Chapter 25

Chronic fatigue syndrome

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INTRODUCTION

Most people feel unduly tired at some time or another. For some, the experience of fatigue is unpleasant or incapacitating enough to encourage them to seek medical advice. A psychiatric or medical diagnosis can often account for their symptoms (Epstein, 1995). However, a proportion of patients experience a profound ongoing fatigue that cannot be explained by any single diagnosis. This fatigue is usually accompanied by a range of other somatic and neuropsychiatric symptoms. Over the past 25 years special attention has been given to these patients, and the causes of this debilitating fatigue have been hotly debated.

Early reports in the 1980s labelled the illness “yuppie flu,” regarding the malady as a psychosomatic reaction to the stressors of modern society (Wessely, 1997). Sufferers of the illness and their advocates strongly opposed these aspersions, insisting that the cause of the illness was organic. A series of names for the condition were advanced, such as chronic mononucleosis, postviral fatigue syndrome, and myalgic encephalomyelitis (ME), reflecting assumptions about the possible organic nature of the illness (Steincamp, 1989). In response to the nomenclature controversy and in an attempt to define a homogeneous group of patients for research purposes, the Centers for Disease Control in Atlanta renamed the condition chronic fatigue syndrome (CFS) and published the first standardized diagnostic criteria for the illness. This was followed by the publication of related definitions from Australia, the UK, and Canada (Lloyd et al., 1988; Sharpe et al., 1991; Carruthers et al., 2003).

In an attempt to standardize the CFS diagnosis across countries, a group of international researchers published a consensus definition (Fukuda et al., 1994). They specified that, in addition to being present for at least 6 months, the fatigue must have a definite onset, cause substantial disruption to the individual’s day to day activities, and should not be caused by continual exertion. At least four additional key symptoms, such as muscle and joint pain, headaches, unrefreshing sleep, and cognitive dysfunction, needed to be reported. Medical conditions that may explain the presence of chronic fatigue, psychiatric illnesses with psychotic features, and recent substance abuse problems precluded a diagnosis of CFS.

Epidemiological studies using the 1994 consensus definition report rates of CFS in adults of between 0.23% and 0.42% in the USA (Jason et al., 1999; Reyes et al., 2003) but as high as 2.6% in the UK (Wessely et al., 1997). The reasons for these discrepancies are not clear, but when patients with comorbid psychological disorders were excluded from the UK sample the rate dropped to 0.5% (Wessely et al., 1997).

Although early claims suggested that CFS was an illness of the white middle classes, this finding appeared to be a treatment presentation bias and has not been upheld in community-based epidemiological studies (Lloyd et al., 1990; Euba et al., 1995). However, there does seem to be a gender bias, with most studies suggesting that around 75% of patients are female (Cairns and Hotopf, 2005). Prospective studies of the onset of CFS also show that around 75% of patients are female (Cairns and Hotopf, 2004; Moss-Morris and Spence, 2006; Harvey et al., 2008).

A systematic review of longitudinal studies of untreated CFS patients suggests that the prognosis is bleak. On average around 5% of patients reported full recovery over a 1–5-year period and only around 40%
reported some improvement during this time (Cairns and Hotopf, 2005). However, it is worth noting that most studies focused on patients presenting to specialist centers, who are likely to be more severe cases of CFS.

In 2007, the UK published new National Institute of Health and Clinical Excellence (NICE) guidance on the diagnosis and treatment of CFS (Baker and Shaw, 2007). The recommendations for diagnosis are similar to the Fukuda criteria (Fukuda et al., 1994). However, the new criteria specify that CFS should be diagnosed after symptoms have persisted for 4 rather than 6 months, and that the fatigue criteria must be present with one or more of a list of related symptoms rather than a minimum of four symptoms (Baker and Shaw, 2007). The UK criteria also label the illness CFS/ME, where ME stands for myalgic encephalomyelitis or myalgic encephalopathy. This change arose because of a patient lobby around the classification of the illness in the World Health Organization (WHO) International Classification of Diseases (ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision, 2007). ICD-10 includes two illnesses, neurasthenia and postviral fatigue syndrome (or benign myalgic encephalomyelitis), which have almost identical criteria that map onto CFS. However, the former is classified under psychiatry: other neurotic disorders, whereas the latter is classified under diseases of the nervous system. Consequently, patient organizations that do not like the term CFS successfully lobbied to adopt the name CFS/ME, where ME stands for myalgic encephalomyelitis or myalgic encephalopathy. This change arose because of a patient lobby around the classification of the illness in the World Health Organization (WHO) International Classification of Diseases (ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision, 2007). ICD-10 includes two illnesses, neurasthenia and postviral fatigue syndrome (or benign myalgic encephalomyelitis), which have almost identical criteria that map onto CFS. However, the former is classified under psychiatry: other neurotic disorders, whereas the latter is classified under diseases of the nervous system. Consequently, patient organizations that do not like the term CFS successfully lobbied to adopt the name CFS/ME. So, is CFS/ME a postviral syndrome and/or a neurological disorder? In the following two sections, we review the evidence for this. The remainder of the chapter argues for an integrated, multifactorial cognitive behavioral model of CFS/ME, reviews treatment studies based on this model, and outlines therapeutic approaches that appear to be helpful in treating CFS/ME.

**IS CFS A POSTVIRAL ILLNESS?**

Most CFS patients seen in tertiary clinics predate the onset of their condition to an acute infective episode (Wessely and Powell, 1989; Lloyd et al., 1990; Komaroff and Buchwald, 1991). This is not altogether surprising as CFS shares a number of qualities with viral illnesses such as a sudden onset, fatigue, muscle aches and pains, and fuzzy-headedness. In response to these reports researchers worked hard in the 1980s and 1990s to pin down the elusive pathogen. A number of retrospective studies investigated the possible role of herpesviruses including Epstein–Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus 6 (HHV6); enteroviruses – largely Coxsackie B; retroviruses such as human T-cell leukemia virus type 2 (HTLV-2) and the spumaviruses; **Borrelia burgdorferi** and Borna disease virus. Although some studies reported elevated levels of viral antibodies in groups of CFS patients, the results were inconsistent and there was often considerable overlap between CFS patients and controls (Hotchin et al., 1989; Landay et al., 1991; Kawai and Kawai, 1992; Ablashi, 1994; Levy, 1994; MacDonald et al., 1996).

A more definitive large study which tested for antibodies to 13 viruses found that none of these could either discriminate CFS patients from healthy controls, or CFS patients who reported a viral onset from those who did not (Buchwald et al., 1996). Straus and colleagues (1988) tested the effectiveness of aciclovir, an antiviral drug, in a randomized controlled trial of CFS patients. They were unable to demonstrate any clinical efficacy for the drug, with clinical improvement more likely to be correlated with improved psychological status than changes in the immune system. Overall, retrospective studies showed little evidence for the role of elevated viral antibodies in the diagnosis or prognosis of CFS.

More recently, prospective studies investigated whether acute viral infections could predict the onset of CFS. Two of the earlier studies showed that common viral infections, such as upper respiratory tract infections, were not associated with the subsequent development of either chronic fatigue or CFS, and concluded that viruses did not play a role in the onset of CFS (Cope et al., 1994; Wessely et al., 1995). Subsequent studies, however, showed that certain more severe infections played a role in the onset of CFS including infectious mononucleosis (glandular fever) (White et al., 2001; Moss-Morris and Spence, 2006), hepatitis (Berelowitz et al., 1995), viral meningitis (Hotopf et al., 1996), Q fever (Wildman et al., 2002), and Ross River virus (Hickie et al., 2006).

Despite these findings, there are three reasons why it is unlikely that it is the virus itself that is responsible for the ongoing symptoms of CFS. First, a range of severe infections (both viral and bacterial) seem to predict CFS, rather than one specific virus. Second, we have already seen that antibody titers are not associated with CFS. Third, a detailed analysis of viral load and antiviral immune responses in an infectious mononucleosis cohort failed to show differences between patients who developed a post-infectious syndrome and those who recovered promptly (Cameron et al., 2006).

Following on from this, in a detailed study of the course of multiple viral infections, Hickie et al. (2006) argued that it is the host response to a severe infection rather than the virus itself that is important in the onset of CFS. They proposed that alternative neurobiological mechanisms triggered during the severe, acute illness and sustained in the absence of ongoing infection underpin the persistent symptoms leading to CFS (Hickie et al., 2006). So, are there neurobiological mechanisms in CFS patients?
THE NEUROBIOLOGY OF CFS

Studies that have attempted to answer this question have employed a range of methodologies including neuroimaging and measurements of neurotrophic factors, neurotransmitters, and cytokines. The most convincing evidence comes from research of the hypothalamic–pituitary–adrenal (HPA) axis. A number of studies have shown that CFS patients when compared to controls demonstrate a lower salivary cortisol response to awakening, hypocortisolism, a blunted HPA response to challenge, and an increased sensitivity of the HPA to the negative feedback effect of glucocorticoids (Cleare, 2004; Roberts et al., 2004; Cho et al., 2006; Van Den Eede et al., 2007). There is also some evidence that these changes are associated with fatigue and pain in CFS but not neurocognitive and psychological functioning (Torres-Harding et al., 2008). Cortisol replacement in CFS patients also appears to ameliorate fatigue in the short term but with substantial side-effects (Cleare et al., 1999).

These studies appear to lend support to the idea that an infection may trigger a neurobiological reaction which leads to dysfunction of the HPA in susceptible hosts, which in turn maintains some of the symptoms. However, not all studies report differences between CFS patients and controls in the HPA basal hormone and challenge studies (Cleare, 2004). One reason for this may be that hypofunctioning of the HPA only occurs in a specific subgroup of CFS patients. In support of this idea, two studies have found that decreased salivary cortisol and reduced cortisol response to dexamethasone/corticotrophin releasing factor were evident only in patients who had a history of childhood trauma or early life stress (Van Den Eede et al., 2008; Heim et al., 2009). This suggests that changes in the responsiveness of the HPA axis in CFS might be a prolonged or early stress response rather than a reaction to a pathogen. Whilst stress has more typically been associated with HPA axis hyperactivity, chronic stress and conditions such as posttraumatic stress disorder have been associated with hypoactivity (Gold and Chrousos, 2002; Fries et al., 2005). Tanriverdi et al. (2007) in a review of this topic suggest that hypocortisolism is an adaptive response to chronic stress. This is similar to Dantzer’s (2005) hypothesis that hypocortisolism may be a marker of an evolved “recuperative” response, marked by activity abrogation and lassitude, which, in illnesses such as CFS, may become sensitized to previously benign cues and stressors.

Others argue that the changes to the HPA axis occur later on in the illness and may reflect prolonged behavioral change or reduced activity, deconditioning, and sleep disturbance as a consequence of having a prolonged chronic illness (Cleare, 2004). In line with this proposal, Gaab et al. (2004) showed that HPA axis dysfunction in CFS is associated with length of illness. Others have demonstrated that the development of chronic fatigue 6 months after glandular fever is not related to HPA dysfunction measured at the time of infection (Buchwald et al., 2000). Even more compelling are findings from a recent study showing that CFS patients who are rated as clinically improved after cognitive behavioral therapy (CBT) also show a significant rise in cortisol levels (Roberts et al., 2004). CBT as discussed in detail below, focuses amongst other things on increasing activity and establishing a good sleep/wake routine.

Other neurobiological findings suggest that CFS patients have a hyperserotonergic state (Cho et al., 2006). Immunologically there is also evidence of increased cytokine production and HPA axis responsiveness to cytokines, and reduced natural killer cell activity (Gaab et al., 2005; Cho et al., 2006). This may be because if hypothalamic neurons fail to respond adequately to cytokine stimulation, the resultant failure of adequate glucocorticoid-mediated restraint of the immune system results in a hyper-immune state (Gold and Chrousos, 2002; Gerrity et al., 2004). Imaging studies have reported abnormal perfusion in specific regions of the brain, decreased brain volume, and some minor structural cerebral changes in the frontal lobe of CFS patients when compared to controls (Chen et al., 2008). However, it is difficult to interpret these findings as they are not consistent across studies, have not been replicated in studies where CFS patients are compared with healthy twin siblings, and are based on very small samples (Lewis et al., 2001; Chen et al., 2008).

Taken together, there is accumulating evidence that there are neurobiological changes in at least some CFS patients. None of the findings is consistent enough to suggest a diagnostic marker for CFS or a clear neurological etiology for the illness. The question as to whether the findings reflect a central pathogenic mechanism, as part of a more systemic problem, or whether they are the consequence of behavioral changes associated with the illness or related psychological states such as chronic stress, cannot as yet be answered.

We suspect that the likely answer is that CFS cannot be understood through one etiological mechanism, whether it be viral, neurobiological, or psychological. Rather it is a complex illness that is best explained in terms of a multifactorial cognitive behavioral (CB) model that incorporates predisposing, precipitating, and perpetuating factors (Surawy et al., 1995). This model comprises biological, affective, behavioral, and cognitive elements of the illness. The fundamental assumption of a CB model is that the perpetuating domains interact to maintain symptoms and distress, and that change in one domain will effect change in
the others (Chalder, 1997). What should perhaps be highlighted in the application of this model to medically unexplained symptoms in general and CFS in particular is that this constitutes a previously undescribed disease mechanism, one that produces and/or maintains physical symptoms in the absence of either frank physical pathology or psychopathology. These conditions, if the CB theories are right, constitute a unique and distinct species of illness. The basic hypothesis at work here is that of a systemic dysregulation which becomes self perpetuating (Sharpe et al., 1996). In the remainder of this chapter, we review the evidence for the application of this model to CFS and the effectiveness of treatment approaches based on the model.

**PREDISPOSING FACTORS**

The CB model suggests that certain individuals are predisposed to or more at risk of illnesses such as CFS. There is good evidence that a history of psychopathology or elevated premorbid levels of distress are significant risk factors. A recent prospective study looked at prior psychiatric disorder and the onset of chronic fatigue at age 53 in a 1946 UK birth cohort of approximately 5000 individuals. Those who had experienced a psychiatric disorder, particularly anxiety and depression, before age 36 were almost two and a half times as likely to develop CFS. Other prospective studies that have investigated the role of psychosocial factors and viruses in the onset of CFS have also shown that premorbid distress, depression, and anxiety appear to be better predictors of the onset of CFS than the viruses themselves (Wessely et al., 1995; White et al., 2001; Moss-Morris and Spence, 2006).

It is possible that the heightened levels of distress are linked to a genetic predisposition. Kato et al. (2006) charted the incidence of CFS in a Swedish twin cohort of almost 20 000 individuals and found that the personality trait of emotional instability, a tendency to experience psychological distress, and premorbid levels of perceived stress significantly predicted onset of fatigue. Controlling for genetic factors ameliorated the impact of personality and increased the impact of stress. The authors concluded that some genes may predispose to both emotional instability and fatigue whilst others may be protective. Several twin studies (Buchwald et al., 2001; Schur et al., 2007) also suggested that CFS is partly heritable, though in their review of this evidence Cho et al. (2006) argued that environmental influence predominates.

Retrospective studies highlight the possible role of the environment and early experience in the development of CFS. Heim and coworkers (Heim et al., 2006, 2009) have replicated findings of an increased reporting of childhood sexual abuse in adult CFS patients. Their most recent study found abuse was associated with a six-fold increase in the likelihood of developing CFS. Taylor and Jason (2001) reported a similar finding.

Another key finding from the 1946 UK cohort study was that people who were more physically active in childhood and adulthood, those who continued to be active after onset of fatigue, and those with a lower adult BMI were more likely to develop CFS (Harvey et al., 2008). This finding is in accord with CFS patients’ personal accounts that before their illness they were very active, driven individuals (Moss-Morris and Petrie, 2000). A cross-sectional study showed that both CFS patients and their partners report patients as having an “overactive” premorbid lifestyle compared to controls (Van Houdenhove et al., 2001). It may be that this overactive lifestyle is linked to personality characteristics such as perfectionism. Perfectionism, particularly the so-called negative aspects of it, where people base their self-esteem and the respect from others on their abilities to live up to certain high standards, has been shown to be one of the psychosocial predictors of CFS post glandular fever (Moss-Morris et al., 2011). Similarly, cross-sectional studies have also shown an association between negative perfectionism and CFS, and between perfectionism in CFS and distress (White and Schweitzer, 2000; Deary and Chalder, 2010). Predisposing genetics, personality factors, activity patterns, and distress may all be closely interlinked. In turn, these factors may affect the neurobiology of susceptible individuals as discussed earlier.

Interestingly, it is not only overactivity that appears to be a risk for CFS. Another large birth cohort study of data collected in 1970 found that childhood experience of a limiting illness and a more sedentary lifestyle were predictors of fatigue (Viner and Hotopf, 2004). Therefore there may be different or even opposing predisposing factors in different individuals.

**PRECIPITATING FACTORS**

Precipitating events are those that trigger the illness in susceptible individuals. In support of this, we have already seen that a range of more severe viruses act as precipitants for CFS. Stress may also be an important precipitant. A prospective study of 150 patients with glandular fever found that those who experienced more life events in the 6 months prior to the infection were more likely to develop an ongoing chronic fatigue (Buchwald et al., 2000). Other retrospective studies have shown that CFS patients reported a higher incidence of stressful life events premorbidly (Salit, 1997; Chalder, 1998). A study by Hatcher and House (2003) reported that dilemmas, forced choices between equally undesirable alternatives, were particularly associated with CFS.
MAINTAININ/PERPETUATING FACTORS
Illness cognitions and behaviors

The CB model of CFS posits that patients’ illness beliefs and coping strategies are key factors in both the onset and perpetuation of the condition (Surawy et al., 1995). In particular, the model suggests that when patients high in negative perfectionism and/or distress are faced with precipitating factors that affect their ability to perform, their initial reaction is to press on and keep coping. This behavior leads to the experience of ongoing symptoms which may be more closely related to pushing too hard than to the initial insult or injury. However, in making sense of the situation, patients attribute the ongoing symptoms to physical factors. The common response to a physical illness is rest. However, reduced activity conflicts with achievement orientation and may result in bursts of activity in an attempt to meet expectations (all-or-nothing behavior). These periodic bursts of activity inevitably exacerbate symptoms and result in failure, which further reinforces the belief that they have a serious illness. As time goes by, efforts to meet previous standards of achievement are abandoned and patients become increasingly preoccupied with their symptoms and illness. This results in chronic disability and the belief that one has an ongoing incurable illness, which is eventually diagnosed as CFS.

In support of this model, two prospective glandular fever studies have shown that patients who had a propensity to label a wide range of everyday symptoms as part of their acute illness and had more negative perceptions of their acute symptoms were more likely to develop CFS than those who did not (Candy et al., 2004; Moss-Morris et al., 2011). In addition, Moss-Morris et al. (2011) found that those who were more likely to respond to their symptoms in an all-or-nothing fashion were more likely to develop CFS. There is a large number of cross-sectional and treatment studies that provide further evidence for the role of cognitions and behavior in CFS (see Moss-Morris, 2005 for review). For instance, when compared to other patient groups with illnesses such as rheumatoid arthritis and heart disease, CFS patients have stronger beliefs that the illness is largely physical in origin and has very serious consequences (Moss-Morris et al., 2002; Moss-Morris and Chalder, 2003). CFS patients also tend to be hypervigilant to illness and symptom information (Hou et al., 2008). They are often fearful of the aftermath of overactivity, which is reflected in two characteristic ways of coping with the illness including a passive disengagement response or an all-or-nothing erratic pattern of behavior. These beliefs and coping strategies are related to disability and fatigue. This may be in part, as discussed in the section on neurobiology, because these behavioral changes contribute to hypofunctioning of the HPA axis and some of the other neurological changes recorded in CFS populations. There is also evidence of sleep disturbance in CFS which may contribute to fatigue and other symptoms (Morriss et al., 1997).

Ongoing stress, distress, and social factors

Various social and environmental factors may also help to maintain the syndrome. Van Houdenhove et al. (2002) compared recently diagnosed CFS patients to multiple sclerosis and rheumatoid arthritis patients and demonstrated that the former group was significantly more likely to report both a higher frequency of daily hassles and a higher negative impact of these on mood. Prins et al. (2004) studied social support over the course of a year, comparing CFS patients with cancer patients, people on fatigue sick leave, and healthy controls. They found that both fatigue groups complained of more negative social interactions, which changed only in those receiving CBT. Fatigue severity after 8 months was predicted by negative social interactions at baseline. Chalder (1998) has shown that social support has a U-shaped relationship to fatigue. Too much appeared to be as bad as too little, suggesting that perhaps too much support served to maintain illness behavior, whereas too little may increase distress and therefore fatigue. Bentall et al. (2002) have shown that being in receipt or in the process of applying for benefits was related to poor prognosis in CFS. Medical advice may also be a factor. Candy et al.’s study (2004) showed that advice to rest in response to glandular fever significantly predicted chronic fatigue development.

Looper and Kirmayer (2004) highlighted that compared to other functional syndromes such as irritable bowel syndrome (IBS) and fibromyalgia, and to rheumatoid arthritis patients, CFS had a higher perceived stigma. Kirmayer et al. (2004) demonstrated that individuals who cannot make sense of their symptoms are more likely to suffer more from them. The role of health professionals may be important here in providing validation and explanation, or not. Several studies (Dowrick et al., 2004; Salmon et al., 2004) showed that a poor relationship with a general practitioner in patients who have medically unexplained symptoms leads to increased symptom focus and reporting.

In summary, a generic CBT model of CFS hypothesizes that vulnerable individuals, such as those who are prone to distress, high achievement, overactivity, and/or being under stress, are precipitated by life events and viral illness into a self-perpetuating cycle where physiological changes, illness beliefs, reduced and inconsistent activity, sleep disturbance, medical uncertainty, and lack of guidance interact to maintain symptoms. Whilst intuitively persuasive, the evidence for multisystem interaction is far weaker than the evidence for the
individual factors cited above (see Deary et al., 2007, for a review of CB model). However, as we shall discuss below in the sections on treatment guidance, the strength of the CB model is its flexibility, which can be used to help a patient make sense of the particular constellation of factors involved in their illness experience.

**REHABILITATION IN CHRONIC FATIGUE SYNDROME**

A number of treatments have been developed to assist those with CFS, reflecting the various hypotheses formulated to explain its pathogenesis. These interventions range from pharmacological (e.g., McKenzie et al., 1998; Cleare, 2002; Blacker et al., 2004) to immunological (e.g., Vollmer-Conna et al., 1997; Zachrission et al., 2002), and from complementary (e.g., Weatherley-Jones et al., 2004) to cognitive and behavioral (e.g., Wearden et al., 2010; White et al., 2011). A qualitative review by Chambers et al. (2006) evaluated 70 trials of a broad range of treatments, concluding that behavioral therapies held the strongest base of evidence supporting their efficacy. These therapies include CBT, which has already been described (e.g., O'Dowd et al., 2006; Jason et al., 2007; Knoop et al., 2008; Chalder et al., 2010; White et al., 2011); pragmatic rehabilitation (Powell et al., 2001; Wearden et al., 2010), being a similar treatment to CBT without an explicit focus on targeting illness-related beliefs; and graded exercise therapy (GET; Fulcher and White, 1997; Wearden et al., 1998; Moss-Morris et al., 2005; Gordon et al., 2010; White et al., 2011), being similar to the behavioral component of CBT. Additionally, CBT and GET are recommended as best practice in the UK NICE guidance for the treatment of CFS (Baker and Shaw, 2007).

A recent meta-analysis comparing the post-treatment effects of GET, CBT, and pragmatic rehabilitation concluded that all three interventions demonstrated comparable small to moderate effects, with CBT tending towards slightly more positive outcomes for measures of mood symptomatology (Castell et al., 2011). The overall findings of a positive effect for GET and CBT are supported by earlier quantitative reviews (Edmonds et al., 2004; Malouff et al., 2008; Price et al., 2008). A Cochrane Review of CBT for CFS (Price et al., 2008), for example, found that 40% of patients showed a good clinical response compared to usual care (26%). Although evidence for the long-term effect of these treatments is less conclusive (Price et al., 2008; Castell et al., 2011), a recent randomized controlled trial comparing GET and CBT with medical care and adaptive pacing found that patients treated with GET or CBT had slightly improved their positive gains between end of treatment and 12-month follow-up (White et al., 2011). Similarly, a 5-year follow-up of a well-designed unbiased CFS trial of individual CBT showed that 70% of CFS patients still reported improvements at this time point (Deale et al., 2001).

An analysis of potential moderators of CBT concluded there is a stronger base of evidence supporting the use of CBT for CFS in secondary care settings, potentially due to the provision of too few treatment sessions in primary care (Castell et al., 2011). Additionally, CBT delivered in a group format was found to be as effective as delivery in a dyadic format. There is also emerging evidence for the use of CBT with adolescents and their families (Stulemeijer et al., 2005; Chalder et al., 2010); these trials have shown a clinically significant impact on school attendance and physical functioning. At the present time, too few trials of GET and pragmatic rehabilitation have been published for quantitative analyses to determine optimal treatment conditions. However, as the greatest level of support has been found for CBT and GET, the following discussion will outline the standard treatment procedures for both.

**Cognitive behavioral therapy**

Factors involved in the perpetuation, rather than the precipitation, of fatigue are the primary focus of intervention in CBT. Following from the CB model of CFS, illness-related cognitions and behaviors that work to maintain and perpetuate symptoms become the target of treatment. Ultimately, the aim of CBT for CFS is recovery from symptoms through an increased sense of control over symptoms, symptom re-attribution, reduced symptom monitoring, gradual return to physical and mental activity, and improvements in mood (Chalder et al., 1999; Bazelmans et al., 2006).

A number of protocols for CBT exist (e.g., Sharpe et al., 1996; Deale et al., 1997; Prins et al., 2001), although these are consistent with initial protocol recommendations made by researchers in London (Wessely et al., 1989; Chalder et al., 1999). More recently, recognition of differing perpetuating factors for relatively passive versus relatively active patients has resulted in theory-driven variations in standard treatment procedure (Stulemeijer et al., 2005; Bazelmans et al., 2006). These variations are based on the premise that the symptoms of passive patients are thought to be perpetuated by fear and avoidance of activity, while those of relatively active patients are thought to be perpetuated by high self-expectations, self-criticism, and non-acceptance of symptoms concomitant with all-or-nothing patterns of behavior.

At the outset of treatment, acknowledgment of the patient’s illness experience and validation of distress is
long-term exacerbation of symptoms, hence providing an initial, acute stage of illness (Wessely et al., 1989), that avoidance of activity may have been adaptive at demonstrating a passive activity pattern, a graduated re-

patients' established activity patterns. For patients who demonstrate an all-or-nothing cycle of activity, initial work in CBT focuses on maintaining a realistic and consistent level of activity. As some CFS patients tend to overestimate their level of exertion (Wallman and Sacco, 2007), while at other times attempt to exceed the abilities of their present physical conditioning, patients are encouraged to neither exceed exercise limits when feeling well or fall short of them when experiencing a temporary increase in symptomatology, which is to be expected following scheduled activity but unlikely to be detrimental to long-term health status (Nijs et al., 2008).

A substantial number of patients with CFS experience clinically significant sleep difficulties, a proportion of which has been attributed to excessive diurnal sleeping (Morriss et al., 1997; Unger et al., 2004). A sleep schedule, therefore, is negotiated to reduce daytime sleeping and establish stimulus control for nighttime sleep (Deale et al., 1997; Chalder et al., 1999).

The establishment of behavioral strategies is followed by a focus on cognitive factors in CFS. Patients are encouraged to monitor and seek alternative explanations for negative and/or unrealistic beliefs regarding activity and symptoms. These may include, among others: beliefs about control over symptoms; the dangerousness, functional impact, and prognosis of symptoms; negative beliefs concerning the role of activity and associated postactivity symptoms; and unrealistically high self-expectations (Chalder et al., 1999; Moss-Morris, 2005; Bazelmans et al., 2006; Knoop et al., 2010; Moss-Morris et al., 2011).

Ultimately, treatment should progress towards realistic goals set collaboratively with the patient at the outset of treatment and carefully plan for setbacks during and following treatment.

Graded exercise therapy

Similar to the behavioral component of CBT for CFS, graded exercise therapy involves a progressive return to activity. However, unlike CBT, the underlying theoretical model proposes that chronic fatigue is perpetuated primarily by the physiological process of deconditioning and sensitization to exertion (Clarke and White, 2005). Treatment, therefore, aims to improve the levels of physical activity and conditioning of the patient. Graded exercise also works through principles of graded exposure where exercise and overexertion are viewed as the feared stimuli.

Most commonly delivered by physiotherapists or exercise physiologists, graded exercise therapy involves a regimen of regular and gradually increasing aerobic exercise prescribed on the basis of exercise testing and
agreed-upon activities and goals (Fulcher and White, 1997). The principles of collaboration and the provision of a rationale for the treatment approach based on the underlying theoretical model apply here also. Initial exercise duration is usually set between 5 and 15 minutes depending on the physical conditioning of the patient and gradually increased to 30 minutes for 4–5 days per week. In one published protocol, initial intensity is set at a target heart rate of 40% of maximal oxygen consumption and gradually increased to 60–70% (cf. Fulcher and White, 1997; Moss-Morris et al., 2005; White et al., 2011). Observations from treatment trials suggest it may not be prudent to set initial intensity and duration too high (Castell et al., 2011). In some protocols, a heart rate monitor is provided to patients to ensure targets are met and not exceeded; this also offers an objective indicator of exertion and assists in reducing patients’ focus on physiological sensations (Fulcher and White, 1997; Moss-Morris et al., 2005).

Despite no explicit attempt being made to restructure illness-related beliefs, limited evidence suggests that improvements observed following graded exercise are mediated by cognitive change, specifically by decreasing the patient’s focus on fatigue, improving subjective self-efficacy, and decreasing negative beliefs associated with activity and fatigue (Moss-Morris et al., 2005; Knoop et al., 2010). Interestingly, recent evidence suggests that graded exercise therapy may be viewed as more credible by patients, at least prior to engagement in therapy (White et al., 2011). Graded exercise, therefore, may be indicated for patients who would otherwise find CBT and/or referral to a mental health professional difficult to accept (Clark et al., 2002). There is some preliminary evidence to suggest, however, that compared with graded exercise therapy, patients with comorbid mood symptoms may experience greater reductions in depression and, to a lesser extent, anxiety, when treated with CBT (Castell et al., 2011).

**Future directions in treatment**

Thus far, CBT and GET have received the most support in terms of treatment efficacy. However, clinically significant improvement should not be overstated for either treatment (Quarmby et al., 2007; Knoop, 2011); few trials have reported significant improvement in more than 50% of patients. Further, effect sizes reported in meta-analyses are of a small to moderate magnitude, and outcomes between trials are highly variable. Hence, more work needs to be done to optimize treatment efficacy. To achieve this, research efforts have shifted towards identifying optimum treatment conditions, therapeutic mechanisms of change, and predictors of natural course (e.g., Knoop et al., 2010; Moss-Morris et al., 2011; Wiborg et al., 2010, 2011; Castell et al., 2011). Cognitive-attentional processes have been recently highlighted as important predictors of severity and treatment outcome—specifically, the role of symptom-focusing (Moss-Morris, 2005; Wiborg et al., 2011), secondary beliefs regarding the harmfulness and controllability of said symptoms (Noonan et al., 2009; Moss-Morris et al., 2011), and relatedly, metacognitive beliefs regarding the controllability and benefits of symptom-focused thinking (Maher-Edwards et al., 2010). Future treatment approaches could do more to target these processes.

Two pilot studies of mindfulness-based CBT for CFS have shown promising outcomes (Surawy et al., 2005; Rimes and Wingrove, 2011), reporting improvements across a range of outcome domains. Mindfulness-based approaches aim to reduce the distress arising from negative appraisals of internal experience (physiological sensations, thoughts, and emotions) by encouraging the patient to notice these experiences without evaluating or avoiding them. This approach may be of use in targeting secondary beliefs and meta-cognitions (Wells, 2005). In addition, mindfulness-based approaches have been found to be effective for reducing anxiety (Hofmann et al., 2010), an outcome traditionally difficult to achieve in treatments for CFS (Castell et al., 2011). Notably, relatively large reductions in anxiety (effect sizes = 0.84–1.32) were replicated across three small pilot studies of mindfulness for CFS delivered in a group setting (Surawy et al., 2005).

Clinicians should be aware that research attempting to elucidate factors contributing to positive outcomes is still in its infancy, and the approaches described here may not be beneficial for all patients. However, these approaches, if collaboratively applied to the unique situation of the particular patient, can at least provide a framework for agreeing what can be usefully worked on, whilst providing a structure to aid substantial recovery for others.

**References**


