

# Chronic Fatigue Syndrome

## A Practical Guide to Assessment and Management

M. Sharpe, M.A., M.R.C.P., M.R.C.Psych., T. Chalder, R.M.N., M.Sc.,  
I. Palmer, B.M., B.Ch., M.R.C.Psych., and  
Simon Wessely, M.A., M.Sc., M.D., F.R.C.P., M.R.C.Psych.

**Abstract:** *Chronic fatigue and chronic fatigue syndrome (CFS) have become increasingly recognized as a common clinical problem, yet one that physicians often find difficult to manage. In this review we suggest a practical, pragmatic, evidence-based approach to the assessment and initial management of the patient whose presentation suggests this diagnosis. The basic principles are simple and for each aspect of management we point out both potential pitfalls and strategies to overcome them. The first, and most important task is to develop mutual trust and collaboration. The second is to complete an adequate assessment, the aim of which is either to make a diagnosis of CFS or to identify an alternative cause for the patient's symptoms. The history is most important and should include a detailed account of the symptoms, the associated disability, the choice of coping strategies, and importantly, the patient's own understanding of his/her illness. The assessment of possible comorbid psychiatric disorders such as depression or anxiety is mandatory. When the physician is satisfied that no alternative physical or psychiatric disorder can be found to explain symptoms, we suggest that a firm and positive diagnosis of CFS be made. The treatment of CFS requires that the patient is given a positive explanation of the cause of his symptoms, emphasizing the distinction among factors that may have predisposed them to develop the illness (lifestyle, work stress, personality), triggered the illness (viral infection, life events) and perpetuated the illness (cerebral dysfunction, sleep disorder, depression, inconsistent activity, and misunderstanding of the illness and fear of making it worse). Interventions are then aimed to overcoming these illness-perpetuating factors. The role of antidepressants remains uncertain but may be tried on a prag-*

*matic basis. Other medications should be avoided. The only treatment strategies of proven efficacy are cognitive behavioral ones. The most important starting point is to promote a consistent pattern of activity, rest, and sleep, followed by a gradual return to normal activity; ongoing review of any 'catastrophic' misinterpretation of symptoms and the problem solving of current life difficulties. We regard chronic fatigue syndrome as important not only because it represents potentially treatable disability and suffering but also because it provides an example for the positive management of medically unexplained illness in general. © 1997 by Elsevier Science Inc.*

### Introduction

Chronic fatigue syndrome (CFS) denotes a syndrome of severe disabling physical and mental fatigue, exacerbated by minimal exertion and unexplained by a conventional biomedical diagnosis. It is typically accompanied by other symptoms such as myalgia, sleep disturbance, and mood disorder. Several operational definitions have been published (see Table 1). CFS is a relatively new diagnostic label, but the syndrome itself is far from new and was clearly described 100 years ago under the diagnosis of neurasthenia [1]. It also has marked similarities to the modern syndrome of fibromyalgia [2].

Numerous general reviews of CFS have been published, but few of these have provided practical guidance on the assessment and treatment of patients [3]. In the following article we attempt to rectify this deficiency.

### *The Clinical Problem*

The clinical problem we address is the assessment and management of the patient with a possible CFS.

---

University of Edinburgh, UK (M.S.), Academic Department of Psychological Medicine, King's College School of Medicine and Institute of Psychiatry, University of London, UK (T.C.), Royal Army Medical College, Millbank, London, UK, (I.P.), and Department of Psychological Medicine, King's College Hospital Medical School and Institute of Psychiatry, University of London, UK (S.W.).

Address reprint requests to: Prof. Simon Wessely, Department of Psychological Medicine, King's College School of Medicine, 103 Denmark Hill, London, SE5 9RS.

**Table 1.** Case definitions for chronic fatigue syndrome

	CDC-1988 [128]	CDC-1994 [34]	UK [33]
Minimum duration (months)	6	6	6
Functional impairment	50% Decrease in activity	Substantial	Disabling
Cognitive or neuropsychiatric symptoms (subjectively impaired concentration, memory and word-finding difficulties)	May be present	May be present	Mental fatigue required
Other symptoms	6 or 8 Required	4 Required	Not specified
New onset	Required	Required	Required
Medical exclusions	Extensive list of known physical causes	Clinically important	Known physical causes
Psychiatric exclusions	Psychosis, bipolar disorder, substance abuse,	melancholic, depression, substance abuse, bipolar disorders, psychosis, eating disorder	Psychosis, bipolar, eating disorder, organic brain disease

Two presentations may suggest this possibility. One is the patient who complains of the *symptoms* of severe persistent fatigue or exhaustion. The other is the patient who arrives with a *belief* that he/she has a fatiguing illness such as CFS, chronic fatigue, and immune deficiency syndrome (CFIDS) or myalgic encephalomyelitis (ME). It is important to note that although these two groups of patients overlap, they are not identical; many with fatigue do not have specific diagnostic beliefs and some with the aforementioned specific illness beliefs actually have other readily diagnosable diseases. The patients who cause the greatest clinical difficulty are those with both severe symptoms and strong beliefs. This is the group we will focus on in this review.

**Clinical Example.** Susan was referred by her family doctor to the infectious diseases clinic of the local teaching doctor. She is a 35-year-old teacher who complained of intense fatigue, poor concentration, and muscle pain. All of these symptoms were exacerbated by minor physical and mental exertion. She had abandoned all her previous social and leisure activities, and had not worked for the last year. She had been ill for 2 years following an otherwise unremarkable febrile episode, labelled by both her and her doctor as influenza. She had no serious illnesses in the past, although had suffered from irritable bowel syndrome for some years. Physical examination was entirely normal, as were routine investigations. She was frustrated about her illness, and admitted to periods of depression, par-

ticularly when contemplating her future. However, there was no evidence of abnormal guilt or suicidal ideation. She was certain her illness was 'medical' rather than 'psychiatric,' and had been very offended when her doctor had suggested taking a course of antidepressants.

How should the clinician approach this clinical problem? We suggest a three-stage strategy: 1) forming a positive relationship with the patient, 2) making an adequate clinical assessment, and 3) planning and implementing effective individualized management. The problems encountered at each of these stages will be described and solutions to these suggested.

### Forming a Positive Relationship with the Patient

Nothing can be achieved without a good doctor-patient relationship. Establishing this is therefore the first task facing the clinician. One of the main causes of difficulty is conflict between the doctor and patients in their beliefs about the nature and cause of the illness. The majority of patients seen in specialist clinics typically believe that their symptoms are the result of an organic disease process, and resent any suggestion that they are psychological in origin or psychiatric in nature [4-6]. Many doctors believe the converse.

Such illness beliefs are not merely abstractions but may be associated with strong emotion. The reasons for this emotion can be discerned from the

views expressed by both patient literature and individual patients. The literature is replete with statements such as “CFS is a real illness—it is not psychiatric,” and “CFS is a genuine physical disorder and not a psychiatric problem” (see [7] for these and other examples). Individuals explain that a psychiatric label implies not only that the symptoms are unreal, but also that they are at fault for developing them. This defensive function of a physical attribution is supported by systematic studies [8,9]. Consequently, any suggestion by the clinician that the patient’s symptoms are psychiatric is almost certain to be perceived as a personal attack, lead to anger, and irretrievably damage the relationship [10].

The patient may not be the only one with idiosyncratic beliefs about the illness; physicians’ beliefs and attitudes are also important in determining whether a positive relationship is established [11]. Some physicians appear to believe that somatic symptoms in the absence of demonstrable disease are imaginary and dismiss them as not deserving their attention. Even if the assessing clinician is sympathetic, the patient’s behavior may be influenced by previous encounters with others who were not.

We believe that the most effective way of avoiding such difficulties is for the physician to inquire into the patient’s beliefs and to treat them with respect (even if he/she does not agree with them). It is also important that he/she avoid the tendency to automatically translate somatic complaints into psychiatric jargon or to imply that they are psychogenic in origin. This acceptance of the patient is combined with empathy for his predicament which is often not only one of distress and disability but also disbelief. We routinely ask patients have ever experienced ‘illness disconfirmation’ from others, including professionals, in order to permit them to ventilate previous dissatisfaction. Such experiences are surprisingly common (e.g. “There’s nothing wrong with you” or “This illness doesn’t exist”) [12–14]. We also emphasize how difficult it must be to face directly the limits of medicine—“It must have been difficult for you, since no one has given an adequate explanation for your illness let alone an effective treatment” [15] or “No doubt you have received many conflicting messages from other doctors about what is wrong.” It is our experience that this combination of open-mindedness, empathy, and awareness of the difficulties the patient is likely to have experienced makes it possible to establish a therapeutic alliance in most cases.

## Assessment

We will already have begun our assessment while establishing a relationship with the patient. This task is essential both to exclude other diagnoses and to develop an adequate individualized understanding of the patient’s illness. The aims of the assessment are to 1) form a therapeutic alliance, 2) identify organic disease, 3) identify treatable psychiatric syndromes, and 4) adapt a broad perspective.

### *Identify Diagnosable Organic Disease*

Many physicians can recount stories of patients who were labelled as having CFS and then found to have an alternative diagnosis [16–18]. The list of possible medical causes of CFS is long, but in practice their exclusion is relatively straightforward [19]. It is, however, wise to be always willing to reconsider the diagnosis should new clinical findings appear.

### *Identify Treatable Psychiatric Syndromes*

It is important to identify ‘psychiatric’ syndromes when these have implications for treatment. This is a more difficult task than excluding physical disease because, like psychiatric syndromes, CFS is defined in terms of symptoms. To quote Anthony Komaroff: “One problem is that CFS is defined by a group of symptoms, without any objective abnormalities on physical examination or laboratory testing that readily establish the diagnosis. Another problem is that the same is true of depression and somatization disorder” [20]. The theoretical relationship between psychiatric syndromes such as depressive disorder and CFS is indeed problematic [21,22], but rather than becoming bogged down in such unresolved nosological difficulties we would encourage the assessing clinician to be pragmatic. This means making psychiatric diagnoses when the requisite symptoms are present and when specific treatment strategies follow. The difficulties in making psychiatric diagnoses in patients with CFS are discussed below.

### *Adopt a Broad Perspective on the Illness*

The third task of assessment is to obtain a full assessment of all the relevant aspects of the patient’s illness. This means not only symptoms but also beliefs, coping behavior, and physiological abnormalities such as sleep disturbance and the per-

sons social and occupational circumstances. Both the available evidence and our clinical experience indicate the need to go beyond simple diagnosis and to take this 'multidimensional' view [23–26]. It is particularly important to focus on factors that may be *perpetuating* the illness, irrespective of what originally caused it as these represent potential obstacles to recovery.

## Taking the History

The most important part of the assessment is the history. Though history taking is a standard procedure we outline below a number of potential problems and the strategies we have developed to overcome them. The components of the history are listed in Table 2.

### Presenting Complaints

Patients may complain simply of fatigue or 'chronic fatigue syndrome.' We find it essential to elicit an exhaustive list of the patient's presenting problems and listen to them—an experience he or she may not have had before. This is especially true for the symptom of fatigue which is given more importance by patients than by the medical profession [27]. It may also reveal the presence of symptoms other than fatigue (e.g., major depressive disorder). The inclusion of problems other than symptoms in the list may reveal major social stressors and occupational difficulties and help to avoid a premature focus on somatic complaints.

**Table 2.** Elements of the history

---

Presenting problems
List all problems (somatic, psychological and social)
Clarify nature of symptoms, especially fatigue
Inquire into changes in life, activity, and sleep, and associated distress
History of illness
Onset and course
Patient's understanding
Coping strategies
Treatment
Current situation
Family
Employment and financial benefits
Background
Family and personal history
Past medical and psychiatric history
Personality

---

**Fatigue.** It is especially important to obtain a clear description of the complaint of 'fatigue' as the word is used in various ways [28], as well as its relation to activity, duration, and effect on activity. The fatigue of CFS is a profound feeling of lack of energy exacerbated by exertion. Lack of energy must be distinguished from sleepiness which is more suggestive of a major sleep disorder [29] and from lack of interest and pleasure or anhedonia which is typical of a depressive syndrome. The exacerbation of fatigue by exertion has long been the hallmark of chronic fatigue states [30]. It appears to be due to central processes rather than abnormalities in the muscles themselves [31,32]. In order to meet current criteria for a diagnosis of CFS the fatigue must not only be chronic (more than 6 months) but must also impair activities [33]. It is important therefore to determine just how much the fatigue interferes with activity (see below).

**Other Somatic Symptoms.** Other somatic symptoms commonly associated with CFS (and required by some definitions) [34] include muscle pain, sore throats, and tender lymph glands. Although the value of any specific symptom is uncertain [35], a large number of somatic symptoms suggests a greater likelihood of psychiatric disorder and a poorer outcome [36].

**Sleep.** Sleep disturbance is common in patients with CFS, and may play a role in the development of symptoms [37]. Experimental sleep deprivation can reproduce both the symptoms [38] and neuroendocrine profile of CFS [39]. Excessive time in bed, as described by many patients with CFS, can also lead to similar symptoms [40]. A detailed sleep history, including periods of daytime rest or sleep, is therefore always indicated as it will also be a target for treatment interventions.

**Cognitive Problems.** Cognitive symptoms, such as poor concentration and memory, are often as prominent as complaints of physical fatigue. Characteristically patients describe frequent cognitive errors, such as making slips of the tongue or being unable to find the correct word. Recent memory may also appear impaired. Systematic neuropsychological testing does not, however, confirm any particular disorder of memory, and objective impairment rarely matches the severity of the subjective complaints [41,42]. Instead, the most consistent pattern observed is an impairment of selective attention leading to difficulties with effort that par-

allel the increased effort with physical exercise. This observation may be used as evidence to convince the patients of the role of the central nervous system in the illness and consequently of the relevance of treatments aimed at modifying CNS functioning.

**Disability and Distress.** In order to assess disability it is essential to identify how the illness has changed the patient's life. Both pre/post illness activities and going through a typical day are useful devices to elicit this. In the interview it is also useful to ask about mood, the implication being that distress is an understandable, albeit important, reaction to the illness. Although the relationship between mood and chronic fatigue is in fact complex, this approach is the least likely to make the patient think you are reinterpreting their illness experience as 'merely psychiatric.'

#### *History of the Illness*

Although recent research has cast doubt on the etiological importance of common infections [43], many patients seen in specialist settings report that their illness began with an acute viral infection [4,44,45]. While acknowledging the patient's experience it is essential to maintain a wider perspective. Further inquiry often reveals a period of ill health *prior* to the apparent triggering infection [46] and there is some evidence that stress is associated with exacerbations of illness [9,47,48]. However, caution is required. If a sufferer believes that his or her illness is postviral in origin, direct inquiry about psychosocial stress may be regarded as a further unwelcome attempt to 'psychologize' the illness. We find it helpful to remind sufferers that they have inevitably experienced viral infections in the past that did not lead to long-term ill health—hence, "Was there anything different at the time?" may be a more productive question. Though the precise role that 'stress' plays in triggering CFS remains uncertain [49], it is a concept that most patients find both understandable and acceptable, particularly if linked with what is known about stress and immunity. Stresses and events occurring after the onset of illness also need elucidation. Many sufferers report that their illness was exacerbated by a premature return to work. This concern can provide a useful introduction to the concepts of gradual rehabilitation outlined below.

**Course.** By the time patients present to a specialist center the illness has often lasted many months,

if not years, therefore it is important to obtain a longitudinal perspective. In particular, patients may have suffered from major depressive disorder at other points in their illness, even if they do not currently meet diagnostic criteria [50].

**Patient's Understanding of the Illness.** It is particularly important that the patient's own understanding of the illness be explored. This process is essential not only to avoid misunderstandings and conflicts arising in the communication between doctor and patient, but also forms the basis for education of the patient. It may be achieved by asking open-ended questions such as 'What do you think is wrong?' and 'What do you think causes the symptoms?' It is also important to gain an impression of the strength in which the patient holds his illness beliefs, as a conviction of a *solely* physical cause for symptoms is the single most consistent predictor of poor outcome [51–53]. Beliefs are consequently probable illness-maintaining factors and targets for therapeutic intervention (see below).

**Coping Strategies.** Patients have often spent considerable time thinking about and trying out different ways of coping with their symptoms [54]. Most patients will have reduced their amount of activity for fear of exacerbating their symptoms, and will continue to monitor both activity and its immediate consequences in order to avoid "relapse;" this is an understandable response in the short term, but is not helpful in the longer term. Similar strategies and focussing on symptoms are associated with worse disability, whereas maintaining activity and being distracted from symptoms are associated with less functional impairment [55–58]. An inquiry into coping methods used may not only reveal potential perpetuating factors such as excessive rest, but also set the scene for an examination of alternatives. Useful questions are "What do you do when you feel very fatigued?", and "Is there anything you avoid because it would make the symptoms worse?" It is also important to establish how the patient arrived at his current strategy. For example, previous attempts to be active may have been too sudden and have resulted in the adoption of rest and avoidance as principle strategies. Suggesting that both strategies failed because they were too extreme sets the scene for a trial of gradually increasing activity.

**Treatment History.** An inquiry into previous treatment experience should be made for two rea-

sons: first, in order to avoid repeating failed treatments such as trials of particular antidepressants, and second, to find out why previous attempted therapies failed (e.g., was the antidepressant discontinued too early, or were exercise targets too ambitious?).

It is also necessary that the assessing physician knows about concurrent therapies. Patients may be consulting a variety of physicians and nonmedical therapies. In our experience either agreement among all those treating the patient or suspension of competing models of treatment is necessary. This may be achieved by explaining to the patient the dangers of competing therapies and therapeutic models, as well as pointing out that mixing treatments makes it impossible to know who to credit for any successes (and also who to blame for any failures).

### *Current Situation*

**Family Members.** It is a mistake to neglect the patient's family in the assessment. Like the families of patients with chronic pain [59], they often have strong ideas about what is wrong—and about what should be done. This is nowhere more important than in the case of children [60]. It is valuable to interview the family directly, and subsequently to involve them in the patient's rehabilitation.

**Employment and Financial Benefits.** The patient's current employment and his attitude toward it are important factors in his/her rehabilitation. In an outpatient chronic pain rehabilitation program patients who had a job to return to had a better outcome [61]. We suspect that similar predictors operate in patients with CFS. The attitude of employers toward changes in duties and a gradual return to work is important to ascertain [62]. Finally, it is sensible to learn whether the patient actually wants to return to his previous job by asking him directly. If he does not, his motivation for return to that employment is likely to be poor [10].

Many patients receive financial benefits and payments which may be contingent on their remaining unwell. Gradual recovery may therefore pose a threat of financial loss before a permanent earned income is confidently established. It may be necessary to explore ways of allowing some overlap of work and payments in order to avoid this difficulty.

### *Background*

**Family and Personal History.** It is helpful to know if there is a family history of depression. This may indicate both a genetic vulnerability and early experience that shaped the patient's attitude to mental illness. The patient's recollection of childhood may reveal evidence of early trauma including physical and sexual abuse. Long absences from school, or a history of such "diagnoses" as "grumbling appendix" or "hypoglycemia" may be useful pointers to a diagnosis of somatization disorder.

**Past Medical and Psychiatric History.** Inquiry into previous history should include the depression, unexplained somatic complaints, and episodes of similar illness. The patient's account may be usefully supplemented by obtaining all the relevant records. Previous episodes of depression, and of unexplained symptoms, may offer useful clues to both the current diagnosis and the treatments that are likely to be effective. In our experience care must be taken in accepting previous labels—illnesses described as 'Epstein-Barr virus infection' may, on detailed inquiry, be better described as major depressive disorder.

**Premorbid Personality and Lifestyle.** Personality is important but its assessment is difficult. The account of an informant is often helpful. The role of premorbid personality in the genesis of CFS is controversial. Clearly patients who have never functioned well are unlikely to do so after treatment for CFS. Others report that prior to the onset of illness their lifestyles could be characterized by high levels of activity and a tendency to "oversubscribe to social norms that dictate exhaustion as a way of life" [63–65]. Such a history highlights a potential vulnerability to CFS, may explain previous failed attempts at rehabilitation (either undertaking too much too soon or frustration leading to inconsistent activity), and may also indicate lifestyle modifications required to prevent relapse.

### *Mental State Examination*

This should be performed in the standard way. It is important to specifically inquire about specific symptoms with a view to excluding important alternative diagnoses. Psychotic disorders, eating disorders, and substance misuse are usually clearly distinguishable. Depression and anxiety syndromes are more difficult to differentiate from CFS because the symptoms are similar.

**Depression.** Although patients with CFS frequently describe report 'mood swings' (which on further inquiry are typically of low mood), they rarely report the pervasive and persistent lowering of mood typical of major depressive disorder. The presence of anhedonia (the feeling of loss of interest and pleasure) may be a more useful pointer to depressive disorder. However, loss of pleasure can be difficult to differentiate from a physical inability to perform the activity. We therefore inquire not only if someone has ceased the activity (e.g., playing football) but also whether they are still interested in and enjoy more sedentary equivalents (e.g., watching sports on television).

Suicide is the only cause of death in CFS. A sensitive inquiry about suicidal thoughts, "This illness has been very hard for you. Have things ever been so bad that you felt like ending your life?" is essential.

**Anxiety.** Anxiety disorders may be more common in patients who present with fatigue than realized hitherto [66]. Although many of the somatic symptoms patients complain of are similar to those listed under generalized anxiety disorder, CFS patients rarely spontaneously describe worry (and if they do it is worry about the effect of the illness). Further inquiry should therefore focus on feelings of tension and apprehension.

It is particularly important to be on the look out for phobic anxiety with avoidance. Patients may report ceasing certain activities such as shopping or socializing because of fatigue, but careful inquiry may reveal a possible phobic basis to such symptoms. Examples include patients who report being able to enter anxiety-provoking situations such as supermarkets only in the presence of a spouse and patients who describe marked sensitivity to noise or light (particularly if sensitive to artificial rather than natural light). Episodes of acute symptoms, especially if accompanied by paraesthesia, should be suspected as being panic attacks and require further exploration.

**Somatoform Disorders.** Although many patients will be best described as having undifferentiated somatoform disorder this diagnosis has no specific implications for treatment; hypochondriasis and somatization disorder do, however, and are therefore worth seeking. The validity of these diagnoses is theoretically problematic in CFS because of the medical uncertainty about its cause [67]. This casts doubt on whether symptoms are unexplained or illness beliefs incorrect. As we have argued before,

our bias is to err on the side of making diagnoses that have positive implications for management.

Hypochondriasis describes a syndrome in which the person's preoccupation is with the fear that they have a physical disease. There is evidence that reassurance may be unhelpful for such persons and that they may respond to a particular form of cognitive behavior therapy (CBT) [68]. However, in our experience, typical anxious hypochondriasis is rare in patients presenting with CFS—most sufferers are seeking confirmation of their own intuition that they are suffering from a particular condition, rather than reassurance that they are not.

Somatization disorder describes a syndrome of multiple, recurrent, *medically unexplained* symptoms, with onset usually in adolescence or early adult life. A small number of patients with CFS will meet criteria for this disorder [69], the prognosis for which is poor. The goals of management are usually limited to long-term support and reducing use of medical resources [70].

### *Physical Examination*

Brief physical examination is always appropriate but often neglected. Abnormal physical signs should not be accepted as compatible with a diagnosis of CFS. For example, although many patients complain of swollen or tender lymph nodes, this is a symptom, not a sign. Clinically significant lymphadenopathy demands investigation. Similarly, patients may experience a sensation of 'feverishness', but true pyrexia ( $>38^{\circ}\text{C}$ ) also indicates the need for investigation.

Certain physical abnormalities may be found that reflect the consequence of chronic ill health and inactivity. Muscle wasting might be the result of prolonged bedrest, and suggests that active rehabilitation is an urgent priority, but will be prolonged. Another possible consequence of chronic inactivity is postural hypotension [71,72]. We routinely test for this, since, if present, it can explain, and hence help the patient to understand, symptoms such as dizziness. In our experience it usually resolves with increased activity.

### *Investigations and Specialist Referral*

Fatigue is a symptom of many illnesses, both medical and psychiatric. It is essential that an appropriate history and basic investigations are carried out in every patient (Table 3). This is based on systematic research [73–76], supplemented by clinical experience. The yield of conventional investigations is low—the highest number of alternative diagnoses

**Table 3.** Recommended investigations

All patients	Full blood count, erythrocyte sedimentation rate or C-reactive protein, urea and electrolytes, thyroid function tests, urinalysis for protein and sugar
Can be helpful	Epstein Barr serology, chest x-ray film, rheumatoid factor, anti-nuclear factor, serological testing for cytomegalovirus, Q fever, toxoplasmosis or HIV
Not helpful	Enteroviral serology, neuroimaging

found after further investigation is 5% [77]—most are lower. Reports from specialist settings have shown statistically increased rates of abnormal results on tests for parameters such as antinuclear factor, immune complexes, cholesterol, immunoglobulin subsets, and so forth. These are encountered only in a minority, and are rarely substantial [78]. Their significance is for researchers rather than clinicians, and we feel that routine testing for such variables is more likely to result in iatrogenic harm than good. There is currently no diagnostic test or pattern of tests that can assist in the diagnosis of CFS.

The problem of when or if to ask a specialist physician for help in the assessment of possible CFS often concerns primary care physicians. We do not believe this should be routine, as the primary care physician remains the mainstay of effective management [79,80]. We do suggest that referral to a specialist physician should be considered when there is an increased probability of an alternative diagnosis. These could be circumstances such as the very young or old, recent foreign travel, weight loss, any neurological signs, difficulty walking, pyrexia of unknown origin (objectively confirmed), or any abnormal results from the basic screening investigations.

## Diagnosis

### *Should the Diagnosis be Made at All?*

Many physicians are reluctant to make the diagnosis of CFS (although those who are primary care physicians may be less so) [81,82]. There are several reasons for this: First, the physician may harbor doubts about the nosological status of CFS. Second, he/she may, with good reason, be wary of the power of labels, and of reinforcing what may be

unhelpful illness beliefs (vide infra). Finally, the absence of any pathognomic symptom, sign, or diagnostic test may undermine the physician's diagnostic confidence.

We have sympathy with all these reservations, but suggest that such high-minded scepticism is rarely beneficial in the clinical situation. Patients need a diagnosis in order to make sense of their illness [83]. Without such a label it is almost impossible for them to organize their dealings with the world of work and benefits [26]. We therefore advise that if a patient already believes his illness is best described as CFS or one of its variants, challenging that belief is unlikely to be helpful. We also believe that the making of a positive diagnosis of CFS has a place in clinical practice, providing it is used in a constructive fashion. This means that the etiological neutrality and purely descriptive nature of the diagnosis is emphasized. The meaning that the diagnosis carries for the individual patient should be explored so that inaccurate and unhelpful ideas can be corrected. These may be acquired from the popular literature, for example: "The only hope is that one day some substance will be isolated that has the power to zap the ME virus," and until then "the most doctors can do is to advise patients to rest, and wait for the ME to go away" [84].

### *A multidimensional Approach to Description of the Illness*

A multidimensional description of the patient's illness provides a comprehensive picture of the factors that may be relevant to its perpetuation in that individual. It is a useful supplement to a bland diagnosis of CFS. A return to the case example will illustrate its use.

**Clinical Example.** Assessment of the patient described at the beginning of this review revealed that she believed her symptoms were caused by an ongoing virus infection and was worried about making them worse. She consequently avoided activity and had been profoundly inactive for over a year, often lying in bed and sleeping for long periods. She was therefore likely to be physiologically deconditioned. She was frustrated with her inability to do things and sometimes felt low in mood about her predicament. Her teaching job had been stressful but since becoming ill she had been unable to work. She had lost her job and was cared for by her mother who also believed she had permanent disability. Her doctor said that the best thing was rest.



As well as seeking the information to make a diagnosis it is important to observe potential illness perpetuating factors, as these provide targets for interventions. In the case described above these are listed in Table 4.

## The Management Plan

### General Aspects of Management

Before beginning treatment it is essential that physician and patient agree, at least tentatively, on a positive understanding of the illness that is acceptable to both. The precise mechanisms involved in the symptom of CFS are uncertain and controversial. Rather than doctor and patient becoming bogged down in such disputes, we advocate a pragmatic approach that promotes those illness beliefs and models that lead to positive action. Etiological theories for CFS abound but none are established. Some of these theories are clinically unhelpful whatever their scientific merits. Thus, the belief that symptoms are due to a persistent viral infection of muscle may or may not be true [85,86] but more importantly is clinically unhelpful. Such a belief can lead to the patient interpreting myalgia as evidence of worsening disease, and consequently being reluctant to engage in rehabilitation. In general, beliefs implying that activity will have adverse or even 'catastrophic' consequences lead to its avoidance [87].

Other beliefs for which there is (at least as good) scientific support have more constructive implications. For example, the idea that many symptoms of CFS are due to the neurophysiological consequences of inactivity (deconditioning) and the delayed onset of postexertional muscle pain [88] offers a positive alternative to the disease explanations

**Table 4.** Possible illness perpetuating factors in case example

Perpetuating factors	
Biological	Effect of profound inactivity Effect of chronic emotional arousal Neurobiological factors as yet unknown
Cognitive and behavioural	Belief in viral infection Fear of making disease worse Reduction of activity
Social	No job Reinforcement of sick role by mother and doctor

described above. The belief that symptoms are due to disturbed hypothalamic pituitary function [89,90] does not interfere with rehabilitation and may also provide a rationale for the prescription of antidepressant drugs if relevant. Similarly, the idea that CFS can be *triggered* by an episode of acute Epstein Barr virus infection [91] does not imply a progressive pathology, and leaves the way open for a discussion of other perpetuating factors. Other positive explanations, all of which might be correct, and none of which are known to be incorrect, are listed in Table 5.

The physician's overall aim is to broaden, rather than confront, patients' beliefs and behaviors so that they embrace a wider range of possible explanations for continuing ill health, and hence a wider range of treatment options [92-94]. Its essence is to move the discussion from what started the illness to what obstacles stand in the way of recovery. Such a model naturally leads to a discussion of how these obstacles may be overcome.

**Making a Treatment Plan.** The treatment plan should be pragmatic. For some patients depression may appear to be the predominant illness perpetuating factor and a trial of an antidepressant drug may be the first priority. For others, unhelpful beliefs about the illness (such as the idea that all activity is potentially damaging) may need to be addressed, initially by simple discussion and education and if necessary, by more formal cognitive behavioral therapy. For still others, a life predicament such as an occupation that has become intolerable will require an open-minded problem-solving approach. The principal treatment strategies are shown in Table 6.

### Specific Treatment Strategies

The treatment strategies employed will depend on the individual patient assessment. They may need

**Table 5.** Illness models

Illness models to promote	Illness models to avoid
Glandular fever as trigger	Persistent virus
Stress altering immune function	Primary muscle disorder
Secondary handicap	Severe allergy
Sleep disorder	Progressive immune deficiency
Hypothalamic dysfunction	

**Table 6.** Treatment strategies

---

Antidepressant drugs
Novel pharmacological agents
Activity scheduling
Graded exercise program
Establish sleep routine and introduce sleep hygiene measures
Cognitive behavior therapy
Negotiated return to work

---

to be combined to target multiple illness-perpetuating factors. An important task of treatment is to return responsibility to the patient for management and rehabilitation without inducing a sense of guilt, blame, or culpability for his/her predicament.

**Role of Activity, Exercise and Sleep.** The literature on the malign effects of inactivity is large and its conclusions inescapable. The profound consequences of lack of physical activity, and the changes in the neuromuscular system that result, have been known to clinicians for a generation or more [95–97]. Though extreme inactivity should be discouraged, is it also desirable to advocate increased activity? We believe the answer is yes, as long as this is done *gradually*, and the increases are tailored to the patient’s progress. A simple exhortation to “do more” is inadequate and may even be counterproductive. In our experience such a suggestion is likely to invite the response that they have already tried it and it failed. Indeed, many will blame precisely such efforts as playing a role in their current disability. They may also interpret it as a thinly veiled accusation of not trying hard enough or being lazy. We therefore introduce the subject by concentrating not on lack of activity, but on the need for planned rest and avoiding inconsistent and variable activity [9]. By building up a consistent approach to activity, the link between symptoms and reducing activity is gradually weakened. The belief that “the symptoms are controlling me” gives way to “I am in control of my symptoms,” but not necessarily “I no longer experience symptoms.” Some form of activity monitoring, for example, with a diary, is helpful, followed by careful scheduling of periods of activity and rest.

Patients will also need to be warned that the resumption of activity is likely to lead to some initial discomfort. Such a warning, accompanied by an explanation of the physiological basis of such symptoms, is necessary to avoid triggering the

anxiety-provoking or catastrophic thoughts (“I must be damaging myself. . . I am going to have a relapse”) that are otherwise common [87]. Targets for increases in activity must be appropriate. That means they should be realistically achievable in the light of the patient’s disability, and activities that the patient currently avoids but wishes to resume. Simple exercise programs, although logical [98], may fail at this point, since many patients did not perform regular exercise when well, and are thus not motivated to do so when sick.

Many patients with CFS have chaotic sleep patterns and may spend a considerable length of time in bed [37]. Both these sleep behaviors may exacerbate daytime fatigue. It is therefore likely to be helpful for patients to adopt regular sleeping patterns and to limit the time spent in bed. Simple behavioral measures of diary keeping and gradual adjustment of sleeping time can be helpful [99].

**Role of Cognitive Behavior Therapy.** Cognitive behavior therapy (CBT) can offer a pragmatic, individualized approach to rehabilitation. The form of therapy we use comprises aims to assist patients to reevaluate their understanding of illness (as described above), and to gradually and consistently increase their activity. We have described how we plan and carry out cognitive behavior therapy for CFS in other publications [100–103]. Does it work? An early randomized trial from Sydney Australia was not encouraging and found that their form of CBT was no better than good quality medical care [104]. We have developed a more intensive therapy that has been evaluated in two randomized, controlled trials [101,105]. These show that this form of therapy is acceptable to patients, safe, and more effective than either standard medical care or relaxation therapy. It has also been shown to be cost-effective [106].

**Antidepressant Medication.** Antidepressant drugs are frequently prescribed for patients with CFS. It is usually possible to persuade these patients to try antidepressants, provided the doctor is aware of the potentially negative implications of taking them (“antidepressants are for psychological illness—my problem is different”). We justify their use either on the basis that depression is an understandable consequence of CFS, or as ‘broad spectrum’ agents that affect pain, sleep, and energy, as well as mood. Recent research finding possible serotonergic abnormalities in patients with CFS [90,107,108] provides an additional argument.

Despite their widespread use in CFS the evidence

for their efficacy in this syndrome is surprisingly scanty. Though the overlap with depressive disorder [109,110] provides indirect evidence, controlled trials in CFS and the related syndrome of fibromyalgia are less encouraging. Antidepressants are effective in the short-term management of pain and fatigue, usually in lower doses than are routinely prescribed in psychiatric practice, but evidence for their long-term efficacy is still lacking [111–112]. Looking specifically at CFS, most evidence comes from uncontrolled, open, or single case studies [113–117]. The only two well-conducted clinical trials to date give contradictory findings, one finding evidence of benefit from an selective serotonin reuptake inhibiting antidepressant drug (SSRI), the other not [118,119]. At present we advocate the use of antidepressants for patients who are clearly depressed.

There is no good evidence to guide choice of agent although sedative drugs are unlikely to be tolerated other than as an aid to sleep. Tolerance of serotonin re-uptake inhibitors is variable. CFS sufferers are also markedly sensitive to side effects so doses need to begin as low as possible. Given the overlap between the symptoms of CFS and those of atypical depression, a good case can be made for trying monoamine oxidase inhibitors (MAOIs), supported by a recent small but encouraging study in CFS [120].

**Novel Pharmacological Agents.** Many treatments have been proposed for chronic fatigue states over the years [121] but few have been adequately evaluated. Ineffective treatments include the antiviral drug Acyclovir and anti-candida treatments. Several other therapies have gained preliminary support in clinical trials including magnesium injections, immunoglobulin infusions and fish oil. None of these agents have been convincingly demonstrated to be efficacious [80,93]. Such treatments may be expensive and even harmful and distract both patient and doctor from efforts at rehabilitation, which at present appear more likely to be effective in the longer term. Patients should be discouraged from pursuing unproven treatments unless they are part of a carefully conducted clinical trial.

**Return to Work.** Before planning a return to work it is wise to check that the patient *wants* to return to this particular occupation and employer. In our experience some patients with CFS seek a change in career and simply pushing them in an unwanted direction is unlikely to be effective. If the

patient acknowledges that a change in career or work practice is desired, a problem-solving approach is appropriate [122]. Return to work, like all other activities, needs to be gradual and planned [62].

### *Special Issues*

**The Angry Patient.** Many patients are initially hostile to the idea of a further referral, particularly to any unit with a perceived psychological orientation. We have found it best to confront such feelings immediately on seeing the patients, and to openly sympathize with their plight. “Did you think that seeing us meant that doctors weren’t taking your symptoms seriously?” can lead to questions directly about the experience of disconfirmation and perceived stigmatization implicit in referral to a psychological or general hospital psychiatry service.

**The Insurance Assessment.** The issue of benefits and insurance payments is exceptionally difficult in this area, and likely to lead to confrontation unless carefully handled. Disability systems and insurance agencies are sceptical about CFS—the combination of a disorder based entirely on self-report, without any agreed diagnostic test and sometimes profound disability, understandably causes some concern [123]. Much of the self-help literature on both sides of the Atlantic concerns the iniquities of the various benefits systems, and both personal and political strategies to overcome them. We have adopted a pragmatic approach to this problem. When asked to comment on benefits or insurance claims we support the patient as much as is possible, but do not support claims for permanent disability or medical retirement until all reasonable efforts at rehabilitation have been tried.

**Role of the spouse/parent.** A poor marital relationship is relevant as part of a range of social stressors. However, researchers recently reported an apparently paradoxical result in the context of CFS. Greater marital satisfaction was associated with more fatigue—the presumed link being via overprotective and oversolicitous behaviors [124]. Hence, if it is felt that either partners or parents are encouraging disability—albeit inadvertently—it will be as important to try and engage them in treatment of the patient [60,125].

### Services

The traditional division of medical knowledge and services into either medical or psychiatric, and the stigma attached to the latter, means that many patients who might benefit from appropriate treatment do not receive it. Albeit good quality primary care and outpatient consultation-liaison psychiatry offer partial solutions to this problem, a more satisfactory answer would require a fundamental revision of medical services. These services would combine high quality biopsychosocial assessment and management in primary care, complemented by integrated medical-psychiatric clinics [80,126].

### Summary and Conclusions

Chronic fatigue syndrome is best regarded as a descriptive term for a type of clinical presentation. The patient group it defines is almost certainly etiologically heterogeneous and needs to be subclassified. Psychiatric diagnosis provides one approach to subclassification, but the current diagnostic systems have significant limitations, and a multidimensional description of the patient's characteristics may be more clinically useful. We have suggested a practical, evidence-based approach to the assessment and initial management of the patient who presents with a CFS syndrome. The basic principles are simple and are those required in the management of medically unexplained somatic symptoms in general [127]. The illness defined by the term "chronic fatigue syndrome" is important not only because it represents potentially treatable disability and suffering but also because of the light it sheds on the shortcomings in our present approach to medically unexplained illness.

A structured interview guide for CFS can be obtained from the authors.

### References

1. Wessely S: The history of chronic fatigue syndrome. In Straus S (ed), *Chronic Fatigue Syndrome*. New York; Mark Dekker, 1994; pp. 41-82
2. Goldenberg D: Fibromyalgia, chronic fatigue syndrome and myofascial pain syndrome. *Curr Opin Rheumatol* 5:199-208, 1993
3. Anfinson T: Diagnostic assessment of chronic fatigue syndrome. In Stoudemire A, Fogel B (eds), *Medical-Psychiatric Practice*, Vol 3, Washington, DC, London, Am Psychiatric Press, 1995, pp 215-256
4. Wessely S, Powell R: Fatigue syndromes: a comparison of chronic 'postviral' fatigue with neuromuscu-

- lar and affective disorder. *J Neurol Neurosurg Psychiatry* 52:940-948, 1989
5. Lane T, Manu P, Matthews D: Depression and somatization in the chronic fatigue syndrome. *Am J Med* 91:335-344, 1991
6. Hickie I, Lloyd A, Wakefield D, Parker G: The psychiatric status of patients with chronic fatigue syndrome. *Br J Psychiatry* 156:534-540, 1990
7. Wessely S: Neurasthenia and chronic fatigue: theory and practice in Britain and America. *Transcultural Psychiatric Res Rev* 31:173-209, 1994
8. Powell R, Dolan R, Wessely S: Attributions and self-esteem in depression and chronic fatigue syndromes. *J Psychosom Res* 34:665-673, 1990
9. Surawy C, Hackmann A, Hawton K, Sharpe M: Chronic fatigue syndrome: a cognitive approach. *Behav Res Ther* 33:535-544, 1995
10. Butler C, Rollnick S: Missing the meaning and provoking resistance: a case of myalgic encephalomyelitis. *Fam Pract* 13:106-109, 1996
11. Scott S, Deary I, Pelosi A: General practitioners' attitudes towards patients with a self-diagnosis of myalgic encephalomyelitis. *Br Med J* 310:508, 1995
12. Henriksson C: Living with continuous muscle pain-patient perspectives. Part I. Encounters and consequences. *Scand J Caring Sci* 9:67-76, 1995
13. English T: Skeptical of skeptics. *J Am Med Assoc* 265:964, 1991
14. Ware N: Suffering and the social construction of illness: the delegitimation of illness experience in chronic fatigue syndrome. *Med Anthropol Q* 6:347-361, 1992
15. House A: The patients with medically unexplained symptoms: making the initial psychiatric contract. In Mayou R, Bass C, Sharpe M (eds), *The Treatment of Functional Somatic Symptoms*. Oxford, Oxford University Press, 1995, pp 89-102
16. Gray J, Bridges A, McNeill G: Atrial myxoma: a rare cause of progressive exertional dyspnoea. *Scot Med J* 37:186-187, 1992
17. Hurel S, Abuiasha B, Bayliss P, Harris P: Patients with a self-diagnosis of myalgic encephalomyelitis. *Br Med J* 311:329, 1995
18. Mesch U, Lowenthal R, Coleman D: Lead poisoning masquerading as chronic fatigue syndrome. *Lancet* 347:1193, 1996
19. Matthews D, Manu T, Lane T: Evaluation and management of patients with chronic fatigue. *Am J Med Science* 302:269-277, 1991
20. Komaroff A: Clinical presentation of chronic fatigue syndrome. In Straus S, Kleinman A (eds), *Chronic Fatigue Syndrome*, CIBA Foundation Symposium; Vol 173, Chichester, John Wiley, 1993, pp 43-61
21. Abbey S, Garfinkel P: Chronic fatigue syndrome and depression: cause, effect or covariate. *Rev Infect Diseases* 13 (Suppl 1):S73-S83, 1991
22. Sharpe M: Chronic fatigue syndrome. *Psychiatr Clin North Am* 19:549-573, 1996
23. Demitrack M, Greden J: Chronic fatigue syndrome: the need for an integrative approach. *Biol Psychiatry* 30:747-752, 1991
24. Vercoulen J, Swanink C, Fennis J, Galama J, van der Meer J, Bleijenberg G: Dimensional assessment of

- chronic fatigue syndrome. *J Psychosom Res* 38:383-392, 1994
25. Mayou R, Bass C, Sharpe M: Overview of epidemiology, classification and aetiology. In Mayou R, Bass C, Sharpe M (eds), *Treatment of Functional Somatic Symptoms*. Oxford, Oxford University Press, 1995, pp 42-65
  26. Mayou R, Sharpe M: Diagnosis, illness and disease. *Quart J Med* 88:827-831, 1995
  27. Dohrenwend B, Crandell D: Psychiatric symptoms in community, clinic and mental hospital groups. *Am J Psychiatry* 126:1611-1621, 1970
  28. Berrios G: Feelings of fatigue and psychopathology. *Comp Psychiatry* 31:140-151, 1990
  29. Horne J: Dimension to sleepiness. In Monk T (ed), *Sleep, sleepiness and performance*. New York, John Wiley, 1991, pp 169-195
  30. Waller A: The sense of effort: an objective study. *Brain* 14:179-239, 1891
  31. Lloyd A: Muscle versus brain: chronic fatigue syndrome. *Med J Aust* 152:186-189, 1990
  32. Edwards R, Gibson H, Clague J, Helliwell T: Muscle physiology and histopathology in chronic fatigue syndrome. In Kleinman A, Straus S (eds), *Chronic Fatigue Syndrome*. CIBA Foundation Symposium, Vol 173, Chichester, John Wiley, 1993, pp 101-131
  33. Sharpe M, Archard L, Banatvala J, et al: Chronic fatigue syndrome: guidelines for research. *J Roy Soc Med* 84:118-121, 1991
  34. Fukuda K, Straus S, Hickie I, Sharpe M, Dobbins J, Komaroff A: The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 121:953-959, 1994
  35. Wessely S, Chalder T, Hirsch S, Wallace P, Wright D: Psychological symptoms, somatic symptoms and psychiatric disorder in chronic fatigue and chronic fatigue syndrome: a prospective study in primary care. *Am J Psychiatry* 153:1050-1059, 1996
  36. Clark M, Katon W, Russo J, Kith P, Sintay M, Buchwald D: Chronic fatigue: risk factors for symptom persistence in a 2.5-year follow-up study. *Am J Med* 98:187-195, 1995
  37. Morriss R, Sharpe M, Sharpley A, Cowen P, Hawton K, Morris J: Abnormalities of sleep in patients with the chronic fatigue syndrome. *Br Med J* 306:1161-1164, 1993
  38. Moldofsky H, Scarisbrick P: Induction of neurasthenia musculoskeletal pain syndrome by selective sleep deprivations. *Psychosom Med* 38:35-44, 1976
  39. Leese G, Chattington P, Fraser W, Vora J, Edwards R, Williams G: Short-term night-shift working mimics the pituitary-adrenocortical dysfunction of chronic fatigue syndrome. *J Clin Endocrinol Metabol* 81:1867-1870, 1996
  40. Globus G: Sleep duration and feeling state. *Int Psychiatr Clin* 7:78-84, 1970
  41. Moss-Morris R, Petrie K, Large R, Kydd R: Neuropsychological deficits in chronic fatigue syndrome: artifact or reality? *J Neurol Neurosurg Psychiatry* 60:474-477, 1996
  42. Wearden A, Appleby L: Research on cognitive complaints and cognitive functioning in patients with chronic fatigue syndrome (CFS): What conclusions can we draw? *J Psychosom Res* 41:197-211, 1996
  43. Wessely S, Chalder T, Hirsch S, Pawlikowska T, Wallace P, Wright D: Post-infectious fatigue: a prospective study in primary care. *Lancet* 345:1333-1338, 1995
  44. Behan P, Behan W: Postviral fatigue syndrome. *Crit Rev Neurobiol* 4:157-179, 1988
  45. Petersen P, Schenck C, Sherman R: Chronic fatigue syndrome in Minnesota. *Minn Med* 74:21-26, 1991
  46. Gunn W: Kleinman A, Straus S (eds), *Chronic Fatigue Syndrome*, CIBA Foundation Symposium, Vol 173, Chichester, John Wiley, 1993, p 288
  47. Dobbins J, Natelson B, Brassloff I, Drastal S, Sisto S: Physical, behavioral and psychological risk factors for chronic fatigue syndrome: a central role for stress? *J Chronic Fatigue Syndrome* 1:43-58, 1995
  48. Lutgendorf S, Antoni M, Ironson G, et al: Physical symptoms of chronic fatigue syndrome are exacerbated by the stress of Hurricane Andrew. *Psychosom Med* 57:310-323, 1995
  49. Bruce-Jones W, White P, Thomas J, Clare A: The effect of social disadvantage on the fatigue syndrome, psychiatric disorders and physical recovery, following glandular fever. *Psychol Med* 24:651-659, 1994
  50. Manu P, Matthews D, Lane T, et al: Depression among patients with a chief complaint of chronic fatigue. *J Affective Disord* 17:165-172, 1989
  51. Sharpe M, Hawton K, Seagroatt V, Pasvol G: Follow-up of patients with fatigue presenting to an infectious disease clinic. *Br Med J* 302:347-352, 1992
  52. Wilson A, Hickie I, Lloyd A, et al: Longitudinal study of the outcome of chronic fatigue syndrome. *Br Med J* 308:756-760, 1994
  53. Vercoulen J, Swanink C, Fennis J, Galama J, van der Meer J, Bleijenberg G: Prognosis in chronic fatigue syndrome: a prospective study on the natural course. *J Neurol Neurosurg Psychiatry* 60:489-494, 1996
  54. Clements A, Sharpe M, Borrill J, Hawton K: Illness beliefs of patients with chronic fatigue syndrome: a quantitative investigation. *J Psychosom Res* (in press)
  55. Ray C, Weir W, Stewart D, Miller P, Hyde G: Ways of coping with chronic fatigue syndrome: development of an illness management questionnaire. *Soc Sci Med* 37:385-391, 1993
  56. Antoni M, Brickman A, Lutgendorf S, et al: Psychosocial correlates of illness burden in chronic fatigue syndrome. *Clin Infect Dis* 18 (Suppl 1):S73-S78, 1994
  57. Ray C, Jeffries S, Weir W: Coping with chronic fatigue syndrome: illness responses and their relationship with fatigue, functional impairment and emotional status. *Psychol Med* 25:937-945, 1995
  58. Moss-Morris R: The role of illness cognitions and coping in the aetiology and maintenance of the chronic fatigue syndrome (CFS). In Weinman J, Petrie K (eds), *Perceptions of Health and Illness: Current Research and Applications*. Reading, Harwood Academic Publishers (in press)
  59. Benjamin S, Mawer J, Lennon S: The knowledge and

- beliefs of family caregivers about chronic pain patients. *J Psychosom Res* 36:211–217, 1992
60. Vereker M: Chronic fatigue syndrome: a joint paediatric-psychiatric approach. *Arch Dis Childhood* 67:550–555, 1992
  61. Cott A, Anchel H, Goldberg W, Fabich M, Parkinson W: Non-institutional treatment of chronic pain by field management: an outcome study with comparison group. *Pain* 40:183–194, 1990
  62. Peel M: Rehabilitation in postviral syndrome. *J Soc Occupation Med* 38:44–45, 1988
  63. Ware N: Society, mind and body in chronic fatigue syndrome: an anthropological view. In Kleinman A, Straus S (eds), *Chronic Fatigue syndrome*, CIBA Foundation Symposium, Vol 173, Chichester: John Wiley, 1993:62–82
  64. Van Houdenhove B, Onghena P, Neerinckx E, Hellin J: Does high 'action-proneness' make people more vulnerable to chronic fatigue syndrome? A controlled psychometric study. *J Psychosom Res* 39:633–640, 1995
  65. MacDonald K, Osterholm M, LeDell K, et al: A case control study to assess possible triggers and cofactors in chronic fatigue syndrome. *Am J Med* 100:548–554, 1996
  66. Fischler B, Cluydts R, De Gucht V, Kaufman L, DeMeirleir K: Generalised anxiety disorders in chronic fatigue syndrome. *Acta Psychiatr Scand* (in press)
  67. Johnson S, Deluca J, Natelson B: Assessing somatization disorder in the chronic fatigue syndrome. *Psychosom Med* 58:50–57, 1996
  68. Warwick H, Clark D, Cobb A, Salkovskis P: A controlled trial of cognitive behavioural treatment of hypochondriasis. *Br J Psychiatry* 169:189–195, 1996
  69. Manu P, Lane T, Matthews D: Somatization disorder in patients with chronic fatigue. *Psychosomatics* 30:388–395, 1989
  70. Smith G, Monson R, Ray D: Psychiatric consultation in somatization disorder: a randomized controlled study. *N Engl J Med* 314:1407–1413, 1986
  71. Sharpe M, Bass C: Pathophysiological mechanisms in somatization. *Int Rev Psychiatry* 4:81–97, 1992
  72. Rowe P, Bou-Holaigah I, Kan J, Calkins H: Is neurally mediated hypotension an unrecognised cause of chronic fatigue? *Lancet* 345:623–624, 1995
  73. Kroenke K, Wood D, Mangelsdorff D, Meier N, Powell J: Chronic fatigue in primary care: prevalence, patient characteristics and outcome. *J Am Med Assoc* 260:929–934, 1988
  74. Lane T, Matthews D, Manu P: the low yield of physical examinations and laboratory investigations of patients with chronic fatigue. *Am J Med Sci* 299:313–318, 1990
  75. Valdini A, Steinhardt S, Feldman E: Usefulness of a standard battery of laboratory tests in investigating chronic fatigue in adults. *Fam Pract* 6:286–291, 1989
  76. Ridsdale L, Evans A, Jerrett W, Mandalia S, Osler K, Vora H: Patients with fatigue in general practice: a prospective study. *Br Med J* 307:103–106, 1993
  77. Swanink C, Vercoulen J, Bleijenberg G, Fennis J, Galama J, Van Der Meer J: Chronic fatigue syndrome: a clinical and laboratory study with a well-matched control group. *J Intern Med* 237:499–506, 1995
  78. Bates D, Buchwald D, Lee J, et al: Clinical laboratory test findings in patients with chronic fatigue syndrome. *Arch Intern Med* 155:97–103, 1995
  79. Wessely S, David A, Butler S, Chalder T: The management of chronic "post-viral" fatigue syndrome. *J Royal Coll Gen Practitioners* 39:26–29, 1989
  80. Anonymous: *Chronic Fatigue syndrome: Report of a Committee of the Royal Colleges of Physicians, Psychiatrists and General Practitioners*. London, Royal Colleges of Physicians, 1996
  81. Ho-Yen D: General practitioners' experience with the chronic fatigue syndrome. *Br J Gen Practice* 41:324–326, 1991
  82. Denz-Penhey H, Murdoch J: General practitioners acceptance of the validity of chronic fatigue syndrome as a diagnosis. *NZ Med J* 106:122–124, 1993
  83. Woodward R, Broom D, Legge D: Diagnosis in chronic illness: disabling or enabling the case of chronic fatigue syndrome. *J Roy Soc Med* 88:325–329, 1995
  84. Hodgkinson L: ME: the mystery disease. *Woman's J* November 1988
  85. Gow J, Behan P, Simpson K, McGarry F, Keir S, Behan P: Studies of enteroviruses in patients with chronic fatigue syndrome. *Clin Infect Dis* 18 (Suppl 1):S126–129, 1994
  86. McArdle A, McArdle F, Jackson M, Page S, Fahal I, Edwards R: Investigation by polymerase chain reaction of enteroviral infection in patients with chronic fatigue syndrome. *Clin Sci* 90:295–300, 1996
  87. Petrie K, Moss-Morris R, Weinman J: The impact of catastrophic beliefs on functioning in chronic fatigue syndrome. *J Psychosom Res* 39:31–37, 1995
  88. Klug G, McAuley E, Clark S: Factors influencing the development and maintenance of aerobic fitness: lessons applicable to the fibrositis syndrome. *J Rheumatol* 16 (Suppl 19):30–39, 1989
  89. Demitrack M, Dale J, Straus S, et al: Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. *J Clin Endocrinol Metab* 73:1224–1234, 1991
  90. Cleare A, Bearn J, Allain T, et al: Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. *J Affective Disord* 35:283–289, 1995
  91. White P, Thomas J, Amess J, Grover S, Kangro H, Clare A: The existence of a fatigue syndrome after glandular fever. *Psychol Med* 25:907–916, 1995
  92. Wessely S, Edwards R: *Chronic Fatigue*. In Greenwood R, Barnes M, McMillan T, Ward C (eds), *Neurological Rehabilitation*. Edinburgh, Churchill Livingstone, 1991, pp 311–325
  93. Wilson A, Hickie I, Lloyd A, Wakefield D: The treatment of chronic fatigue syndrome: science and speculation. *Am J Med* 96:544–549, 1994
  94. Sharpe M, Chalder T: *Management of the Chronic Fatigue Syndrome*. In Illis L (ed), *Neurological Rehabilitation*. Oxford, Blackwell, 1994, pp 282–294
  95. Kottke F: The effects of limitation of activity upon the human body. *J Am Med Assoc* 196:117:122, 1966

96. Booth F: Physiologic and biochemical effects of immobilization on muscle. *Clin Orthop* 10:15–20, 1987
97. Jaffe D, Terry R, Spiro A: disuse atrophy of skeletal muscle. *J Neurol Sci* 35:189–200, 1978
98. McCully K, Sisto S, Natelson B: Use of exercise for treatment of chronic fatigue syndrome. *Sports Med* 21:35–48, 1996
99. Sloan E, Hauri P, Bootzin R, Morin C, Stevenson M, Shapiro C: The nuts and bolts of behavioural therapy for insomnia. *J Psychosom Res* 37 (Suppl 1):19–37, 1993
100. Deale A, Wessely S: A cognitive behavioural approach to chronic fatigue syndrome: a randomized controlled trial. *Br Med J* 312:22–26, 1996
101. Sharpe M, Hawton K, Simkin S, et al: Cognitive behaviour therapy for chronic fatigue syndrome: a randomized controlled trial. *Br Med J* 312:22–16, 1996
102. Wessely S: Cognitive behavioral therapy for patients with chronic fatigue syndrome: Why? In Demitrack M, Abbey S (eds), *Chronic Fatigue Syndrome: An Integrative Approach to Evaluation and Treatment*. New York, Guildford Press, 1996, pp 212–239
103. Sharpe M: Cognitive-behavioral therapy for patients with chronic fatigue syndrome: How? In Demitrack M, Abbey S (eds), *Chronic Fatigue Syndrome: An Integrative Approach to Evaluation and Treatment*. New York, Guildford Press, 1996, pp 240–262
104. Lloyd A, Hickie I, Brockman A, et al: Immunologic and psychological therapy for patients with chronic fatigue syndrome. *Am J Med* 94:197–203, 1993
105. Deale A, Chalder T, Marks I, Wessely S: A randomized controlled trial of cognitive behaviour versus relaxation therapy for chronic fatigue syndrome. *Am J Psychiatry* 154:408–414, 1997
106. Best L: *Cognitive Behavioural Therapy in the Treatment of Chronic Fatigue Syndrome*. Southampton, Wessex Institute of Public Health Medicine, 1996
107. Lane R: Aetiology, diagnosis and treatment of chronic fatigue syndrome. *J Serotonin Res* 1:47–60, 1994
108. Bakheit A, Behan P, Dinan T, Gray C, O'Keane V: Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome. *Br Med J* 304:1010–1012, 1992
109. David AS: Postviral fatigue syndrome and psychiatry. *Br Med Bull* 47:966–988
110. Kendell R: Chronic fatigue, viruses and depression. *Lancet* 337:160–162, 1991
111. Carrette S: What have clinical trials taught us about the treatment of fibromyalgia? *J Musculoskeletal Pain* 3:133–140, 1995
112. Godfrey R: A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 156:1047–1052, 1996
113. Goodnick P, Sandoval R: Psychotropic treatment of chronic fatigue syndrome and related disorders. *J Clin Psychiatry* 54:13–20, 1993
114. Lynch S, Seth R, Montgomery S: Antidepressant therapy in the chronic fatigue syndrome. *Br J Gen Pract* 41:339–342, 1991
115. Gracious B, Wisner K: Nortriptyline in chronic fatigue syndrome; a double-blind, placebo-controlled single case study. *Biol Psychiatry* 30:405–408, 1991
116. Behan P, Hannifah B, Doogan D, Loudon M: A pilot study of sertraline for the treatment of chronic fatigue syndrome. *Clin Infect Dis* 18 (Suppl 1):S111, 1994
117. Goodnick P: Treatment of chronic fatigue syndrome with venlafaxine. *Am J Psychiatry* 153:294, 1996
118. Wearden A, Morriss R, Mullis R, et al: A double-blind, placebo-controlled treatment trial of fluoxetine and a graded exercise programme for chronic fatigue syndrome. *Br Med J* (in press)
119. Vercoelen J, Swanink C, Zitman F, et al: Fluoxetine in chronic fatigue syndrome: a randomized, double-blind, placebo-controlled study. *Lancet* 347:858–861, 1996
120. Natelson B, Cheu J, Pareja J, Ellis S, Policastro T, Findley T: Randomized, double-blind, controlled placebo-phase in trial of low-dose phenelzine in the chronic fatigue syndrome. *Psychopharmacology* 124:226–230, 1996
121. Stea J, Fried W: Remedies for a society's debilities: medicines for neurasthenia in Victorian America. *NY State J Med* 93:120–127, 1993
122. Wilkinson P, Mynors Wallis L: Problem-solving therapy in the treatment of unexplained physical symptoms of primary care: a preliminary study. *J Psychosom Res* 38:591–598, 1994
123. Lechky O: Life insurance MDs sceptical when chronic fatigue syndrome diagnosed. *Can Med Assoc J* 143:413–415, 1990
124. Schmalzing K, diClementi J: Interpersonal stressors in chronic fatigue syndrome: a pilot study. *J Chronic Fatigue Syndrome* 1:153–158, 1995
125. Feder H, Dworkin P, Orkin C: Outcome of 48 pediatric patients with chronic fatigue; a clinical experience. *Arch Fam Med* 3:1049–1055, 1994
126. Anonymous: *The Psychological Care of Medical Patients: Recognition of Need and Service Provision*. London, The Royal College of Physicians and the Royal College of Psychiatrists, 1995
127. Sharpe M, Peveler R, Mayou R: The psychological treatment of patients with functional somatic symptoms: a practical guide. *J Psychosom Res* 36: 515–529, 1992
128. Holmes G, Kaplan J, Gantz N, et al: Chronic fatigue syndrome: a working case definition. *Ann Intern Med* 108:387–389, 1988