94, 180–185). Other pharmacological substances, including anticholinergics, hormones, nicotinamide adenine dinucleotide, and antidepressants, have been studied, essentially without positive results (75, 76, 150, 188–194). One trial found decreased fatigue after treatment with steroids, compared to placebo (195), but another steroid trial did not (188). Response to selective serotonin reuptake inhibitors such as fluoxetine has been minimal, possibly because of the aforementioned serotonergic hypersensitivity demonstrated in chronic fatigue syndrome (67, 150). Monoamine oxidase inhibitors have demonstrated modest promise, especially, as expected, in populations with significant vegetative symptoms (196, 218). Although the benefit of antidepressant medications has not been conclusively demonstrated in controlled trials, their success in treatment of the related disorder of fibromyalgia (219) makes them a reasonable intervention. Anecdotal evidence suggests that low doses of these medications (e.g., 10–30 mg of nortriptyline) administered at bedtime improve sleep and diminish pain (95). In addition, the use of acetaminophen or other nonsteroidal anti-inflammatory agents may be worthwhile in patients with prominent musculoskeletal complaints.

Nonpharmacological and Behavioral Interventions

Nonpharmacological treatments—specifically, graded exercise programs and cognitive behavior therapy—have shown promise in improving the outcome of chronic fatigue syndrome. Their use is based on research suggesting that cognitive and behavioral factors play a role in perpetuating the symptoms of chronic fatigue syndrome. In this regard, cognitive behavior therapy, which has been effective in treating depression and pain conditions such as chronic low back pain and atypical chest pain, can be used to increase activity and teach effective coping strategies (220).

Although earlier studies of cognitive behavior therapy for chronic fatigue syndrome had mixed results (187, 202), more recent and well-controlled trials found that more than 70% of patients who received 13–16 sessions of cognitive behavior therapy improved in their physical and other functioning, compared to about 20%–27% of participants assigned to relaxation (203, 204) or usual medical care (205, 206). Counseling also may be as useful as a cognitive behavioral approach in treating chronic fatigue and chronic fatigue syndrome in primary care (207, 208).

In addition, randomized controlled trials of graded aerobic exercise in comparison with flexibility/relaxation interventions have reported significant improvements in fatigue, functional status, and fitness (197, 198, 221). Education about the benefits of exercise also has been shown to be effective in increasing chronic fatigue syndrome patients' activity level (199). It is important to note that improvements resulting from these behavioral approaches appear to be sustained over 6–14 months of follow-up (203, 205, 209) and even as long as 5 years after treatment (222). Taken together, these studies provide some evidence that graded exercise and cognitive restructuring can positively affect the physical health and functioning of many patients with chronic fatigue syndrome. A useful focus for future studies would be to delineate the patient population that would obtain the most benefit from these treatments.

Alternative and Complementary Approaches

Like patients with other chronic illnesses for which conventional medicine has been unable to provide a cure or adequate symptom relief, many patients with chronic fatigue syndrome use alternative treatments with unknown outcome (9, 32, 223). These treatments include megavitamins, energy healing, herbal therapies, and special diets (223–225). However, controlled studies to determine the effectiveness of these treatments are almost nonexistent. Magnesium sulfate is the only substance shown to positively affect the health and functioning of chronic fatigue syndrome patients in a randomized, double-blind, placebo-controlled study (212). However, three subsequent reports, one open trial, and two assessment studies found no evidence of magnesium deficiency in chronic fatigue syndrome patients (226).

Patient Advocacy and Self-Help

The chronic fatigue syndrome patient population as a whole is well informed and has a strong community support network. A quick search of one Internet search engine using the key words "chronic fatigue syndrome," "self-help," and "patient advocacy" located more than 5,000 sites. Because the causes and adequate treatment of chronic fatigue syndrome are not firmly established, self-help and support groups can provide patients with information and a sense of community. Some of this information about chronic fatigue syndrome and popular treatments, however, may not be consistent with evidence-based medicine (227). Patient advocacy groups also provide information, promote research, and provide encouragement and support services to chronic fatigue syndrome patients. These groups have focused primarily on the social and medical/treatment implications of labeling chronic fatigue syndrome as a medical or psychiatric disorder. Ultimately, however, the goal of these advocacy

groups is to promote continued research to obtain adequate treatment.

Prognosis

Longitudinal studies of varying duration have shown that although 17%–64% of patients with chronic fatigue syndrome improve, less than 10% fully recover, and another 10%–20% worsen during follow-up (105, 175, 228, 229). However, most of these studies were conducted among patients in tertiary treatment or referral settings; outcomes in primary care settings have a substantially better prognosis (229). Older age, longer illness duration, fatigue severity, comorbid psychiatric illness, and a physical attribution for chronic fatigue syndrome tend to be risk factors for poorer prognosis (229). Conversely, children and adolescents appear to recover more readily (230). Specific therapies directed at underlying mechanisms may significantly improve outcome and should offer hope for chronic fatigue syndrome patients.

Conclusions

Chronic fatigue syndrome is an illness characterized by debilitating fatigue, along with cognitive, musculoskeletal, and sleep symptoms. Since there are no specific diagnostic tests or biological markers for chronic fatigue syndrome, the diagnosis is made by ruling out other causes of fatigue. Regardless of the lack of specific markers for chronic fatigue syndrome, individuals who fulfill the criteria for the syndrome may experience significant physical and psychosocial impairment. The pathophysiology of chronic fatigue syndrome is still unclear. However, a growing body of literature suggests that abnormal biological processes are present in many patients, including subtle abnormalities of the CNS and of neuroendocrine regulation and chronic activation of the immune system. These abnormalities across many domains suggest that chronic fatigue syndrome is a heterogeneous condition of complex and multifactorial etiology.

Additional evidence is emerging that chronic fatigue syndrome may be familial; future studies will examine the extent to which genetic and environmental factors play a role in the development of chronic fatigue syndrome. There is significant comorbidity with psychiatric conditions, yet some evidence suggests that chronic fatigue syndrome is not solely a manifestation of an underlying psychiatric disorder. However, patients' perceptions, illness attributions, and coping skills may help to perpetuate the illness. Taken together, current knowledge about chronic fatigue syndrome suggests that genetic, physiological, and psychological factors work together to predispose an individual to the condition and to precipitate and perpetuate the illness.

Given the heterogeneity of the syndrome and the present state of research, an instant cure for chronic fatigue syndrome is unlikely. Treatment is symptom-based and includes pharmacological and behavioral strategies. Cognitive behavior therapy and graded exercise programs can be especially effective in treating fatigue and the associated symptoms and disability in some patients. In addition, successful treatment can focus on improving comorbid conditions such as major depression and sleep apnea, reducing painful symptoms, increasing activity, improving coping skills, and reducing catastrophic thinking, with the goal of improving the patient's level of functioning. Any effective treatment is built on a foundation of patient-physician respect and advocacy, and treatment must be individualized, reflecting the heterogeneity of the chronic fatigue syndrome population.

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